IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
FLORENCE DNISION

HUANNI YANG-WEISSMAN, Plaintiff, v. SOUTH CAROLINA PRESTRESS CORPORATION, Defendant.	)	Civil Action No: 4:07-cv-03643-RBH **PLAINTIFF'S MEMORANDUM IN OPPOSITION TO DEFENDANT'S MOTION *IN LIMINE* CONCERNING DIFFUSION TENSOR IMAGING STUDIES**

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HUANNI YANG-WEISSMAN,	)	Civil Action No: 4:07-cv-03643-RBH
Plaintiff,	)	
v.	)	**PLAINTIFF'S MEMORANDUM**
	)	IN **OPPOSffiON TO DEFENDANT'S**
SOUTH CAROLINA PRESTRESS CORPORATION,	)	**MOTION** *IN* ***LIMINE*** **CONCERNING DIFFUSION TENSOR IMAGING STUDIES**
Defendant.	)	

TO: E. DALE LANG, JR., AND DUKE R. HIGHFIELD, ATTORNEYS FOR DEFENDANT

I. Introduction

On November 9, 2004, Plaintiff Huanni Yang-Weissman was critically injured when Defendant's employee, operating a fully-loaded cernent truck weighing approximately 90,000 pounds, ran a red light and crashed broadside into the driver's side of the sedan being driven by Plaintiff. As a result of the collision Plaintiff sustained numerous injuries including a traumatic brain injury.

This matter is before the Court on Defendant's Motion *in Limine* to exclude the introduction of any evidence or testimony concerning the diffusion tensor imaging ("DTI") study performed by and interpreted in the report of Michael L. Lipton, **M.D.,** Ph.D. A copy of that report is attached as Exhibit 1. Dr. Lipton is not a retained expert. He is Plaintiff's treating physician. Because the DTI study and Dr. Lipton's utilization of the study is sufficiently reliable and relevant, Defendant's Motion must be denied.

n. Dr. Lipton

Dr. Lipton is a neuroradiologist and is board certified by the American Board of Radiology in diagnostic radiology. He is a Neuroscientist. He also has a Certificate of Added Qualification and a current Maintenance of Certification, both in the field of neuroradiology. In addition to being the Associate Director of the Gross Magnetic Resonance Research Center at the Albert Einstein College of Medicine, he serves as its Director of Research for the Departrnent of Radiology and is an associate professor of radiology, psychiatry, behavioral sciences and neuroscience. Dr. Lipton is also the Medical Director for the clinical MRI services at Montefiore Medical Center. Dr. Lipton is an attending physician at Montefiore Medical Center, Jacobi Medical Center, and North Central Bronx Hospital. Dr. Lipton's curriculum vitae is attached as Exhibit2.

m. <u>Diffusion Tensor Imaging: An Overview</u>

In his treatment and evaluation of Plaintiff, Dr. Lipton performed an MRI study on Plaintiff's brain additionally using a modality known as diffusion tensor imaging ("DTI"). Based upon his review and assessment of the DTI study, Dr. Lipton concluded that Plaintiff sustained a traumatic brain injury. (<u>See</u> Trial Deposition of Michael L. Lipton, M.D., Ph.D, pp. 23, 47, attached as Exhibit 3). This is the same diagnosis that has been made by a number of Plaintiff's treating physicians and retained experts, including: Dr. Steven Stein, a neuropsychologist; Dr. Seymour Gendelman, a neurologist; Dr. Morton Finkel, a neurologist; Dr. Brian Greenwald, a physiatrist; Dr. Daniel Kuhn, a neuropsychiatrist; Dr. Daniel Luciano, a neurologist; and Dr. Randolph Waid, a neuropsychologist.

A traditional MRI shows the structure of the brain. Most people who have sustained mild head injuries have normal MRI findings even if they have significant impairment. (Lipton Trial Depo., pp. 104-105.) DTI is a more sensitive technology that can reveal abnormalities that are

not visible on standard MRis. (Lipton Trial Depo., p. 53; also Affidavit of Michael L. Lipton, M.D., Ph.D., ,r 7, attached as Exhibit 4.) DTI measures the direction of movement or flow (known as diffusion) of water molecules through tissue. (Lipton Trial Depo., p. 53; Aff. of Lipton, ,r 12.) Unlike other imaging technologies, DTI permits examination of the microscopie structure of the white matter of the brain, allowing for the detection of microscopie pathology or abnormality of the white matter. (Lipton Trial Depo., p. 53; Aff. of Lipton, ,r 13.) In the white matter of a normal/healthy brain, the direction of water diffusion is very uniform. (Aff. of Lipton, ,r 14.) Injury disrupts the normal structure of white matter leading to less uniform direction of diffusion. (Aff. of Lipton, ,r 14.) DTI is an FDA approved, peer reviewed and approved, commercially marketed, and widely available MRI method which bas been in clinical use for many years. (Lipton Trial Depo., pp. 28, 55-56; Aff. of Lipton, ,i,r 8-9.)

Just as with standard MRis, DTI produces digital images. (Lipton Trial Depo., p. 89.) In such images, the brain is represented as many slices which, when stacked one upon the other yield a "volume" representing the entire brain. (Lipton Trial Depo., p. 89.) Each slice comprises a rectangular array of pixels, in the same manner as does the image captured by a digital camera. (Lipton Trial Depo., p. 89.) Unlike an image from a digital camera, however, each of the MRI pixels bas three dimensions, the left-right and up-down dimensions of the slice as well as the thickness of the slice. (Lipton Trial Depo., p. 89.) Each "pixel" thus represents a volume of tissue, known as a "voxel." (Lipton Trial Depo., p. 89.) When multiple slices are stacked atop one another, the result is the full volumetric representation of the brain. (Lipton Trial Depo., p. 89.)

In the clinical setting, DTI can be, and is, used to diagnose individual patients. (Lipton Trial Depo., p. 28.) Regions of abnormally nonuniform diffusion (called low anisotropy) due to

brain injury may be visible on visual inspection of the fractional anisotropy images (known as "FA images"). (Aff. of Lipton, ,r 16.) However, visual assessment of such images has limite<! sensitivity and may miss significant abnormalities. (Aff. of Lipton, ,r 16.) It is for this reason that quantitative measurement of the images is necessary to ensure sensitivity, reliability, and objectivity. (Aff. of Lipton, ,r 17.) This can be accomplished by performing a voxel-wise analysis. (Aff. ofLipton, ,r 17.) In short, a voxel-wise analysis consists of examining each voxel in the patient's DTI images and determining whether that voxel is significantly different from the same location in a group of normal or "control" individuals. (Lipton Trial Depo., p. 90; Aff. of Lipton,,r 18.)

In performing a voxel-wise analysis, Dr. Lipton initially determines the voxels in the patient's brain that are significantly different from the range of values found in the same voxel in the normal or "control" group. (Lipton Trial Depo., p. 90; Aff. of Lipton, ,r 18.) The control subjects used by Dr. Lipton to determine the "normal range" are selected through an extensive testing and screening process designed to eliminate any unsuitable candidates. (Lipton Trial Depo., p. 54; Aff. of Lipton, ,r 19.) This screening process eliminates any control subjects with evidence of medical illness, substance abuse, medication usage, psychiatrie disease, and neurological disease. (Aff. of Lipton, ,r 19.) The control subjects used in any diagnostic analysis are carefully selecte<l to match the patient's age and gender. (Aff. of Lipton, ,r 19.) The control subjects are also image<! using the exact same equipment and imaging parameters as the patients. (Aff. of Lipton, ,r 19.)

The resulting range of measurements obtainoo from the DTI studies performed on the control subjects are use<! to define the normal distribution for each voxel. (Lipton Trial Depo., p. 67; Aff. of Lipton, ,r 20.) The normal distribution will have a mean, or, an average, and

abnormalities in a patient's DTI measurements are detected according to how far they deviate from tb.at mean. (Lipton Trial Depo., p. 67; Aff. ofLipton, ,r 20.) This comparison is thus done on a voxel-by-voxel basis. (Lipton Trial Depo., p. 90; Aff. of Lipton, ,r 20.) Typically, any measurement of a patient that is two standard deviations or more from the mean is considered significantly abnormal. (Lipton Trial Depo., p. 68; Aff. of Lipton, ,r 21.) In such a situation, where a patient's measurement is two standard deviations or more away from the mean of the normal distribution, there is only a 5% chance that the finding of abnormality is a false positive, or, due to inherent variability rather than actual abnormality. (Lipton Trial Depo., p. 68; Aff. of Lipton, ,r 21.) In other words, the error rate when accepting a measurement a minimum of two standard deviations from the normal mean as abnormal is a maximum of 5%. (Lipton Trial Depo., p. 68.) Notably, this 5% criterion is the standard for determination of clinically significant findings in medical research. (Lipton Trial Depo., pp. 65-66; Aff. ofLipton, ,r 21.)

In performing the voxel-wise analysis on Plaintiff's DTI study, only those measurements that fell at least five standard deviations from the mean of the normal distribution were considered abnormal. (Lipton Trial Depo., p. 68; Aff. ofLipton, ,r 22.) In so doing, the error rate is decreased to less than one tenth-of-a-percent, meaning tb.at the chance that the finding of abnormality is due to inherent variability, rather than actual abnormality, is less than 0.1%. (Lipton Trial Depo., p. 66.)

The result of this analysis is a determination of all the voxels tb.at vary significantly from the mean and therefore are presumptively abnormal. (Lipton Trial Depo., p. 90; Aff. ofLipton, ,r 23.) However, Dr. Lipton takes his analysis a step further and does not conclude that all ofthose single-voxel abnormalities indicate true abnormal findings. (Lipton Trial Depo., p. 90; Aff. of Lipton, ,r 23.) Rather, to reach the conclusion that an abnormality is present in a patient's brain,

Dr. Lipton looks for clusters of voxel abnormalities. (Lipton Trial Depo., p. 90; Aff. ofLipton, ,r 23.) Specifically, in bis analysis of Plaintifrs DTI study, Dr. Lipton required that a minimum of 100 single-voxel abnormalities be adjacent or touching before concluding that an abnormality was present. (Lipton Trial Depo., pp. 90, 92-93; Aff. of Lipton, ,r 23.) That means that any abnormality reported by Dr. Lipton affects a volume of the patient's brain that amounts to, at the very least, a cubic centimeter of tissue that is a11 consistently abnormal. (Lipton Trial Depo., p. 90.)

Dr. Lipton has used DTI for over ten years total and bas used it for over eight of those years in connection with the clinical assessment, evaluation, and diagnosis ofbrain injury. (Aff. ofLipton, ,r 9.) The methods employed by Dr. Lipton in his analysis ofDTI studies to diagnose brain injury are peer reviewed and are scientifically reliable.

IV. Argument

A. Legal Standard

Defendant argues in its Motion that Dr. Lipton's utilization of DTI study of the Plaintiff does not comport with the second and third reliability requirements of FED. R. Evm. 702. FED. R. Evrn. 702 acts as the guidepost for the admissibility of expert testimony. U.S. v. Wilson, 484 F. 3d 267, 274-75 (4th Cir. 2007). The rule provides:

> 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, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

FED. R. Evrn. 702. The proponent of the testimony must establish its admissibility by a preponderance ofproof. Cooperv. Smith & Nephew, Inc., 259 F.3d 194, 199 (4th Cir. 2001).

In response to Daubert v. Merrell Dow Pharmaceuticals. Inc., 509 U.S. 579 (1993), and to the many cases applying Daubert, including Kumho Tire Co. v. Carmichael, 526 U.S. 137 (1999), Rule 702 was amended in 2000 to a:ffirm the trial court's role as gatekeeper and to provide some general standards to be used in assessing the reliability and helpfulness of proffered expert testimony. See FED. R Evm. 702 advisory committee's note; see also Daubert, 509 U.S. at 589 (in considering the admissibility of expert testimony, a district court acts as a gatekeeper and must assess whether an expert's proffered testimony is both sufficiently reliable and relevant).

Rule 702 was intended to liberalize the introduction of relevant expert evidence. Cavallo v. Star Enter., 100 F.3d 1150, 1158-59 (4th Cir. 1996). It is not necessary for the Court to determine that the proffered evidence is irrefutable or certainly correct. See id. As stated by the Daubert Court, "it would be unreasonable to conclude that the subject of scientific testimony must be 'known' to a certainty; arguably there are no certainties in science." Daubrn, 509 U.S. at 591. As with ail other admissible evidence, expert testimony is subject to being tested by "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof." Id. at 596.

The Daubert Court gave a non-exclusive list of factors that may be valuable tools in assessing the reliability of an expert's opinion, including: (1) whether the reasoning or methodology underlying the expert's opinion has been or could be tested; (2) whether the reasoning or methodology has been subject to peer review and publication; (3) whether the technique has a high known or potential rate of error and whether there are standards controlling its operations; and (4) the level of acceptance of the reasoning or methodology by the relevant professional community. Daubrn, 509 U.S. at 593-94.

In its Motion, Defendant argues that the DTI study of the Plaintiff fails to satisfy the second and third reliability requirements of FED. R. Evm. 702 because it fails to satisfy the four considerations set forth in Daubert. This argument is somewhat misguided.

Rather than providing a definitive or exhaustive list, Daubert merely illustrates the types of factors that will "bear on the inquiry." U.S. v. Crisp, 324 F.3d 261, 266 (4th Cir. 2003). As Daubert emphasized, the analysis must be "a flexible one." Id. (citing Daube;ct, 509 U.S. at 593; Kumho, 526 U.S. at 141-42).

The Daubert factors do not ail necessarily apply in every instance in which the reliability of scientific testimony is challenged. Kumho Tire, 526 U.S. at 151. Rather, "the factors identified in Daubert may or may not be pertinent in assessing reliability, depending on the nature of the issue, the expert's particular expertise, and the subject ofhis testimony." Id. at 150 (quoting Brief for United States as *Amicus Curiae* 19). This position was reaffirmed by the 2000 amendment to FED. R. Evm. 702. See FED. R. Evm. 702 advisory committee's note ("No attempt has been made to 'codify' these specific factors. Daubert itself emphasized that the factors were neither exclusive nor dispositive. Other cases have recognized that not all of the specific Daubert factors can apply to every type of expert testimony....The standards set forth in the amendment are broad enough to require consideration of any or all of the specific Daubert factors where appropriate.").

In fact, both before and after Daube;ct, courts have found other factors relevant in determining whether expert testimony is sufficiently reliable to be considered by the trier of fact. One such factor applicable here is whether experts are "proposing to testify about matters

growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying." Daubert v.

Merrell Dow Pharmaceuticals. Inc., 43 F.3d 1311, 1317 (9th Cir. 1995). In the present matter, Dr. Lipton did not develop any opinions expressly for the purpose of testifying. Rather, Dr. Lipton is Plaintifrs treating clinician. Dr. Lipton's treatment of Plaintiff, his analysis of the DTI study, and the testimony he is expected to give at trial concerning these matters have a11 grown naturally and directly out of research and other activities conducted completely independent of this lawsuit. In fact, Dr. Lipton's practice only accepts referrals from other physicians who generally are referring the patient for a specific clinical question. (Lipton Trial Depo., p. 96.) In his clinical practice, Dr. Lipton performs the type of DTI analysis performed on Plaintiff for approximately three patients per month and has been doing so for years. (Lipton Trial Depo., p. 109.)

However, even if the analysis of the reliability of DTI and its use by Dr. Lipton was confined to the factors set forth in Daub Defendant's Motion must still be denied.

B. Dr. Lipton's Utilization of the DTI Study Satisfies the Daubert Factors

i. DTI has been tested.

In its Motion, Defendant represents that the use of the DTI study for diagnosis of an individual patient has not been confirmed by testing to be a reliable method and cites the report of its retained expert, Dr. Maldjian. As an initial matter, it does not appear that Dr. Maldjian's report actually contains this statement or a similar statement of opinion. It also does not appear to contain a statement that reliability testing is impossible in the individual context

The theory, or technique, being challenged is the use of DTI to diagnose brain injury in an individual. There is no question that DTI is a reliable method for indicating the presence of brain injury and that it is being used in the clinical setting to diagnose brain injury in individual patients. (Lipton Trial Depo., pp. 28, 53-54, 57-58; Aff. of Lipton, 18.) As described in more

detail below, there is ample peer-reviewed literature endorsing the methodology used by Dr. Lipton in bis assessment of Plaintiff. There have been numerous studies in which DTI has been shown to reliably indicate the presence of brain injury. Finally, the reliability of the results obtained by Dr. Lipton in bis assessment of DTI for the purposes of diagnosing brain injury is ensured by the various safeguards and tests employed as part of bis methodology to minimize erroneous findings.

li. DTI has been subjected to extensive peer review and publication.

As explained by the Daubert Court, wbile peer review and publication are pertinent considerations, "[p]ublication (wbich is but one element of peer review) is not a *sine qua non* of admissibility; it does not necessarily correlate with reliability, and in some instances well-grounded but innovative theories will not have been published. Sorne propositions, moreover, are too particular, too new, or of too limited interest to be published." Daubert, 509 U.S. at 593. However, "submission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." Id.

Defendant submits that its retained expert, Dr. Maldjian, "recounts at Paragraph 3 of [bis] affidavit that there is no 'medical literature establishing or otherwise endorsing this single subject versus group statistical analysis for DTI data as a reliable method of diagnosing individual brain injuries.'" (See Defendant's Motion, p. 3.) In actuality, in his affidavit, Dr. Maldjian states he is merely *unaware* of any such medical literature. (Aff. of Maldjian, ***,I*** 3.) Regardless, the fact of the matter is that such medical literature does exist. Thousands of papers have been published in peer reviewed journals concerning the use and applications of DTI, many

of wbich have specifically concerned DTI and traumatic brain injury. (Aff. of Lipton, ***,I*** 11.) In

fact, numerous peer-reviewed studies have established that abnormal anisotropy as measured by DTI demonstrates evidence of traumatic brain injury pathology not detectable using other imaging methods. (Aff. ofLipton,, 11.) The classic paper describing the basis of using DTI for examining white matter in the brain was published in 1995. (Lipton Trial Depo., p. 28.) **A** collection of articles addressing this subject is attached hereto as Exhibit *5*.

Dr. Lipton himself bas authored numerous peer-reviewed papers concerning the use of DTI to diagnose traumatic brain injury. (Lipton Trial Depo., p. 14; see also Exhibit 5.) One of these papers reported bath group and single subject analyses of DTI in chronic mild traumatic brain injured patients, showing the ability of DTI to detect evidence of brain injury in individual subjects. (Lipton Trial Depo., pp. 58-60; see also Exhibit 5.)

The use of DTI to diagnose brain injury bas certainly been submitted to, and has withstood the scrutiny of, the scientific community.

iii. Known/Potential Rate of Error

In assessing the reliability of a particular scientific technique, consideration should generally be given the known or potential rate of error and the existence and maintenance of standards controlling the technique's operation. Daubert, 509 U.S. at 594.

While Dr. Maldjian notes in his report that Dr. Lipton "never describes the method he used to perform the quantitative analysis," he nevertheless goes on to note his perceived shortcomings of Dr. Lipton's method based solely on his assumptions as to the methodology used. (Maldjian Report, p. 1; Affidavit of Maldjian,, 3.) It is true that Dr. Lipton's report does not delve into technical details and, therefore, Dr. Maldjian, at the time he created his report and affidavit, would not have known the method used by Dr. Lipton. The technical details are

specifically not included in Dr. Lipton's report, just as the technical details of any other MRI

examination are not included in reports. (Lipton Trial Depo., pp. 194-96.) Dr. Lipton is one of Plaintiff's treating clinicians and the purpose of Dr. Lipton's report was to convey his findings to the referring physician, Dr. Morton Finkel, Plaintiff's treating neurologist, and not to serve as a retained expert witness. It is a clinical, diagnostic report from a neuroradiologist in the regular course of his care and treatment of a patient prepared for the purpose of reporting his findings to another treating clinician. (Lipton Trial Depo., p. 22.)

Regardless, Dr. Maldjian assumes that Dr. Lipton employed a simple voxel-wise Hest, comparing Plaintiff's fractional anisotropy images to a group of normal controls. (Maldjian Report p. 3.) Such an approach, particularly if standard statistical thresholds were used, could yield spurious results in addition to any real findings that might be present due to inherent variability in the measurement as opposed to true differences between the patient and the normal group. (Aff. of Lipton, ,r 26.) Dr. Lipton did not employ a simple voxel-wise t-test. (Aff. of Lipton, ,r 27.) Rather, he performed a standardized z-score analysis, where Mrs. Yang-Weissman's DTI measurements were compared to the measurements of a comparable control group and the standardized z-score was computed for each voxel, describing the patient's fractional anisotropy relative to that of the normal population. (Lipton Trial Depo., p. 142; Aff. of Lipton, ,r 27.) Then, as described in more detail below, Dr. Lipton utilized a very strict criterion for abnormality and only accepted large clusters of abnormal voxels as true abnormalities. (Lipton Trial Depo., pp. 90-93; Aff. ofLipton, ,r,r 23-24.)

There is no question that DTI is a quantitative diagnostic test. (Lipton Trial Depo., p. 60.) Admittedly, an inherent feature in any quantitative test is the possibility of a finding being the result of random variation. (Lipton Trial Depo., p. 62.) If the patient is found to·differ from normal, but due to this random variation, a false positive result will occur. (Lipton Trial Depo.,

pp. 62-63.) However, this is a problem inherent to all types of diagnostic testing and there are several ways to minimize the risk of a false positive. (Lipton Trial Depo., p. 63.)

In performing his quantitative analysis of Plaintiff's DTI study, Dr. Lipton employed numerous safeguards to minimize the likelihood of false positive results. (Lipton Trial Depo., p. 63.) First, Dr. Lipton accepted only findings that deviated from the normal mean by at least five standard deviations. (Lipton Trial Depo., p. 68.) This is equivalent to saying that there is much less than a tenth-of-a-percent chance that there is a difference that is attributable to random chance. (Lipton Trial Depo., p. 66.) Additionally, only where abnormalities were shown in a minimum of 100 adjacent or touching voxels of Plaintiff's brain did Dr. Lipton conclude a true abnormality was present. (Lipton Trial Depo., pp. 92-93.) As stated by Dr. Lipton in his affidavit, since false positive results, by definition, are random errors, it is not statistically plausible to find multiple false positive results clustering in the same brain region in the same individual; random errors will occur as isolated voxels, or clusters of a few voxels, and will be randomly distributed across the brain. (Aff. ofLipton, 24.)

Dr. Maldjian mises the important issue of the control group against which Plaintiff's DTI study was compared. (Maldjian Report, p. 1.) As Dr. Maldjian indicates is essential, the control subjects used by Dr. Lipton were carefully screened, matched for age and gender and imaged using the exact same scanner and the exact same imaging parameters as those employed with Plaintiff. (Aff. ofLipton, 19.) Additional safeguards are employed by Dr. Lipton with regard to the control subjects and the normal range computed from their DTI measurements. In accumulating the control DTI measurements, Dr. Lipton conducted validation tests by comparing controls to other controls as well as controls to their own brains imaged at multiple points over

time. (Aff. of Lipton, 18.) For reasons explained above, Dr. Lipton's implementation of such

safeguards was not noted on his clinical treatment-based report to another treating clinician and was likely not known to Dr. Maldjian at the tinle he form.ed his opinions.

The procedures employed by Dr. Lipton minimize any chance of false positives, and therefore, ascertain the true areas of abnormality.

iv. DTI is accepted by the relevant medical community.

DTI has been approved by the FDA and is widely used as a clinical diagnostic tool. (Lipton Trial Depo., pp. 28, 56.) The use of the DTI modality requires computer-based post-processing of the images, something with which many radiologists may be unfamiliar or uncomfortable. Also, no meaningful diagnostic information can be gained from the review of the "raw" DTI images. These requirements, combined with the fact that normative data has not been widely disseminated, are likely impeding the even greater use of DTI. These issues are not unique to DTI. They apply to many advanced neuroimaging techniques, such as spectroscopy, perfusion imaging and functional MRI. Despite these limitations, these techniques are all in current clinical use.

Regardless, DTI has been accepted by the relevant medical community and is being used clinically for individual diagnostic purposes, including the diagnosis of traumatic brain injury. This fact is confirmed by F. Reed Murtagh, **M.D.,** a neuroradiologist whose affidavit is attached hereto as Exhibit 6. Dr. Murtagh, a member of the Diagnostic Imaging Department of the Moffitt Cancer Center and Research Institute and also a professer in the Department of Oncological Sciences at the University of South Florida College of Medicine at the Moffitt Cancer Center, has been actively involved in **MRI** since 1984 and DTI since 2004. (Aff. of Murtagh, ,r,r 3, 5, 7.) Dr. Murtagh confirms that DTI: is currently being used to diagnose brain

injury in individual patients using the method employed by Dr. Lipton; "is generally accepted by

the medical community;" and "is clinically reimbursable by most insurance companies." (Aff. of Murtagh, 5, 10.)

Also attached hereto is the affidavit of Randall R. Benson, M.D., which provides additional evidence of the relevant medical community's acceptance of the use of DTI to diagnose brain injury in individuals. (See Aff. ofBenson, attached as Exhibit 7.) Mr. Benson is a neurologist employed by Detroit Medical Center and Wayne State University. (Aff. of Benson, 'if 1.) In bis affidavit, submitted in opposition to the defendant's Motion *in Limine* to Preclude Dr. Benson's DTI testimony in the case of Rye v. Kia Motors America. Inc., Case No. 07-701204-NP, th.en pending in the Wayne County, Michigan Circuit Court, Dr. Benson avers that, at least at the time ofhis affidavit, there were 3,472 papers on DTI published in peer-reviewedjournals, of which 83 concemed DTI and traumatic brain injury. (Aff. of Benson, 'il 3.) In the Rye case, the defendant sought to exclude Dr. Benson's testimony that, based on his DTI analysis of the plaintiff, he was of the opinion that the plaintiffhad sustained a traumatic brain injury. The court denied the defendant's motion. (See Rye Order, attached as Exhibit 8.)

Dr. Benson has been using advanced MRI imaging to study brain injuries in former National Football League players. (Aff. of Benson, 'if 2.) On January 4, 2010, Dr. Benson testified before the United States House Judiciary Committee at a field hearing on the subject of brain injuries in football players. (Aff. of Benson, 'if 2.) He suggested that the use of advanced imaging methods, including DTI, would improve the diagnosis and management of concussions in sports. (Aff. of Benson, 'if 2; see also Written Testimony of Randall R. Benson, M.D., attached as Exhibit 9.) In his testimony to the House Judiciary Committee, Dr. Benson explained that "DTI is able to 'visualize' diffuse axonal injury from [traumatic brain injury]." (See Ex. 9.) His testimony also specifically endorses the voxel-based analysis, used by Dr. Lipton, as a diagnostic

tool, stating that it has improved the ability to detect axonal injury in "the milder cases which have less extensive damage." (See Ex. 9.) The opinions and swom testimony ofthese two, well-respected physicians illustrate the fact that the use of DTI to diagnose brain injury in individuals is accepted by the relevant medical community and beyond.

In the present matter, the testimony sought to be excluded by Defendant meets the reliability threshold required of scientific evidence.

C. DTI Has Been Ruled Admissible in Other Jurisdictions

In LaMasa v. Bachman, 2005 WL 1364515 (N.Y. Sup. 2005), following a jury verdict in favor of a plaintiff injured in a collision caused by the defendant, the defendant filed a post-verdict motion seeking relief on the grounds that the trial court erred in permitting the plaintiff's neuroradiologist, Dr. Lipton, to testify regarding the· DTI study performed on plaintiff to diagnose traumatic brain injury. Id. at *2 (attached as Exhibit 10). In denying the defendant's motion, the LaMasa court explained:

> DTI is an imaging technique used to study the random motion of hydrogen atoms within water molecules in biological tissue (e.g., brain white matter) and spatially map this diffusion of water molecules, *in vivo*. DTI provides anatomical information about tissue structure and composition. Changes in these tissue properties can often be correlated with processes that occur, among other causes, as a result of disease and trauma.

Id. at *2, FN3. The court further held that, as to the issues of causation and the precise physical injuries the plaintiff suffered as a result of the collision, "the parties had numerous expert witnesses testifying and in considering the conflicting testimony of the parties' respective expert witnesses, the jury was not required to accept one expert's testimony over that of another, but was entitled to accept or reject either expert's position in whole or in part." Id. at *6 (citations omitted). On appeal, the New York Supreme Court, Appellate Division, upheld the trial court's

admission of the challenged expert testimony. LaMasa v. Bachman, 56 A.D.3d 340 (N.Y. App.

Div. 2008) (attached as Exhibit 11). Specifically, on the issue of foundational support for expert opinion, the appellate court held that "while some of plaintiffs' experts relied on new technology or methodologies, the same experts also opined based on well-established and recognized diagnostic tools, and [therefore] they provided reliable causation opinions." Id. at 341.

CONCLUSION

The DTI study and its analysis by Dr. Lipton are reliable and unquestionably satisfy the requirements of FED. R. Evm. 702.

WHEREFORE, Plaintiff respectfully moves this Court to deny Defendant's Motion *in Limine* Concerning Diffusion Tensor Imaging Studies.

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April 30, 2010
Charleston, SC

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EXHIBIT 1

Monteflore • Moses **Division**
111 East 210th Street
Bronx, NY 10467
Department of Radiology
(718) 920-4879

DOS 07/15/2009 **Ace#** 8281782
Typed 07/27/2009
Typed By JCW-SD

Radiologist LIPTON, MICHAEL L MO

MR# 03223994
Patient WEISSMAN, Huannl yang·
DOB: 10/30/1979
Requested by: FINKEL. MORTON
AUending Name: FINKEL, MORTON
Location PR

Dr. Lipton ; Acc: 8281782; MRN: 03223994 DOS: 07/15/2009 DOD: 07/27/2009; Patient Name: Weissman Hua:ani yan.

EXAMINATION: **MR** imaging of the brain without contrast.

IMPRESSION: Multifocal diffusion abnormalities consistent with axonal injury, as descrlbed below.

CLINICAL INDICATION: Head injury.

INTERP TATION·: NOh contrast MRI of the brain was perforined including diftùsion tensor imaging.

The oveœll configuration of the hrain and ventricles are **unremarkable.** Small areas of signal hyperintensity are present on the FLAIR images in the subcortical white matter at the left frontal convexity. No other area of signal abn.ormality and no evidence of mass effect is present on the structural_images. No evidence of hemorrhage is present.

Quantitative assessment of:fractional anisotropy images demonstrates multiple areas of abnormal FA in the subcortical white matter of the cerebral hemispheres. Arees of low FA are clusteted in the left temporopariet.al region and in the left internal capsule/corona. Addîtional areas of low FA, Qflesser magnitude, are present in the right frontal region. These findings are consistent with axonal iajury due to prior trauma.

Approved by: LIPTON, MICHAEL, MD

EXHIBIT 2

MICHAEL L. LIPTON, M.D., PH.D.

CURRENT POSITION

Ass t p; fes ;n ill logy, P y hi;tty- Ïïkh vioral Scie ;;· d N {io;ci ----·...--·. . . -·

Assooate Director, Gruss Magnette Resonance Research Center, Albert Einstein College of Medicine
Director of Rad10Iogy Research, Albert Einstem College of Medicine

Mechcal Dtrector, MRI Services, Montefiore Medical Center
Visit1ng Sctentist, The Nathan S. Klme Institute for Psychiati;ic Research

CERTIFICATION

National Board of Medical Examiners
Amertcan Board of Radiology

- Diagnostic Rachology (1995)
- Certtficate of Added Qualificanon in Neuroradiology (1997)
- Maintenance of Certification in Neuroracliology (2007)

Basic Llfe Support - Provider Level
Advanced Carchac Llfe Support Provider Level

LICENSURE

New York
New Jersey
DEA Controlled Substance Ltcense

PROFESSIONAL APPOINTMENTS

2009-Present Albert Einstem College ofMechctne Bronx ,NY
Assoaate Dzrector, Gross Magnette "Resonance "Research Center
2009-Present The Nathan S. Kline Institute for Psycluatrtc Research
Vistting Sctentist Orangeburg , NY
2002-Present Montefiore Mechcal Center Bronx, NY
Medical Director, MRI Seruices
2002-Present Albert Emstein College of Medicine Bronx,NY
Director, Division of RadiologJ Researcb
1997-2008 The Nathan S. Kline Insttute for Psychiatrie Research
Sentor Research Scientist Orangeburg, NY
1997-Present Montefiore Mechcal Center Bronx , **NY**
Attending R.adiologjst

1997-2002 The Nathan S. Kline Institute for Psycluattlc Research

Visiting Scientist Orangeburg , NY

1995-Present Jacobi Medical Center Bronx ,NY

Vol[Intary Attending F.adiologist

1995-1998 Woodhull Medkal & Mental Health Center Brooklyn , NY

Visiting Attending F.adiologist

1993-1995 Woodhull Medical & Mental Health Center Brooklyn , NY

Viszting Assistant Attending R.adiologpt

ACADEMIC APPOINTMENTS

2009-Present Albert Einstein Colleg-e of Medicine Bronx , NY

Assoaate Profassor ofR.adiofoo, Pvchiatry and BebatRIJf'al Saences and N(ltlt'()science

2007-Present Albert Emstem College of Medicine Bronx , NY

Assoaate Projessor of Climcal F.adiolog,, Pvcmatry and Behavtoral Sctences

1997-2007 Albert Einstein College of Medicine Bronx , **NY**

Assistant Profassor of F.adiology

1995-Present Albert Einstein College of Medictne Bronx. NY

Clinical Fellow

PROFESSIONAL TRAINING

1995-1997 Montefiore Mechcal Center Bronx ,NY

Fellow tn N(IUroradiology

1991 1995 Montefiore Medical Center Bronx,NY

R asident in Diagnostic &,dio/ogy

1990-1991 Brookdale Hospital Medical Center Brooklyn• NY

Intern zn Internai Medicine

EDUCATION

2002-2007 Albert Einstein College of Medicine Bronx , **NY**

- Doctor of Philosophy
- Department of Neuroscience, Sue Golding Graduate Division
- D1sserta.t1on: *"Not* etched 111 stone: dynamics of the hand map 1n primary somatosensory cortex"
- Advisor. Craig A. Branch, Ph.D

2001-2002 Albert Einstein College of Medicine Bronx , NY

- Master of Science with distinction
- Department of Neurosoence, Sue Golding Graduate DivlSlon

1983-1990 Boston University Boston, MA

- Bachelor of Arts and Doctor of Medicine, *cum laude* in the Six-Year Medical Program

• College of Liberal Arts and the School of Mechctne

• Minor m Spa.rush Literature

HONORS

Harold G Jacobson OutstanchngTeacher Award
Dtpartment of Radiology, Albert Einstein College of Medidne

Outstanding Teacher Award for 2000 Nervous System & Human Behavior Course
Core course for seçom/,year medical students at Albert Emrtem College O/Medicine

Roentgen ReS1dent/Fellow Research Award
Radwlogical Socie!J of North America

Milton E1lcin Outstanchng Graduating ReStdent Awa:rd
Department ofRadiology, Albert Einstein Collegc ofMedicme

Chief ReS1dent 10 Dtagnosnc Radiology
Dtpartfftem ofRadwlogy, Albert Einstein College of Medicine

I..eo M David.off Society Award for Exœllencœ as a House Officer m the Teadmg of Medical Stude nts
Albert Einstein College of Medicine

National Merit Scholar

GRANT SUPPORT

P.L Michael L. l.J.pton, M.D., Ph.D. Active Dates: Pending Effutt;.30%
A.gs;ncyA.gs;ncy; NIH/NINDSNIH/NINDS
Type: 1R01NS06S970

Predicring Long-term Cognitive lmpau:ment after Mild Head InJury

Summar_y; The goal of this study is to validate DTI as a predicrive marker of sîgnificant brain mjury and predictor of long-term. executive dysfonction following mild TBL

P.J.: Michael L. Lipton, M.D., Ph.D., Core Leader Acttye Dates: Renewal Penchng .E.fful.t 20%
Agency: NIH/NIA
Type: P01 AG003949-26
Title: The Etnstem Agmg Study Neurounaging Core

Sutntnary; The Neurotmagrng Core performs magnettc resonance unagmg (MRI) and spectroscopy (MRSI) of the bratn on partiapants 1n the Etnstetn Agtng Study (EAS; P.L Richard B. Lipton, M.D.), for subsequent use 1n addressîn_gfü ecific.auns of the*E_ cts.*

P.I.: Michael L. Lipton, M.D.t Ph.D Active Dates: 3/1/2008-3/31/2010 Effutt;. 5%
Agwcy; Repligen
Type: Corporate Grant
Title: "A Phase III Study to Demonstrate the Efficacy and Safety ofRG1068 (Synthetic Hum.an Secretm)-Enhanced Magnetic Resonance Cholangiopancreatography (MRCP) in the Evaluauon of SubJects with a History of Acute or Acute Recurrent Pancreaitis"
Summat;y: The goal of thts study 1s to demonstrate that RG1068-enhanced MRCP improves sensitivity in the detection of pancreatic duct abnormalittes compared to unenhanced MRCP without loss of specificity, ustng an ERCP-based truth standard

.EJ..;. Nunz.to Pomara, M.D Acti,ye Dates: 6/1/2008-12/31/2009 5%

A,gency: Elan Pharmaceuttcals
Corporate Grant

Title: "ELNl15727-301 · A Phase III, Multtcenter, Randonuzed, Double-Blind, Placebo-Conttolled, Parallel Group, Efficacy and Safety T.nal of Baproeuzuma.b (AAB-001, ELNl15727) tn Patients with Mild to Moderate Alzheimer's D1sease who are Apolipoprotel!l E e4 Non-Camers"

Summru;y:; Tlus IS a Phase III multtcenter, placebo-conttolled study to examme the safety and efficacy of bapmeuzumab, a recombinant humaruzed ant:1-amylo1d beta (anti-Al3) pepttde monoclonal antibody, in outpattents aged 50 to <89 years with mild to moderate Alzhetmer's rusease (AD) who are Apolipoprotein E e4 (APOE4) non-camers.
Agency: NIB/NICMH

P.J .;, Raanan Arens, M.D Active Dates: 12/1/2007 11/30/2012 Effort: 5%

Type: R01-HDOS3693-0182
Summazy; The goal of this study ts to evaluate the anatomtcal and functional risk factors leading to sleep apnea

Title: "Pathophysiologyof OSAS 1n obese children 8-17 years old"

10 obese children, and the effect of adenotonsillectol!Y and weig!lt loss or w t_gamyn these sub1ects.. -.____-·-·
R01-DA021305

U;.Jay N1erenberg, M.D., Ph.D Active Dates: 9/30/2007-5/30/2012 5%
A,gency; NIH/NIDA

Title: "Longitudinal Study of Bram Recovery Following Abstinence from Cocatne"
Summacy:; This project wvestigates the relattonships between white matter integnty, regtonal bram volumes, neuropsychological measures and clirucal variables 111 patients recovenng from cocaine dependence using
... - m ettc reso ce cognitive testin,gand clirucal assessment. -· . --- ----- - - ·- - - - ·- - --- ..·-·

Nunzto Pomara M.D Active Dates: 3/1/2007-2/29 /2012 .l:il'fQru 5%
Agency: NIMH
R01-MH080405
Title: "Plasma and CSF A-Beta peptides m late-onset ma1or depresston"
Summaty; The major goal of this project is to conduct a 3 year longitudinal study to test the hypothesis that elderly individuals with late-onset LLMD will have higher plasma AB42 level and AB42/A840 ratio and greater reduction in AB42 during longitudinal follow-up relative to conttols, and to examme whether measures of AB42 will be associated with greater cognitive decline and/or the development od AD in elderly individuals with late-onset LLMD Another goal is to determine if changes in plasma A842 levels are paralleled by similar
cha mcerebrosp).nal_flwdJCSF}A842 10 a subset of subjects. ... ····-· .. -···-·····- _ -·--

U;. Cra.tg A. Branch Ph.D Acti,ye Dates: 6/1/2007-5/31/2008
Agency:NIH/NCRR
Type: S10 RR023534
·P.ttk;. "7 Tesla upgrade for baste psychiatr1c research"

Surn.maq: The maioi::.goal of this projectis.to. a eexistingMRI equi2ment. _ _

J?J.:Cm.tgA.Branch Ph.D Active Dates: 5/1/2007-4/30/2008
Agency: NIH/NCRR
Type: S10 RR022972

Title; "3 Tesla MRI for psychiatrie applications"

Summacy:; The major goal of thts proJect 1s to upgrade the NKI hlgh field MRI eqwpment to pemut raptd

.functional stud.y of neur?_E chiatric disorders.

EJ.. Michael L. Lt.pton M.D Active Dates: 1/1 /2002-11/30/2007 E.tiru:t. 75%
Agency; NIMH
K08-MH67082
Titk;."Neurophysiologie Basis and Specificity of fMRI"
Summary: Tlus proJect aims to optimize high resolution fMRI m nonhuman pnmates, assess ltmits on spatial and temporal resolutton and correlate with invasive electtophysiology in order to probe the relat10nship between the fMRI effect and neuronal activlt:r.....

Et,Paul Atsen. MD Active Dates: 4/1/2005 1/31/2007 .filfru;t Consultant
Ag.ency; Neurochem, Inc.
Corporate Grant (Protocol (1...758007)
Titk;. "A Phase Iii Study of the Efficacy and Safety of Alzhemed m Patients with Mild to Moderate Alzheimer's Disease"

EJ..Charles Schroeder Ph.D Active Dates: 3/1/2003-2/28/2008 E.ffru:t.10%
Ag.ency; NIMH
RO1
Title; "Neurophys10logical Basis of fMRI"
Summary; The specific aims are: 1 To Idennfy Neural Correlates of BOlD-fMRI 2. To Optimize the Spatial and Temporal Resolution of fMRI3. To Define the Neuropharmacology of Activity-Hemodynam.ic Coupling4. To Detemune the Relattons }>f Cogpitive fMRI to ERPs and to Brain Processes.

P.I.; LeonJ Thal, MD Active Dates: 12/1/2002-11/30/2007 Eff2!:t. 5%
Agmcy:; NIA, Pfizer, Esai and Roche
#3P50AG0513116S4 and addtttonal corporate fonds.
"A Randomized, Double-Blind, Placebo-Conttolled Trial to Evaluate the Safety and Efficacy of Vitam.in E and Donepezil HO (Aricept) to Delay Clinical Progression form Mild Cognitive Impai.o:nent (MCl) to Alzheuner's Disease (AD)"
Sumo:w:y; The goal of this study 1s to determine 1f Vit:an:un E and Donazepil delay progress10n from MCI to AD.

P.L Robert Bilder, Ph.D Active Dates: Ended 1/31/2002 Effort: 10%
Agency; Philip Morris U.S.A. Wotldwide Scienttfic Affairs
Corporate Grant
Title: "Nicotine Effects on Brain Activation"
Summary: The major goals of this project are to determine the effects of inttavenous nicotine infusions on cognitive performance and brain acttvations us.mg funct1onal magnetic resonance .tmag:tng (fJ\IIRI) in healthy non-smoking adults.

CONFERENCE PRESENTATIONS

Lipton M, Bello JA, The supenor ophthalnuc vem on CT- phys1ologtc monitonng of .mttacranial pressure; RSNA 1996

Lipton M, Bello JA, CT autoctstemography m the diagnos1S of cerebral aneutysm.s; ASNR 1996.

Lipton M, Bello JA, Mechal deviation of the cervical internal carotid artei.y clinical importance of an anatomie vanant; ASNR 1997

Lipton M, Bello JA, Baksht S, Many faces of the concha bullosa; **ASNR** 1997

Lipton M, Bello JA, What does CT angiography add to the evaluatton of mtracrarual aneurysms?; RSNA 1997

Lipton,M.L, Branch,C.A., Lewis,D.P., HrabeJ., HelpernJ.A., D1fferences m spatial extent of activation: BOLD vs. CBF (FAIR);ASNR 1999

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Lipton,M.L, Branch,C.A., Lewis,D.P., HrabeJ., HelpernJ.A., Optimized spatial extent of nonselective inversion in flow sensitive altemating inversion recovery (FAIR) maxirotzes CBF contrast; ISMRM 1999

Lipton,M.L, Branch,C.A., LeWJS,l).P., HrabeJ., HelpemJ.A., Dtfferences 10 spatial extent of activat10n: BOLD vs. CBF (FAIR); ISMRM 2000

Lipton, ML, Pell, G, Hrabe,J, Branch, CA, Helpero,JA, T2* variability between bratn reg,.ons ts not greaœr at 3.0T than at 1.5T: implications for BOLD fMRI; RSNA 2000.

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Lipton ML, Pell GS, Hrabe J, Branch CA, Optimizatton of Functional **MR** lmaging Sensitivity· Activation Extent Modulated by TE and Tissue T2* at 1.5 and 3.0 Tesla; ASNR 2002.

Lipton ML, Schroeder CE, Branch CA, Subreg,.ons of *macaque* somatosensory cortex are delineated by fMRI at 7 Tesla; ISMRM 2002.

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Lipton ML, Schroeder CE, Branch CA, Cortical activation ipsilateral to tactile and electrical somatosensory stimulanon detected with high field jMRI tn macaques: a new finding eluodated with 1nvas1Ve electtophys1ology; ISMRM 2003.

Lipton ML, Fu KM, Branch, CA, O'Connell N, Gerum S, Schroeder CE, Ipsilateral response m area 3b: demonsttatlon with fMRI and electtophysiology, Society for Neuroscience 2003.

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IJpton ML, Papolos D, Lombard J, Nierenbetgj, Hoptman M, Yhu S, Neurounaging Findings Specific for Bipolar Disotder in Children: Quantitative Structural and Diffusion Tensor Imaging, Ametican SOC1ety of Neuroradiology 2005.

IJpton ML, Mack D, Fu KMG, O'Connel] MN, Branch *CA,* Schroeder CE, D.tfferent spatial extent of response to digit stimulation in conttalateral and ipsilateral Area 3b, Society for Neuroscience 2005.

Lo C, Slufteh K. BelloJA, IJpton ML, Diffusion Tensor MRI (DTI) Distinguishes Patients with Cognitive lmpairment Following Mild Traumatic Brain Injury (I'Bl), **ASNR** 2006

Zampolln **R,** Papolos A, N1erenbergj, Hoptman M, Papolos D, **IJpton ML.** White ma.tter deficits correlate with limbic structural asymmetry in Pediatric Bipolar Disorder: a diffusion tensor imaging study, Organisation for Human Brain Mapping 2006.

IJpton ML, O'Connel N, Mills A, Branch CA, Schroeder CE, Bimanual integratton begtns at the lowest level of cortical somatosensory processmg. Soaety for Neuroscience 2006.

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Cognitive Impairment Following Mild-Traumatic Brain Injury (TBI), RSNA 2006.
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Gellella EG, Lo C, Gold T. Ardekant BA, Shlfteh K, Bello JA, **IJpton ML,** Evolution of diffusion tensor imaging findings after mild traumatic brain injuty implications for treatment of a major public health problem, RSNA 2007

Musacchia G, Lakatos P, **Lipton ML,** Branch CA, Klinger M, Sch:roeder CE, Neuronal oscillat10ns and excitability control rn primary somatosensory cortex, Neuroscience 2008.

Dym RJ, **Lipton ML,** Is fMRI assessment of herruspheric language dominance as good as the Wada test? A meta-analys1s, RSNA 2008.

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Zimmerman ME, Pan JW, Hetherington HP, Lipton ML, Khosrow B, Llpton RB, Htppocampal correlates of pain 1n healthy eldetly adults: a pilot study, International Conference on Alzheimers Disease, 2009

Lipton ML, Gulko E, Feldman AM, Zimmerman ME, Friedman BW, Kim M, Shifteh K, Lipton **RB,** Branch CA, Early prefrontal wlute matter arusotropy predtcts subsequent executive dysfunction in mild traumatic brain injury, Society for Neuroscience, 2009

Isler JR. **Lipton ML,** O'Connell N, Mills A, Lakatos P, Schroeder CE, lpsilateral response m somatensensory (band) area 3b, Sooety for Neuroscience, 2009

Gulko E, **Lipton ML,** Feldman AM, Zimmerman ME, Friedman B, Slufteh **K,** Branch CA, Dynariuc Changes *m* Prefrontal Amsotropy Predtct Executive Dysfunct1on 3 Months Followmg Mild Traumattc Bratn Injury, Radiological Society of North Amettca, 2009

Bums J, Erdfarb JA, Gmsburg D, Taragin B, **Lipton ML,** Pediatric Lumbar Dise Disease: MRI Abnonnallties m Normal and Overwetght Children, Radiological Sooety of North America, 2009

Buros J. Baron L, **Lipton ML,** Bello J, Slufteh K, Uncommon and Unusual Lesions of the Head and Neck: A Pictonal Review, Amencan Society of Head and Neck Radtology, 2009

Arens R, Sin SH, McDonough JM, Rteder J, Khan U, **Lipton ML,** Shtfteh **K,** Upper Atrway Structure 1n Obese Children with and without OSAS, Amencan Thoracic Soctety, 2009

PAPERS

Lipton M. Sprayregen S, Kutcher R, Frost A, Venous invasion in renal vcin leiomyosarcoma: case report and review of the hterature, Abdomtnal Imag.ing 1995; 20:64-67

Llpton M, Cynamon JC, Balœl CW, Sprayregen S, Percutaneous removal of two Wallstent endoprostheses from the heart through a single Jugular sheath, Journal of Vascular and Intervential Radiology, 1995; 6:469-472.

Lipton M, re: lnttacrarual aneurysms, New England Jouroal of Medicine, 1997 June 12, 336(24)· 1758-9

Goldbetg S, Mahadevia P, **Lipton ML,** Rosenbaum PS, Sinus histiocytosis with massive lymphadenopathy tnvolvmg the orb1t: reversai of compressive opttc neuropathy after chemotherapy,Journal ofNeuro-ophthalmology, 1998; 18(4): 270-275.

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Gold MM, Shifteh K, Bello JA, **Lipton ML,** Kaufman DM and Brown AD, Chorea-Acanthocytosis: A Mirrucker of Huntington Disease Case Report and Revtew of the ùterature The Neurologist 2006; 12(6): 327-9

Parikh T, Shlfteh K, **Lipton ML,** Bello JA, Brook AL, Deep bram revers1ble encephalopathy assoe1ated with secoodary antiphosphohpld syndrome, AmericanJournal ofNeuroradiology, 2007; 28(1): 76-8.

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1342

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Zimmerman ME, Pan JW, Hetherington HP, **Lipton ML,** Baigi K. Lipton RB, Hippocampal Correlates of Pain in Healthy Elderly Adults: A Pilot Study, Neurology, Neurology 2009, 73:1567 1570

Lipton ML, Llpton LG, Eohancing the Ra.diology learrung expenence with an electtoruc whiteboard, Amencan Journal of Roentgenology, *m press*

Lipton ML, LlszewsktMC, O'ConnellMN, MillsA, SmileyJF, Branch CA, Charles E. Schroeder CE, Dynamic hand representati.on in primary somatosensory cortex, *in revision.*

BOOKS

Lipton ML, Totally Accessible MRI. A User's Gutde to Principles, Technology and Applications Springer, New York, 2008.

INVITED LECTURES AND TEACHING POSTS

Albert Emstem College of Medicine

Lecturer - Nervous System and Human Behavior

Laboratory Insttuctor - Nervous System and Human Behavior

- Designed the Neuroimaging cun:iculum
- Developed pnnt and web-based teaclung materials

Clirucal Conference Facihtator Nervous System and Human Behavior

- Semt-weekly meetings with small groups of second-year students to work through chrucal neurology/ neuroscience cases.

Lecturer - Clirucal and Developmental Anatomy - Head and Neck Anatomy

Laboratory Insttuctor Cltmcal and Developmental Anatomy - Head and Neck Anatomy

- Developed web-based teaching materials

Sue Golding Graduate Division - Albert Einstein College of Medicine

Lecturer - Graduate Neuroanatomy

- Developed software CD for teaching and review of neuroanatomy/imaging in

humans and primates

Laboratory Instructor - Graduate Neuroanatomy

Amencan Society of Neurorachology Annual Meeting

Scienti.fic Session Moderator

2004 2005

Montefiore Radiology Rev1ew Course

Multiple lectures

1997 -1998

New York Radiology Review Course

Session Moderator

Multiple lectures

Case-based rev1ews

2003 2005

MRI Phys1cs: Balancing for Opttmal Clirucal lmag!ng

- Semtannual postgraduate course
- Des1gned, organized and taught smgle-handedly
- Developed comprehensive syllabus/text and teachmg materials
- Authored a book based on the course (see above)

1998 present

Visiting Lecturer: St Vmcent's Medical Center

Bndgeport, Connecttcut

2002 - present

Vis1ting Lecturer: Bndgeport Hospital

Bridgeport, Connectlcut

2004 · present

Not etched m stone: dynamics of the band map m primary somatosensory cortex

Ben Gunon Univers1ty and Soroka Medical Center

Beersheba, Israel

June 2006

Diffusion tensor MRI detects white matter lesions that correlate with limbic volume loss in children with bipolar disorder

Ben Gurion University and Soroka Mechcal Center

Beersheba, Israel

June 2006

Not so mild traumatic brain injury: diffusion tensor MRI Iesions distinguish patients with persistent cognitive impairment following mild TBI

Hadassah Uruversity School of Medicine

Jerusalem, Israel

June 2006

Diffusion tensor MRI detects white matter lesions that correlate Wlth limb1c volume loss In children with bipolar disorder

Hadassah Univers1ty School of Medicine

Jerusalem, Israel
June2006

Not etched m Stone: dynam.ics of the band map ID primary somatosensory cortex
NUI-NINDS
June 2007

Improving White Matter Imaging with Diffusion ViS1ting Professor
Staten Island University Hosp1tal- New York
August2007

Advanced unaging of Stroke
Emergenct Radiology Course - New York
October 2007

Imaging Patients With Renal Insufficiency Is Gadolinium Contraindicated Or Relatively Contraindicated?
AIM Sympostum - New York
November 2008

Qock or Brain? Evidence based detemrinations in acute stroke imaging for therapy
AIM Symposium - New York
November 2008

Stroke Management 2008 Moderator
AIM Symposium - New York
November 2008

Neuroradiology Board ReVlew
Jacobi Medtcal Center
March2009

Neuroradtology Board Review
Staten Island Uruversity Hospital
Aprií2009

Stroke Management 2009 Moderator
AIM Symposium - New York
November 2009

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Jordana Schneider, Yeshiva University

Aimee Krausz, Yeshtva Uruversity

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Marc Katzman, MD, Albert Einstein College of Medicine

Gail Yarmish, MD, Albert Etnstein College of Medic.tne

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Mark Lisewski, MD with distinction in research, Albert Einstein College of Medicine

Stella Valdberg, MD, Albert Einstein College ofMediane

Soplùa Rodnguez, Albert Einstein College of Medicine

Edwin Gulko, MD with distinction in research Albert Einstein College of Medicine

Daniel Krieger, MD with distinction in research Albert Einstein College of Medicine

Mendeth WeISs, MD, Albert Etnstetn College of Medicine

Dieudonne M. Nonga. Albert Etnste.m College of Medicme
Gunia P Parikh, New York Medlcal College

Anna Shlionsk.y, Mount S.tna.t School of Medicine

Residents:

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Ar.t Bletcher, MD

Wtlham Gomes, MD, PhD
First prize winner, Montefiore Medical Center Radiology Research Day 2008
"NAA is Reduced During the Latent Period Preceding Pilocarpine-lnduced Epilepsy"

CalV1n Lo, MD
Thtrd prize winner, Monte:fiore Med1cal Center Young Invesugators SympoS1um 2007
"DiffUS1on Tensor MRI ·Dist1nguishes Pat1ents With Cognitive Impattment Following Mild Traumatic Brain Injury"

Erik Gellella, MD
Second pri.ze winner, Montefiore Medical Center Radiology Research Day 2008
"Diffusion Tensor Imaging (DT!) Findings in Acute and Chronic Mild Traumatic Brain lnjury"

Amit R.ahe1a, MD

Robert J Dym, MD

Richard Zampohn. MD

Fellows:

Todd Miller, **MD**

Menachem E. Gold, MD

William Gomes, MD, PhD

Judah Burns, MD

PRESS AND MEDIA

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"Consequences of mild ttaumatic brain injury" Interview on WRTN-FM, December 2009

COMMITTEES

Protocol Review Comm.tttee, Center for Advaoced Bnun Imaglng, The Nathan S. Kline Institute for Psychiatrie Research, Member 2000 - 2008.

Improving Organizational Performance Committee, Department of Radiology, Montefiore Medical Center, Member 2000 - 2002

Advisory Committee, The Gruss Magnette Resonance Research Center, Albert Einstein College of Medicine, Member 2001 - 2007

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MR1 Safety Comm.tttee, Montefiore Medical Center, Foundrng Chatr 2002 - present.

Inc1dental Finding Management Committee, Center for Advanced Brain lmagtng, The Nathan S Kline lnstitute for Psychiatrie Research, Chair 2004 - 2008.

MR1 Safety Corruruttee, Center for Advanced Bratn lmagtng, The Nathan S. Kline Institute for Psychiatrie Research, Chair 2004 - 2008.

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Education Committee of The Amencan Society ofFuncttonal Neuromdiology, Member 2005-Present

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Faculty Senator, Albert Einstem College ofMedlcme, 2008-2010

Committee on Appointments and Promotions Associate Professor's Comm.tttee, Albert Einstein College of MediCllle, 2009 - 2011

Medtcal Student Projects Comnuttee, Albert Einstein College of Medicine, 2009-Present

PEER REVIEW

Acta Radiologica

Amencan Journal of Neuroradiology

Bram

Neuron

Neuroreport

Neuroscience and Btobehavioral Rev1ews

Radiology

PROFESSIONAL SOCIETY MEMBERSHIPS

an Society f F ct1onal Neuroradlology - Charter Me ber

American SoClety of Neuroradiology Sentor Member

Amencan College of Radiology

American Medical Association

American Roentgen Ray Society

International Society for Magnetic Resonance in Medicine

New York Academy of Se1ences

New York Roentgen SOC1ety

Organization for Human Brain Mappmg

SoC1ety for Neuroscience

Radiological SoC1ety of North America

LANGUAGES SPOKEN

Engiish, Sparush, Hebrew

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF SOUTH CAROLINA

FLORENCE DIVISION

-x

HUANNI YANG-WEISSMAN,

Plaintiff,

C.A. NO.

vs

4:07-CV-3643-RBH

SOUTH CAROLINA PRESTRESS CORPORATION,

Defendant.

- - - -x

VIDEOTAPE TRIAL DEPOSITION of MICHAEL L. LIPTON, M.D., Ph.D., taken by Plaintiff at the offices of Fink & Carney Reporting and Video Services, 39 West 37th Street, Sixth Floor, New York, New York, on Thursday, April 8, 2010, commencing at 10:32 a.rn., before Karen Ann Carney, CSR, RPR, CMRS, and Notary Public within and for the State of New York.

the last word on the paper, although they might not have been the nitty-gritty, hands-on in every part. There is some variation.

The people in between also contributed to the paper, or at least that's the way it's supposed to be.

Oftentimes, you know, people get authorship for various reasons and there is, you know, kind of a whole dispute about this. But --

Q You listed your publications in your curriculum vitae?

A Yes, I have.

Q Do any of those deal with magnetic resonance imaging, MRI?

A Yes; most of them do.

Q And many of them deal with diffusion-tensor imaging, or DTI?

A Yes; several of them do.

Q Have you published any books?

A Yes, I have.

Q Can you tell us the books you've published?

A I've published a textbook on

Q Dr. Lipton, how did you get involved in the treatment of Huanni Yang-Weissman?

A The initial contact that I received was a telephone call from Dr. Finkel, Dr. Morton Finkel, regarding the possibility of performing an MRI study on Ms. Weissman.

Q Did he tell you why he wanted you to perform a study?

A Well, he described her as a patient who had had a head injury and who he felt had significant brain injury and cognitive impairment, and he was looking imaging to document evidence of that to support his diagnosis.

Q And did you perform such a study?

A Yes, I did.

Q And did you issue a report?

A Yes, I did.

Q Let me hand to you a document dated July 15th, 2009 (handing}. Would you tell us what that is?

A (Perusing document.) This is my report from the MRI study.

Lipton, M.D.

MR. ROSEN: I would like to have that marked as an exhibit, please.

(One-page report issued by Michael Lipton, M.D., dated July 15, 2009 was marked as Plaintiff's Exhibit No. 2 for identification, as of this date.)

BY MR. ROSEN:

Q Doctor, what does your report show or indicate?

A My report indicates multiple abnormalities consistent with traumatic brain injury.

Q Now, there was another MRI study performed on Mrs. Yang shortly after this collision in 2004. Have you seen that?

A Yes, I have.

Q Did that report report any abnormalities?

A No, it did not.

Q How would you explain that?

A Well, I actually also reviewed that study and -- well, I should say that

Lipton, M.D.

But, it's not just the field strength. There are many changes that have occurred in MRI besides the field strength.

Q How old is diffusion-tensor imaging, DTI?

A Well, the classic paper that really describes the basis of using diffusion-tensor irnaging for understanding things about white matter in the brain was published in 1995.

Q Tell us

A But the I mean, the real application and use of DTI is something that is really a late-1990s-and-beyond technology.

Q Is DTI in clinical use?

A Yes, it is.

Q Is it experirnental?

A No.

Q All right. Is it used --

A People are certainly investigating it and trying to make improvernents. But it's, you know, an FDA-approved technique that's in clinical use.

Q You mentioned white rnatter.

A Based on this study, I would say that she does.

Q Do you have an opinion, based upon a reasonable degree of medical certainty, as to whether or not she has brain damage?

A Yes. That opinion is with reasonable medical certainty.

Q And what is that opinion?

A That she does.

Q Let me ask you this: Do you have an opinion, based upon a reasonable degree of medical certainty, as to the cause of Huanni Yang-Weissman's brain damage?

A Yes. I believe it's due to an impact on the left side of the head.

Q And is that consistent with the history of the collision in 2004 between Mrs. Yang's vehicle and the cernent truck?

A Yes, it is.

Q And you've seen photos of the cernent truck?

A Yes, I have. Well, you mean photos of the collision?

Q The collision.

consistent with her injury.

Q And also some areas on the DTI that show brain damage?

A That's what we just looked at.

Q Let's talk about DTI for a few minutes.

Is it in clinical use?

A Yes, it is.

Q And what does it do that other studies do not do?

A Well, DTI, or diffusion-tensor imaging, allows us to look at the movement of water molecules through tissue.

And specifically, in looking at the white matter of the brain, although DTI does have other uses, it allows us to understand things about the microscopie structure of the brain's white matter that other imaging modalities are notable to demonstrate.

And that could both be the normal anatomy of the white matter or the presence of pathology or abnormality of the white matter.

Q Can diffusion-tensor imaging be used to diagnose a particular patient?

Lipton, **M.D.**

A Yes, it can.

Q How do you do that?

A Well, the way we do that is by generating quantitative images from diffusion-tensor imaging and doing that in a population of normal people and demonstrating what the normal range of those measurements is in the normal population and seeing whether the patient falls inside or outside of that normal range and how far outside of that normal range, if they do indeed fall outside of it.

Q How do you achieve a, quote, normal population?

A Well, we identify the normal -- patients as normal by doing quite an extensive

not have any evidence of any kind of medical illness; they are not taking any medications; no histories of substance abuse, psychiatrie disease or even symptoms that might indicate y phases of a psychiatrie illness; that they don't have any neurological disease.

And it's a pretty extensive process to screen these people and make sure

that they are normal.

Q And what kind of a normal population do you use to compare Huanni Yang-Weissman's studies?

A Well, what I just described.

Q Okay. But is it specifically selected for her as opposed to anyone else?

A Well, we don't go out and find a group of normal people for an individual patient.

We have a population of normal patients, and we do select the ones that are used for the comparison when we want to assess an individual patient based on -- particul y on the age of that patient.

Q And what population do you select based on the age of that patient?

A Well, we want our control subjects to be within a ten-year window of the patient that we're evaluating.

Q Is DTI in use in other medical centers other than nstein and Montefiore?

A Yes, it is.

Q And is it in use throughout the

United States?

A I believe it's in use throughout the world.

Q Have you yourself done studies using DTI?

A Yes, I have.

Q And those studies are listed on your curriculum vitae?

A They are.

Q And are there other studies

A The ones that are published are listed there. There are others that are in the process that are not.

Q Are other studies being published by other doctors and authors?

A Yes.

Q I think we have some of those with us.

And what I would like to do is hand you a summary of those cles -- and I think most of the articles or many of the articles are here -- and I would like for you to tell us whether any of these deal with DTI and its uses (handing)?

Lipton, M.D.

MR. ROSEN: Why don't we go off the record for a second while counsel looks at this.

THE VIDEOGRAPHER: The time is 11:24. We are the record.

{Discussion off the record.)

THE VIDEOGRAPHER: We are back on the record. The time is now 11:26.

BY MR. ROSEN:

Q Dr. Lipton, I've handed you a series of articles and a list of them. Let me ask you before you look at that --

MR. TIERNEY: Let me just put a general objection on the record that these articles haven't been produced. So, I object to the referral to them.

Q Dr. Lipton, is there literature endorsing the assessment of individual subjects using DTI?

A Yes, there is.

Q Can DTI be used to detect abnormali es due to traumatic brain injury?

A Yes.

Q Are there papers dealing with that?

A There are.

Q Are these studies of individuals or groups?

A Both.

Q Are there papers which support the use of DTI to diagnose traumatic brain injury in individual subjects?

A Yes, there are.

Q And could you identify a list of those articles I provided you there -- or you provided us, actually.

A I'm not sure what you mean by "identify."

Q What is that in front of you?

A This is a list of articles.

Q And who produced that list?

A I did.

Q What are those articles?

A Well, this is a -- first of all, this is a partial list of references regarding the use of DTI in traumatic brain injury in

general, as well as, again, a partial list of references regarding the use of DTI in the assessment of individual patients, including the ones that you asked about, which would be the use of DTI in individual , or traumatic brain injury patients.

MR. ROSEN: Madam reporter, we would like to mark this as a composite exhibit. I think it's No. 7.

A Just to be clear, I didn't check the -- because I didn't put this - I didn't check that every article on the list is actually in the pile.

Q Well, let me ask you to check that the articles that are in the pile do deal with DTI and are appropriately within that group of articles. How about that?

A Okay.

(Perusing documents.)

MR. ROSEN: We can go off the record for a minute while you do that.

THE VIDEOGRAPHER: The time

Lipton, M.D.

is now 11:28. We are off the record.

(Discussion off the record.)

THE VIDEOGRAPHER: The time is now 11:28. This marks -- we are back on the record.

A So, all of the articles, both on the list and in the pile of articles, do deal with diffusion-tensor imaging.

BY MR. ROSEN:

Q Is diffusion-tensor imaging similar to the technique in other diagnostic tests?

A I'm not sure exactly what you mean by that.

Q Was anything peculiar or unusual or different about DTI in which the methodology or the technology is suspect compared to, say, echocardiograms or ?

A I mean, DTI is a diagnostic test that is a quantitative diagnostic test. So, I guess in that sense it's similar to other diagnostic tes where they can be quanti ed.

Q me ask you this: You compare

it's normal or not.

Q And that's what was done in your study of Huanni Yang-Weissman?

A Yes.

Q Can there be something called random variability or false positives?

A Those are definitely things that occur whenever you do any kind of testing.

Q And how do you deal with that to make sure that it doesn't affect the study that you are doing?

A Well, whenever you do any type of measurement, an inherent feature of making the measurement is that the test may have some degree of variability that is not -- that is due to chance; that is not due to a true abnormality.

So, for example, if we -- to take kind of a simple concrete example, if we measure your cholesterol and we find that it's high, you need to ask the question, "Well, is the cholesterol high because your cholesterol is really high, or is it high because there might be an error in the measurement of that

cholesterol due to random variation?"

And the way that we address this problem if, by the way, we found that your cholesterol was high and it wasn't real it was due to random variation in the test - we would call that a false positive result, meaning we got a positive finding that doesn't really reflect an abnormality.

And this is a problem that's inherent to all types of diagnostic sting.

The way there are several ways to deal wi this problem.

The most important of these is to characterize the range of normal, first of all; and, secondly, to characterize the reproducibility of the measurement.

So, meaning if we take the same sample and we measure it multiple times, does the test give us the same or a very similar result?

If it gives us results that vary widely, well, then, when we use it on you, we don't know whether it's changing because of the test having variability, or because there's

let's say, the medical benefit of a diagnostic test or a drug the typical finding, if you look at a journal article, is that this is described as a significance value or sometimes called a P value of 0.05.

But to put it in concrete terms, what's generally accepted as being significant, all right, is that there is a 5 percent chance that there might be a false positive.

So, if you, for example, look at a study where they did a certain test and they compared two groups of people and they found that the test showed a significant difference between those two groups, chances are that the interpretation of that study will mean that there is a 5 percent chance that those differences are due to chance.

And those are the types of those are the of criteria that are typically used in medicine for making a decision as to whether something is meaningful or is due to random chance.

Q Does that apply to drugs, as well?

A Yes.

Lipton, M.D.

Q Asto whether they work or not?

A It applies to studies -- to research studies in general.

Q So, what did you use in your analysis here dealing with Huanni Yang-Weissman?

A So, in our case, the criteria that we use to determine whether or not -- and in this case, but also in the way we apply this test to patients in general the criteria that we use are.much stricter.

So, the equivalent, if I can translate into that sort of chance a false positive, is that the equivalent in the study that we use is that there is much less than a tenth-of-a-percent chance that there is a difference that is due to random chance.

Q And how do you accomplish that?

A Well, we define our normal range.

And the 5 percent chance of false positives that I described as sort of being the standard approach -- another way of describing that is if you have a population of patients and you perform the measurement on that population of patients, you will -- patients I'm using

the term loosely; a population of individuals.

If we perform that test, we will get a range of normal that can be plotted as something that some may be familiar with as a bell-shaped curve or what we sometimes call a normal distribution.

It's the same idea when a teacher gives a in class. Right. They expect that if they design a good test, that there is going to be a range of scores on that test, and they will form this sort of bell-shaped curve. And that bell-shaped curve has a mean or an average score.

So, if we go back to our diagnostic test and we perform that on a group of people, we're going to get a mean or average score for that group of people.

That doesn't mean that everyone is going to have that mean or average score. There's going to be a range, but we can define the mean; what the average score is.

We can then define how far we are from that mean in measurements called standard deviations. So, a standard deviation -- or I

should, rather, say two standard deviations is the typical cutoff for what is considered significantly abnormal.

And if you are outside of two standard deviations, that rneans that there is a 5 percent chance, right, that that position on the normal distribution could really be normal.

The cutoff that we typically use is five standard deviations, meaning that you are way, way out on the very edge -- essentially outside of that normal distribution.

QDoes that mean, then, that in your study Huanni Yang-Weissman, had you used the standard deviation, which is used generally in medicine

A Two standard deviations.

Q Two standard right. If you used two standard deviations, how would that have changed the resu s for Ms. Weissman?

A Well, we would have shown many more abnormalities.

And that's actually sornething that I showed by showing this picture (indicating), which is even more strict of a threshold than

clusters that were greater than 100 voxels?

A Smaller.

Q Smaller? Okay. Explain that to me, please.

A Okay. So, what that means is that when **we** do a voxel-wise analysis, actually occurs at multiple stages.

So, in -- I don't know that we described what we mean by a voxel or a voxel-wise analysis.

But, essentially, each MRI -- the MRI exam, as I think we discussed before, is a series of slices. Each one of those slices is a digital image which is composed of a series of pixels, just like any digital picture you might blow up on a computer and see how it becomes a bunch of little boxes.

Of course, each of the pixels in the MRI slice, since that slice has some thickness of a few millimeters, is not a pixel. It's a volume of tissue.

So we then can say that each slice is composed of a bunch of these voxels, and the volume of the brain is composed of then many of

these voxels.

So, a voxel-wise analysis means that we look at each voxel in the patient and determine whether that voxel is significantly different from the same location in the normal control group.

Now, that's the first level, meaning that the first thing that we dois we detect all the locations in the brain where the patient is significantly different from the normal range or from the normal -- normal control group.

However, we don't accept all of those abnormalities as indicating true abnormal findings.

And what we dois we say that it's not good enough for one single individual voxel to show upas looking abnormal. We have to see at least a cluster of 100 of these voxels.

And actually, the one thing that has changed a little bit in our clinical practice is we typically threshold 200. There have to be at least somewhere between one and 200 of these voxels, and they all -- when I say

Lipton, **M.D.**

a cluster, meaning they are all immediately adjacent or touching each other.

So, that means that we have a volume of brain that amounts to, at the very least, a milliliter, all right, or a cubic centimeter of tissue, that is all consistently abnormal; and those abnormalities are all correlated with each other.

So, that last stage is what I mean by thresholding at a minimum of 100 voxels per cluster.

So anything where we might find a difference that just shows up as one voxel, that goes in the garbage. We don't even consider that abnormal.

Q All right. And correct me if I'm wrong, but I believe in the Radiology magazine that --

THE VIDEOGRAPHER: Excuse me. I really need to end the tape. I'm sorry.

MR. TIERNEY: All right.

THE VIDEOGRAPHER: The time is now 12:11. This marks the end of

Lipton, M.D.

Tape 1. We're now off the record.

(Discussion off the record.)

THE VIDEOGRAPHER: The time is 12:12. This marks the beginning of Tape 2. We're back on the record.

BY **MR.** TIERNEY:

Q Doctor, we were discussing the retention of clusters when we had to switch tapes.

And I believe I read in the Radiology in the article published in Radiology magazine, that you retained clusters that were greater than 100 voxels?

A We retain clusters greater than 100. That's correct.

Q Okay. What you had said that were less than at some point earlier.

A We exclude those less than; we retain those greater than.

Q Okay. Thanks for that clarification.

In Ms. Yang-Weissman's case when you did your sting of her in July of 2009, did

you only retain voxels that were greater than a hundred?

A That's correct, yes.

Q Okay. And where do I find that on the MRI that that's part of the process that was performed with Ms. Yang-Weissman?

A I'm not sure what you mean by where do you nd that.

Q Would you put that on the report?

A No.

Q 1 right. Where does that data -- where is that data contained that shows exactly how you tested Ms. Yang-Weissman?

A I'm not sure what you mean by "that data."

Q Well, I've got a study in front of me from Radiology --

A Right.

Q -- magazine, okay?

And then you brought a host of other articles which show exactly how these studies were performed and the conclusions of these studies.

A Um-hum.

Q With Ms. Yang-Weissman, is the jury just to assume that you tested her the same way that you tested in all of these articles -- the other subjects?

A Well, I think you asked me that question. And, yes, the methods are the same. So the steps -- and you read some of them tome those are all the same steps that we use.

Q Okay. And how do you confirm to a jury that you used those steps for Ms. Yang-Weissman?

A I guess it's my testimony.

Q All right. Is there any evidence, objective evidence -- anything written down -- that shows that you used all of those methods with the testing that you did on Ms. Yang-Weissman?

A Is there anything objective written down?

I mean, it's our standard protocol. I have, you know we have summaries of that. These are methods that have been published. It's the way we do things.

I don't know that it's written down in her particular case.

Q Right; in her particular case.

Because what I'rn concerned about is how you know that there wasn't a false positive in your review of Ms. Yang-Weissrnan's MRI?

A Right. And the way we know that is based on the information that I just told you, which is that these are the approaches that we use and these are the rnethods we use -- what I described -- to exclude the possibility or minimize the possibility of false positives.

That's the way.we doit.

It's not my practice for any MRI examination to delineate the methodology that was used in performing or analyzing the exam.

Q But it would seern, based on my review of the articles that you have provided here today, that -- and this is my terminology -- but there's a lot of hoops you have to jump through to do this type of DTI imaging, correct?

A It's a very detailed and

painstaking process which has to be supervised extremely carefully. That's correct.

Q I mean, a patient just doesn't walk in the door and say "I need to get DTI testing," correct?

A Well, we only take referrals from physicians. So typically, it's a physician referring the patient for a specific clinical question.

It is involved, and that's -- at the present time, that's one of the issues we have to deal with, is that this is a time-consuming process. It requires time. And we do -- you know, we doit.

What can I tell you?

Q And in Ms. Yang-Weissman's case, you would have actually had to find what you characterize as a normal population to compare her study to, right?

A Well, that normal population is something that we've developed over time.

So, this isn't something -- just to be clear, we didn't decide that we're going to do this all a sudden on Ms. Yang-Weissman.

A Okay.
Q So, we won't put her in that acute category, okay?
A Um-hum.
Q But we know from reviewing the records that one of the opinions of the treating doctors is that she has a problem with executive function.
A That's correct.
Q All right. *Do* you believe that even in a non-acute setting, such as Ms. Yang-Weissman, that there would be lowered DLPFC white matter or that there would be lower white matter FA in the DLPFC if, in fact, there was a problem with executive function?
A There might be. But it might not be detectable.
Q Why wouldn't it be detectable?
A Well, because with all of our imaging studies, whether it's DTI or any other type of imaging study, the thing that we have to recognize is that there is always a limited sensitivity.
As we know, most people with mild

head injuries have normal MRI, even if they have significant impairment.

That doesn't mean there's nothing wrong with their brain. It just means that the imaging isn't able to detect it.

Q You can't --

A So, we can see what we can see, but it doesn't rule out -- it doesn't make the rest of the brain normal.

Is that clear?

Q Well, in Ms. Yang-Weissman's case, do you believe that there were problems with the images?

A What do you mean by "problems with the images"?

Q Well, I mean, I think you just told me that sometimes you can't always and you fill in the blank for however you want to call the term.

But you can't always get a good image, I guess, where you can see, as an example, whether or not she had low FA?

A Oh, no. I didn't mean that you can't get a good image.

once regarding DT!.

To be honest with you, I don't remember whether I don't remember the exact method that was used for the assessment in that case.

Q And where was that case?

A I was sometime ago. It was in New York.

Q Okay. Do you remember the year? I don't remember offhand. I don't even know it's years ago.

Q Is this something that you frequently do at Montefiore Hospital?

A Yes.

Q You do this DTI ing?

A Yes.

Q How often do you doit?

A I would say that we're doing this on a few ients a month.

Q Okay. And obviously, we're here to discuss what I'll characterize as a medical-legal case, because there is litigation pending, okay?

A Um-hum.

an individual?

A I don't think that's the best way; although, again, it is a peer-reviewed way that has been validated.

I think that a better way to use the standardized z score, which is the approach that we used.

Q All right. And you don't believe that the standardized z score fits into that category of being some type of statistical model or using your definition?

A I don't believe it's a statistical model in the way that we described, no.

Q All right. But that is, in fact, what you did with Ms. Yang-Weissman; you compared her as an individual to a standardized z score, correct?

A Well, no.

I compared her as an individual to a normal population.

And the number describes where she is relative to that normal population is the standardized z score.

MR. TIERNEY: Okay. That's

EXHIBIT 4

IN TIŒ UNITED STATES DISTRICT COURT
FOR TIŒ DISTRICT OF SOUTH CAROLINA
FLORENCE DMSION

HUANNI YANG-WEISSMAN, Plaintiff, v. CORPORATION, SOUTH CAROLINA PRESTRESS Defendant.	)	Civil Action No: 4:07-cv-03643-RBH

AFFIDAVIT OF MICHAEL L. LIPTON, M.D., PH.D.

PERSONALL Y APPEARED before me, Michael L. Lipton, M.D.• Ph.D., who, after being duly sworn, does state as follows:

1. I am above the age of majority, competent to testify to the matters herein, and mak:e this declaration upon my own persona! knowledge and belief.

2. I am a neuroradiologist and am board certified by the American Board of Radiology in diagnostic radiology. I also have a Certificate of Ad.ded Qualification and a current Maintenance of Certification, both in the field of neuroradiology.

3. I am the Associate Director of the Gross Magnetic Resonance Research Center at the Albert Einstein College of Medicine and serve as its Director of Research for the Department of Radiology. I am an associate professor of radiology, psychiatry, behavioral sciences and neuroscience. I am also the Medical Director for the clinical MRI services at Montefiore Medical Center.

4. I am an attending physician at Montefiore Med.ical Center, Jacobi Med.ical Center, and North Central Bronx Hospit.al.

5. Due to my education, training, experience, research and publications in the field of neuroradiology, I am familiar with and knowledgeable conceming the standards and practices of neuroradiologi including the conduct, review, and interpretation of neuroimaging studies acquired by means of magnetic resonance imaging ("MRI"). My curriculum vitae is attached to tbis affidavit as Exhibit A.

6. Heidi Yang-Weissman, the Plaintiff in tbis lawsui4 was referred tome by her treating physician, Morton Finkel, M.D. On Ju1y 15, 2009, a non-contrast MRI ofMrs. Yang-Weissman's brain was performed including diffusion tensor imaging ("DTij on a Philips 3.0 Tesla MRI scanner.

7. While the traditional MRI shows the structure of the brain, DTI is more sensitive and can reveal abnormalities that are not visible on standard MRis.

8. DTI is in widespread clinical use and isalso extensively used in brain research.

9. I have over ten years' experience working with DTI technology and over eight years• experience using DTI technology in conjunction with the diagnosis of brain injury.

10. DTI is capable of reliably and accurately indicating the presence ofbrain injury. This fact is widely documented in the peer-reviewed medical literature and published studies.

11. Thousands of papers endorsing the use of DTI have been published in peer reviewed journals, many of which have specifically concemed DTI and traumatic brain injury. Numerous peer-reviewed studies have established that abnormal anisotropy as measured by DTI demonstrates evidence' of traumatic brain injury pathology not detectable using other imaging methods.

12. DTI measures the direction of movement or tlow (known as diffusion) of water molecules through tissue.

13. Unlike other imaging technologies, DTI permits examination of the microscopie structure of the white matter of the brain, allowing for the detection of microscopie pathology or abnormality of the white matter.

14. In the white matter of a normal/healthy brain, the direction of water diffusion is veey unifonn. Injury disrupts the normal structure of white matter leading to less unifonn direction of diffusion.

15. In the clinical setting, DTI can be, and i used to diagnose individual patients.

16. ' Regions of abnormally nonuniform diffusion (called low anisotropy) due to brain injury may be visible on visual inspection of the fractional anisotropy images (known as "FA images"). However, visual assessment of such images has limited sensitivity and may miss significant abnormalities.

17. It is for this reason that quantitative measurement of the images is necessary to ensure sensitivity, reliabîlity and objectivity. This can be accomplished by performing a voxel-wise analysis.

18. A voxel-wise analysis consists of examining each voxel in the patient's DTI images and determining whether that voxel is significantly different from the same location in a group of normal or"control" individuals.

19. The control subjects used to determine the "normal range" should be selected through an extensive testing and screening process to eliminate any unsuitable candidates. This screening process eliminates any control subjects with evidence of medical illness, substance abuse, medication usage, psychiatrie disease, and neurological disease. The control subjects used in any diagnostic analysi including the analysis ofMrs. Yang-Weissman, are carefully selected

to match the patient's age and gender. The control subjects are also imaged using the exact same equipment and imaging parameters as the patients.

20. The resulting range of measurements obtained ftom the DTI studies performed on the control subjects are used to defme the normal distribution, for each voxel. The normal distribution will have a mean or an average and abnonnalities in a patient's DTI measurements are detected according to how far they deviate ftom that mean. This comparison is thus done on a voxel-by-voxel basis.

21. Typically, any measurement of a patient that is two standard deviations or more ftom the mean is considered significantly abnormal. In such a situation, wbere a patient's measurement is two standard deviations or more away ftom the mean of the normal distribution, therè is only a 5% chance that the finding of abnormality îs a fa1se positive, or, due to inherent variability rather than actual abnormality. Notably, this *5%* criterion is the standard for determination of clinically significant findings in medical researcb.

22. In performing the voxel-wise anaJysis on Mrs. Yang-Weissman's DTI study, only those measurements that fell at least five standard deviations from the mean of the normal distribution were considered to be abnormal.

23. The result of tbis analysis is a determination of ail the voxels that vary significantly ftom the mean and therefore are presumptively abnormal. However. I take the analysis a step further and do not conclude that ail of those single-voxel abnormalities indicate true abnormal fmdings. Rather, to reach the conclusion that an abnormality is present in Mrs. Yang-Weissman's brain, I required that a minimum of 100 single-voxel abnormalities be adjacent or touching before concluding that an abnormality was present.

24. Because false positive results, by definition, are random errors, it is not statistically plausible to find multiple false positive results clustering in the same brain region in the same individual; randQm errors will occur as isolated voxels, or clusters of few voxels, and will be randomly distributed across the brain.

25. Based on bis affidavit dated March 16, 2010, it appears as if Dr. Maldjian, the Defendant's expert, assumes that I employed a simple voxel-wise t-test, comparing Mrs. Yang-Weissman's fractional anisotropy images to a group of normal controls.

26. Such an approach, particularly if standard statistical thresholds were used, could yield spurious results in addition to any rea1 findings that might be present, due to inherent variability in the measurement as opposed to true differences between the patient and the nonnal group.

27. I did not employ a simple voxel-wise t-test. I performed a standardized z-score analysis, where Mrs. Yang-Weissman's DTI measurements were compared to the measurements of a comparable control group and the standardized z-score was computed for each voxel, describing the patient's fractional anisotropy relative to that of the normal population. I then utilized a very strict criterion for abnormality (see above) and only accepted large clusters of abnormal voxels as true abnonnalities (see above).

28. In examining the MRI studies for Mrs. Yang-Weissman and in reporting my findings and conclusions regarding those studies, I relied on my training, experience, and education as a board certified neuroradiologist.

29. The statements and opinions expressed in this affidavit are based upon my training, experience, and education and are rendered to a reasonable degree of medical and scientific certainty.

FURTHER AFFIANT SAYETH NOT.

Michael L. Lipton, M.D., Ph.D.

Subscribed and swom to before me

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This day 0....f""4-.....!...::.1 ...:.'-\----------' 2010.

Notary Pic for the State of New York

My Commm·iiSÎon Expires: , •t9. *ZOto*

JACQUELINE REID
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EXHIBIT 5

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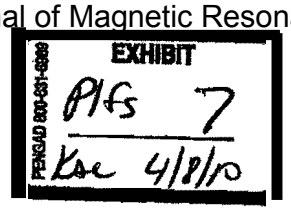

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Multifocal White Matter Ultrastructural Abnormalities in Mild Traumatic Brain Injury with Cognitive Disability: A Vôxel-Wise Analysis of Diffusion Tensor Imaging

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Abstract

The purpose of the present study is to identify otherwise occult white matter abnormalities in patients suffering persistent cognitive impair.ment due to mild traumatic brain injury (TBI). The study had Institutional Review Board (]RB) approval, included informed consent and complied with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of_1996. We retrospectively analyzed diffusion tensor MRI (DTI) of 17 patients (nine women, eight men; age range 26-70 years) who had cognitive impairment due to mild TBI that occurred 8 months to 3 years prior to imaging. Comparison was made to 10 healthy controls. Fractional anisotropy (FA) and mean diffusivity (MD) images derived from OTI (1.5 T; 25 directions; b = 1000) were compared using whole brain histogram and voxel-wise analyses. Histograms of white matter FA show an overall shift toward lower FA in patients. Areas of significantly decreased FA ($p < 0.005$) were found in the subject group in corpus callosum, subcortiœl white matter, and internai capsules bilaterally. Co-located elevation of mean diffusivity (MD) was found in the patients within each region. Similar, though less extensive, findings were demonstrated in each individual patient. Multiple .foci of low white matter FA and high MD are present in cognitîvely impaired mild TBI patients, with a distnôution that confonns to that of diffuse axonal injury. Evaluation of single subjects also reveals foci of low FA, suggesting that DTI may ultimately be useful for cliniœl evaluation of individual patients.

Key words: cognitive impairment; diffusion tensor imaging; magnetic resonance imaging; mild traumatic brain injury

Introduction

'T"R,AUMAnc BRAIN INJURY (TBI) is a major public health .1 problem, affecting more than 1.4 million Amerlcans each year with 2% of the US. population (5.3 million persons) disabled due to TBl (McArthur et al., 2004). While the devastating consequences of severe TBI are well-known, long-term effects of mild injury also have substantial personal and societal impact (Weight, 1998; Holm, 2005; Gamboa et al., 2006). Direct and indirect costs of TBI exœed $80 billion annually in the United States (CDC, 2003).

Following mild TBI (mTBO, patients may corn.plain of an array of symptoms, including headache and impaired concentration and memory (Kushner, 1998). Because symptoms are mild and nonspecific, patients may not seek medical treatment or be seen only briefly and released (Kushner, 1998). Co.tnputed tomography (Cf) or magnetic resonance imaging (MRI) is commonly normal (Jnglese et al., 2005), if it is performed at an. Recovery may occur over months. However, up to 30% of mTBI patients will suffer permanent sequelae of thefr injury and up to 20% will be unable to retum to work (Nolin and Heroux, 2006).

Conventional CT and MRl are quite insensiti.ve to mTBl pathology, likely due to the small size and subtle nature of mTBI lesions (Gentry et al., 1988; Kelly et al., 1988; Arfanakis etal.,2002; Huisman et al.,2004); frank tissuedisruption does not necessarlly occur (Huisman et al., 2003). Hemorrhage may be a sentinelmarker for TBI Iesions (Kushner, 1998), but is uncom.mon in mTBI (Huisman et al., 2003). The full extent of les.ions may not manifest initially, no matter what means

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are used for detection, because TBI lesions evolve over time due to a cascade of cellular events (Nortje and Menon, 2004).

Diffusion tensor MRI (DTI) shows lower fractional anisotropy (FA) in TBI patients that may correlate with disability (Ptak et al, 2003; Huisman et al., 2004). Two reports descrlbed DTI in TBI patients with cognitive impairment (Ewing-Cobbs et al, 2006; Nakayama et al., 2006). However, these and most studies of DTI in TBI have examined patients close to the time of injury (Arfanakis et al., 2002; Ptak et al, 2003; Huisman et al., 2004), and with moderate to severe TBI (Wieshmann et al., 1999; Rugg-Gunn et al., 2001; Huisman et al., 2004; Nakayama et al., 2006; Tisserand et al, 2006). Even in studies of "mTBI," reported brain hemorrhage in the study subjects suggests that more severe injury may have occurred (Arfanakis et al., 2002; lnglese et al, 2005). A recent report on mTBI included a subgroup with reinote injury, but did not address cognitive impairment (lnglese et al., 2005). Jn addition to lower FA, higher mean diffusivity (MD) is characteristic of TBI lesions, likely due to loss of tissue structure that would otherwise impede free diffusion (lnglese et al., 2005).

The purpose of the present study is to identify otherwise occult white matter abnormalities in patients suffering persistent cognitive impairment due to mTBI. We hypothesized that lower FA and higher MD than in healthy normal controls, indicating disorganization of white matter microstructure due to injury, are features of the brains of patients suffering cognitive impairment as a functional consequence of mTBL

Materlal and Methods

Study subjects

AJI aspects of the study were Institutional Review Board (IRB) approved and U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996 compliant. The IRB provided a waiver of informed consent for our retrospective review of the patient data. Control subjects gave inform.ed consent for their participation.

TBI patients. We retrospectively analyzed DTI in seventeen consecutive mTBI patients (nine women, eight men; age range 26-70 years) who met inclusion and exclusion criteria (six patients were excluded due to imaging evidence of hemorrhage or comorbid conditions). Ail patients had suffered a mild head injury to which no significant clinical sequelae were initially ascribed. Jn each case, the patient Jater (8 months to 3 years following injury) sought medical evaluation due to symptoms including difficulty with attention, concentration, memory and job performance. As part of their clinical evaluation, patients were referred for **MRI** to exclude structural brain abnormalities as a cause of their symptoms. DTI was routinely included in brain imaging studies at this time, affording the opportunity to retrospectively assess DTI in this population. Patient data (excluding imaging) was derived from referring clinic records including clinical neuropsychological reports. Jnclusion criteria were as follows: (1) witnessed closed head trauma (motor vehicle accidents [11 = 151 falls [11 = l], struck by construction debris [n = 11); (2) initial evaluation at a clinic or emergency room with findings consistent with mTBI (Glasgow Coma Scale [GCS] score [if available] of 13-15, loss of consciousness for less than 20 min, post-traumatic amnesia of less than 24 h, no other neurological deficit); and (3) persistent cognitive deficits due to TBI diagnosed by a neuropsychologist during the clinical evaluation of the patient's symptoms. Exclusion criteria were as follows: (1) hospitalization due to the injury; (2) abnormal brain imaging at the time of injury; (3) history of other prior head trauma; (4) pre-injury cognitive impairment; (5) other neurological or psychiatrie disease; and (6) substance abuse.

Control subjects. Ten control subjects of similar age and gender distribution to the patient group were recruited and underwent the same imaging protocol on the same scanner as the patients. Similarity of the group demographics was confirmed using χ^2 (gender) and Student's t-test (age). Control exclusion criteria were as follows: (1) history of head injury; (2) history of neurological or psychiatrie disease; or (3) history of substance abuse.

Imaglng protocol

lmaging was performed on a 1.5-Tesla Signa Excite MR/i scanner (General Electric, Waukesha, WI) with Echospeed+ gradients and transmit-receive birdcage head coi!. Whole head structural imaging included sagittal 3D-FSPGR (TR 7.6 msec, TE 1.6 msec, two signal averages, 30" flip angle, and 0.6-mm isotropie resolution) and axial FSE-XL (TR 3155 msec, TE 104 msec, two signal averages, echo train 17, 23 X 23 cm FOV, 512 X 224 matrix, 5-mm section thickness). DTI was acquired using single shot EPI at 5-mm slice thickness, FOV = 260 mm, 128 X 128 matrix, 25 diffusion sensitizing directions, and b = 1000 s/ mm^2. DWI images were corrected for eddy current effects, and FA and MD images were calculated automatically using a console-based algorithm. Axial FLAIR (TR 800 msec, TE 120 msec, one signal average, TI 2250 msec, FOV 22 X 22 cm, 256 X 224 matrix, 5 mm slices) and axial GRH (TR 750 msec, TE 17 msec, two signal averages, 15° flip angle, FOV 22 X 22 cm, 256 X 192 ùnaging matrix, 5-mm slices) images were also obtained.

Data and statlstical ana/ysls

Two American Board of Radiology certified neuroradiologists independent1y reviewed brain images for structural abnonnalities induding assessment for evidence of hemorrhage. Any disagreement in interpretation was resolved by consensus.

Quantitative image analysis was performed offline as discussed next.

Whole brain hlstogram analysis. Jndividual 256-bin histograms were generated from each subjects whole-brain FA dataset, after skull stripping (using a unique brain mask for each subject, derived from that subject's B == 0 image), but prior to any image manipulation. Total number of brain voxels and kurtosis was computed separately for each subject's histogram. Subject and control histograms were compared between groups using Student's t-test and were then group-averaged for display.

Voxel-wlse analysls.

- Skull stripping: Non-brain voxels were removed from the FSPGR and FSE images using Functional Magnetic Reso-

nance Imaging of the Brain (FSL) software (Smith et al., 2004). Each brain volume was inspected slice-by-sliœ, and residual non-braln voxels were removed manually.

- BPI distortion coirection: FSE images were acquired with identical slice position and orientation as DTI. Distortion correction was accomplished using two-dimensional (20) nonlinear deformation algorithm to match eddy current-corrected EPI to FSE volumes (Llm et al., 2006).
- **Intermediate rigid-body registration:** Each subject's FSE images were registered to their three-dlmensional (3D) FSPGR images using the Automated Registration Toolbox (ART) (Ardekani, 1995) 3D rigid-body approach (Ardekani et al., 2005).
- Registration to standard space: The 3D nonlinear registration module of ART registered eachsubject's 3DFSPGR volume to a standard Tl-weighted template (Montreal Neurological Institute [MNI] atlas).
- Transformation of DTI images to standard space: Using ART, distortion correction, intennediate rigid-body registration, and standard space registration (above) were applied to the calculated FA and MD maps using a single reslicing operation. Final cubic voxel size was 1 mm^3, masked to exclude non-brain voxels from the analysis (above).
- Segmentation: The fast automated segmentation tool (FAST) within FSL was used to generate a white matter mask for the template brain. This mask was eroded by 3 pixels to limit edge effects and was used to restrict subsequent statistical analysis of FA to white matter voxels.
- **Voxel-wise** statistical **analysis (VSA):** ART was used to perforrn a t-test separately comparing patient vs. control FA and MD at each voxel, covarying for age and gender. Type I errors (false positives) were controlled using the fa1se discovery rate (FDR) measure in FSL (Benjamini and Hochberg, 1995). FDR is the expected proportion of rejected hypotheses that are false positives. FDR = 0.01 corresponded to $p = 0.0071968$. Thus, we selected a p-value threshold of 0.005 for our analyses to ensure an FDR of <0.01 (1%). As an additional safeguard against false positives, we only retained clusters of size greater than 100 voxels (100 mm^3).
- Statistical images: Those images representing significant group differences are displayed as color overlays superimposed on Tl-weighted images from the MNI template.

Results

The patient and controlpopulations did not differ with respect to age ($p = 0.58$) or gender ($p = 0.91$). Neuropsychological deficits found in the patient population included memory, executive function, attention, mood and affect. Any imaging performed at the time of injury was normal based on records, but the images were not available for review.

No evidence of hemorrhage was found on review of *im*ages. A small area of signal abnormality attributed to gliosis was found in one subject. No other structural abnormalities were detected. Assessments of both reviewers were concordant in ail cases.

Thehistogram (Fig. 1) of whole brain FA from patients reveals a significantly smaller number of brain voxels than in controls ($p = 0.004$). For this reason, we scaled the histograms tocorrect for the volume difference. Both before and after scaling, the patient histogram is shifted to the left with respect to controls and the greatest group difference appears to be at highest FA. Comparison of the kurtosis of patient and control histograms (prior to scaling) confirms that histograms are significantly different ($p = 0.006$), indicating a small, but significant difference in whole brain FA; while most brain voxels express similar FA in patients and controls, a subset of voxels in the patient group have lower FA than controls.

Voxel-wise analysis detected multiple clusters oflower FA ($p < 0.005$) bilaterally in the white matter of patients compared to controls (Fig. 2). Affected areas include corpus cal-

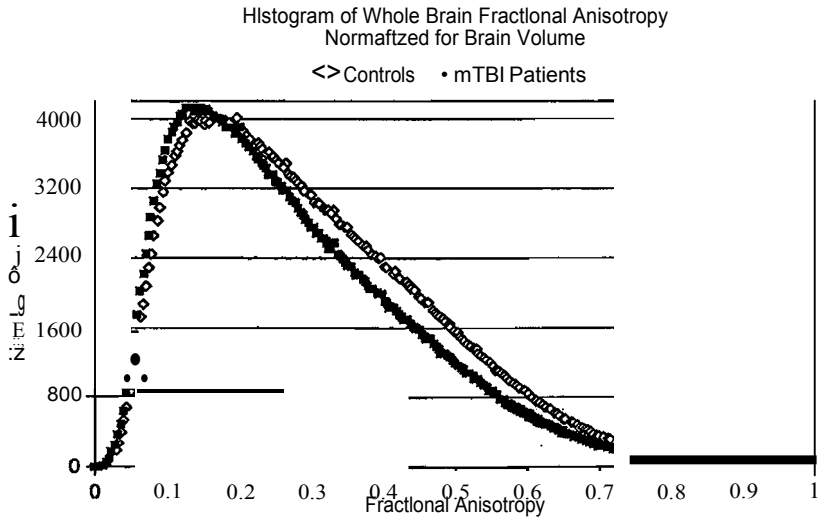

FIG. 1. Histogram of white matter ractional anisotropy (FA) corrected for brain volume. The FA histogram for patients (black) is shifted to the left with respect to controls (gray). This pattern suggests that a subset of voxels in the patient group has lower FA, as detected in subsequent voxel-wise and region of interest (ROI) analyses.

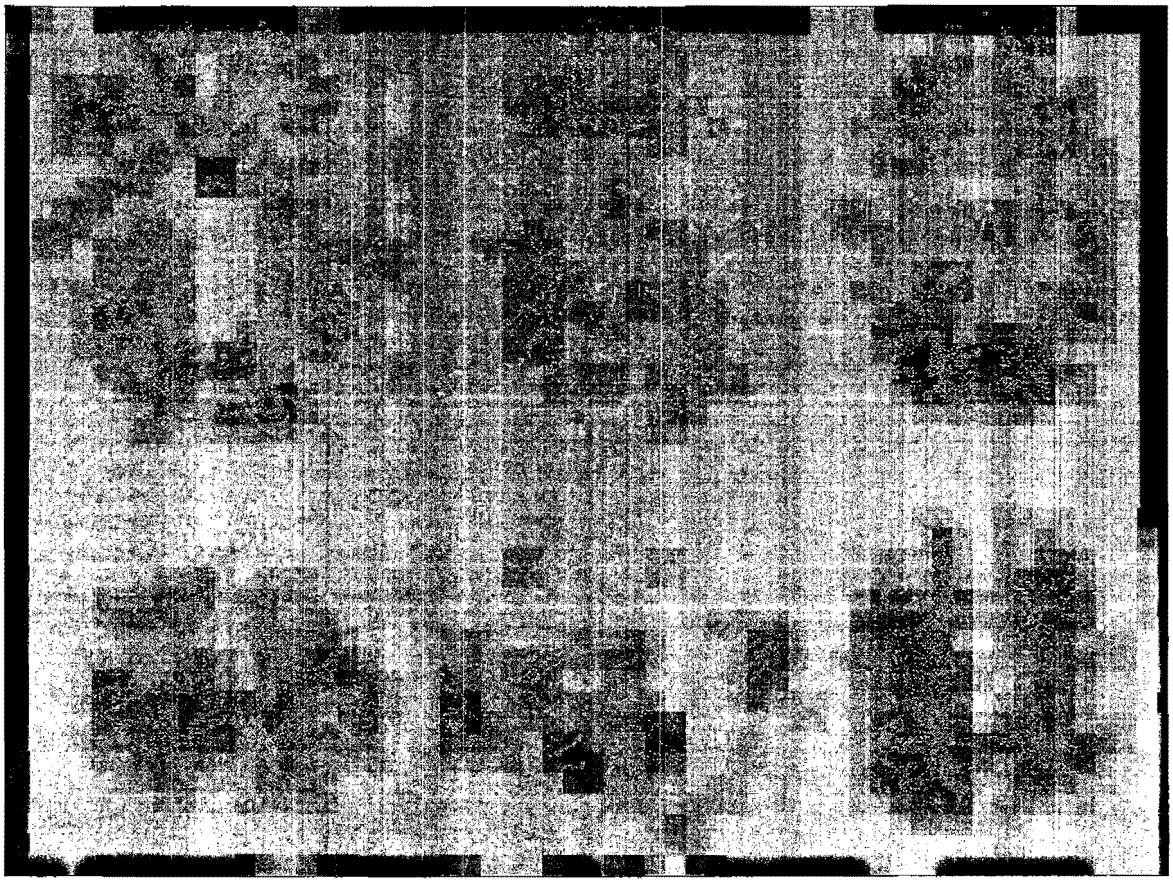

FIG. 2. Voxel-wise analysis comparing fractional anisotropy (FA) in patients andcontrols. Colored regions superlmposed on structural images (axial, top row and lower right; coronal, lower left and sagittal, lower center) from the Montreal Neurological Jnstitute (MNI) template indicate some locations founci to have signifü:antly lower FA in patients. Multiple abnormalities are present in deep and subcortical white matter, a pattern sùnilar to that found in diffuse axonal injury (DAI).

losum, internai capsules, subcortical white matter, œntrum semiovale and deep cerebellar white matter (not all shown), but not the brainstem. Significantly lower FA (Table 1) and higher MD (Table 2) are present in patients compared to controis in each duster.

Comparison of FA values from individual TBI subjects with those from the entire control group showed similar, although less robust decreases of FA in each case. The results from one subject are shown in Figure 3. No evidenœ of pathology is present in FLAIR and GRE images, nor is evidence of the FA deficit dearly visible in the indlvidual subject's FA map. Findings in other subjects were si:tnilar.

Discussion

DTI was usedto identify whitematterabnormalities in patients with persistent cognitive impairment follow.ing mTBI. While other studies have reported diffusion abnormallties in

TAaLE 1. FA {MEAN:!:: STANDARD DEvl.AnON) FOR MTBI PATIl!NTS AND CONTROLS (r-TEST, 2-TAIUID)

Regimt	*MNI coordinates*	*Subjects*	*Controls*	*p-vtllue*
Right orbitofrontal	(75.76, 54.82, 58.11)	0.376 ± 0.052	0.497 ± 0.056	0.00000629
Right anterior litnb of internai capsule	(76.45, 81.63, 70.82)	0.463 ± 0.061	0.605 ± 0.036	0.000000534
Corpus callosum genu	(88,67, 63.32, '71.88)	0.581 :!:: 0.057	0.727 :!:: 0.063	0.00000186
Left occipital	(106.08, 149.69, 74.31)	0.204 ± 0.023	0.303 ± 0.078	0.0000457
Right precuneus	(50.92, 147.74, 82.93)	0.358 ± 0.067	0.511 ± 0.051	0.00000164
Left superior temporal gyrus	(141.42, 119.77, 78.50)	0.291 ± 0.049	0.411 :!:: 0.052	0.00000254
Right parietal operculum	(46.77, 120.15, 93.84)	0.304 ± 0.028	0.422 :!:: 0.038	0.00000000175
Right superlor parietal lobule	(68.65, 127.45, 123.73)	0.438 ± 0.067	0.58,5 ± 0.059	0.00000545

FA, fl'actional anisotropy; TBI, traumatic brain injury; MNl, Montreal Neurological Institute.

TABLE 2. ·MD (MEAN:!: STANDARO DEvtAnoN) FOR MTBI PAT.ŒNTS AND CONTROLS (r-Tesr, 2-TAILI!D)

	MNI coordina.tes	*Stibjects*		
Right orbitofrontal	(75.76, 54.82, 58.11)	0.628 ± 0.054	Q.590 :.!: 0.028	0.0488
Right anterior lbnb of intemal caps}l{e	(76.45, 81.63, 70.82)	0.592 :!: 0.039	0.548 :.!: 0.058	0.0263
Corpus callosum genu	(88.67, 63.32, 71.88)	0.760 ± 0.087	0.674 ± 0.084	0.0189
Left occipital	(106.08, 149.69, 74.31)	0.713 :!: 0.099	0.632 :.!: 0.093	0.0464
Right precuneus	(50.92, 147.74, 82.93)	0.612 ± 0.054	0.524 :.!: 0.046	0.000218
Left superior temporal gyrus	(141.42, 119.77, 78.50)	0.672 ± 0.109	0.586 :.!: 0.018	0.0207
Right partetal operculmn	(46.77, 120.15, 93.84)	0.633 :!: 0.045	0.548 :.!: 0.196	0.00000665
Right superlor parietal lobule	(68.65, 127.45, 123.73)	0.594 ± 0.061	0.514 ± 0.060	0.00296

MD, meandiffusivity; TBI, trawnatic bram:i:njury; MNJ, Montreal Neurological Jnstltute.

TBI (Liu et aL, 1999;Jones et al., 2000; Takayama et al, 2000; Nakahara et al., 2001; Rugg-Gunn et al., 2001; Arfanakis et al., 2002;Hergan et al., 2002; Huisrnan et al.,,2003;Ptak et al, 2003; Hvismal etal, 2004; Inglese et al, 2005; Nakayama et al., 2006; iœserand et al.,2006; Ktauset al, *2007;* Niogi et al., 2008), three aspectsofourstudypopulationaswellasourapproachtodata analysis are noteworthy. Fitst, we report Bndings in a group of cognitively hnpaired mTBI patients who were neurologically normal at the timeof injury.Sud\ late recognition of oognitîve hnpairment is characteristicof mTBI (COC, 2003).

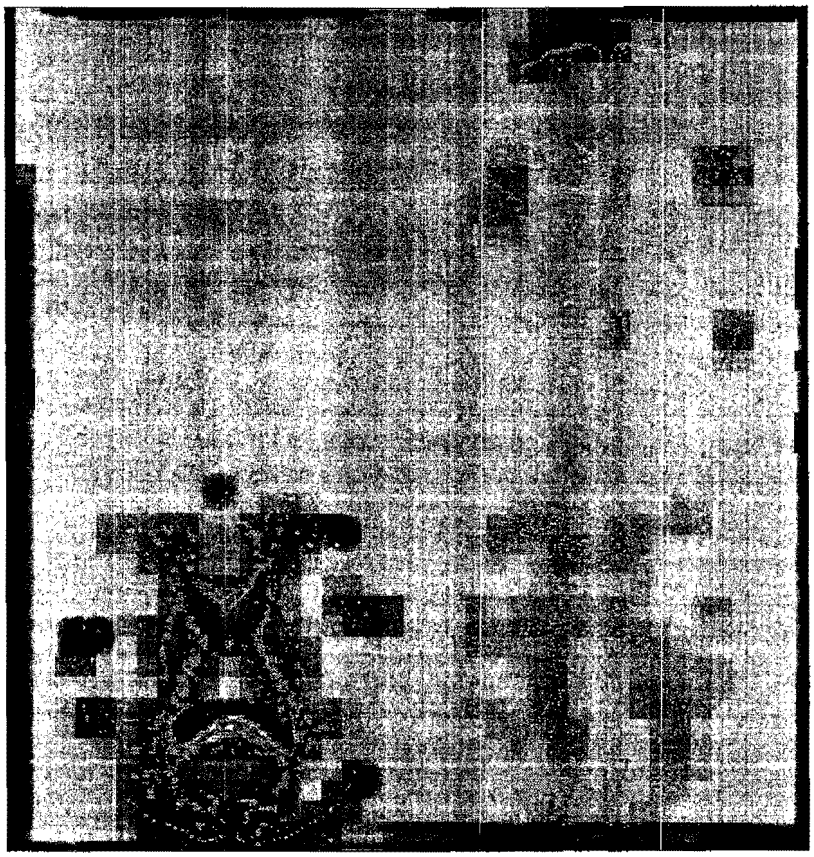

FIG. 3, Voxel-wise analysis of fractional anisotropy {FA) in a single subject. Analysis of FA in a 50-year-old woman following mild traumatic brain injury, Axial noncontrast FLAIR (top left; TR = 11,000 msec, TB = 120 msec, Tl = 2800 msec) and GRE (top right; TR = 650 msec, TB = 16 :msec, flip angle 18°) images from a single subject at the level of the genu of the corpus callosum (top row) show no abnormality, including no evidence of old hemorrhage. Areas where FA is significantly lower in the single subject are shown as colored regions (lower rlght) superhnposed on an axial Montreal Neurologica] lnstitute (MNI) template image. Despite the significantly lower FA found in this subject's genu, no clear abnormal ity is visible in the FA image (lower left). Lower FA than controls was also found at other locations (not shown). While not as numerous, the lesions found in single subjects co-locate with significantly lower FA founci in analysis of the entire patient and control groups.

Second, wehaveaddressed an importantand prevalentout,. come of mTBL Cognitive impa.irment occurs in as many as 30% of patlenls (Alexander, 1995; Kushner, 1998). While the :neurobehavioral sym.ptoms of cognitive impairment may be nonspecific, they Iead to substantial morbidity and dîsabiiity (Kushner, 1998; 2003). Studies of disability and neuropsychologiœl outcomes using DTIhave only been reported in severe TBI (Ptak et al, 2003; Hulsman et al., 2004; Ewing-Cobbs et al, 2006; Nakayama et al, 2006). Kraus et al reported a study of chronic mTBL showing correlation of white matter abnormallties with cognitive impainnent in a region of interest (ROI) analysis (I<raus et al, 2007). Our findings are congruent withthose of Kraus, but sinœ the voxel-wise ana1ysissurveys the entire brain at high resolution,. we are additionally able to depict the distribution of even smail brain lesions, showing a pattern of abnormalities in mTBI that is similar to DAI. Even more reœntly, Niogi et al. reported voxel-wise analysis of DTI inmTBI and showed correlation of whitematter abnormallties with a single reaction time measure (N"mgi et al, 2008). This study evaluated a range of time after injury and was not restrlcted to cluonic patients; imaging occurred as early as 1 month after injury, well within the timeframe over whù:h rerovery from mTBI is still occuning. Thus, we can be more assured that the abnormallties in the present study represent true chronic mTBI pathology.

Third, we have evaluated patients in the chronic phase of the disorder. While both symptoms and brain lesions may manifest at presentation in severe TBI, mTBI generally presentsfew if any findings at the timeof injury (Kuslmer,1998). mTBIpathology evolves following the initial trauma, due to a cascade of cellular and systemk responses (Gentry, 1994; Mc.Arthur et al, 2004; Nortje and Menon, 2004), leading to delayed evolution of bath brain pathology and cliniœl defidts.

Finally, the voxel-wise approach employed in this study reduœs potential biases by standardizing the analysis and improves sensitivity by minimizing partial volume effects. The ROI analysis method that has been used in previous reports of DTI in TBI (Arfanakis et al, 2002; Ptak et al, *2003;* Hulsman et aL, 2004; Lo et al., 2006), has significant limitations including observer bias inherent in ROI placement and partial volume effects when placing white matter ROis in close proximity to gray matter or CSF. Sinœ FA images have relatively low spatial resolution and low contrast-to-noise,it ls difficult to identify.anatomie Jandmarks to guide ROI placement ln this study, sinœ each subject'& brain *is* transformed to a standard brain-space usingvalidated, robustand automated algorithms, we minimize unœrtainty inherent in manual placement of ROIs across subjects. Despite the care taken in performing image registration, small registration errors may occur, particularly at the edges of the brain volume. However, there is no reason to expect these arti.facts to oœur in a systematic manner that selectively affects one group, leading to fal&e positive findings. It is muèh more likely that such errors would rnask real findings. Thus, we feel that our findîngs represent a conservative measure of the extent of true brain abnormalities.

The distribution of abnormalities found in our subject group is concordant with pathological and imaging shldies of diffuse axonal injury (DAI) (McArthur et al., 2004). DAI typically follows severetrauma, with impairment at the time of injury and poor prognosis. The similar distribution of our findings suggests that mTBI represents one end of a DAI spectrwn (Povlishock and Jenkins,1995). Thissimilarity may have great importance for treatment of TBL Treatment trials in DAI, focusing on cellular injury, including neuroprotective, anti-inflamma ory, and receptor blocldng or neqrotransmitter scavenging agents, have been universally disappointing (Meythaler et al, 2001). This may be becausesevere injury causes immedlate tissue disruption that is not reversible. In mTBI, however, treatment initiated at the lime of Injurymight be able to prevent progression to irreversible brain damage. If DTI abnormalities are also present at the lime of injury, mTBI patients at risk for progression to permanent brain damage might be identified before deficits manifest. DTI could th.en be evaluated as a screening tool to stratify patients as to prognosis and need for treatment as well as provide·a cri.terion for use in future treatment trials in TBI. Even if DTI findings are not confirmed at the time of injury, confirmation of latent findings suggestsa progressive lnjury that may be more a:rnenable to treatment than severe TBL

Normalization ofbrain images providesa powerfulmeans for maldng automated and objective inter-subject and intergroup comparisons, but may introduœ error, espedally if distortion is present in the original diffusion-weighted images due to eddy current or magnetk susœptibility-related effects. Our images were corrected for the effects of eddy currents and we employed a validated method to correct for distorti.on prlor to image analysis. Additionally, we registered each subject's DTI images to thelr own 1'2-weighted FSE images, which *were* subsequently registered to their high-resolution 11-weighted images and, finally, to **a** high-resolution TI•weighted template. This approach minimizes the potential for error in inter-modality lnter-subject regi&-tration and assures the m.ost accu.rate regisb:ation of subjects that is possible. The approach we employed has been compared to several other methods, including AIR, AFNI, SPM (Ardekani et al., 2005), and FSL (unpublished results), and perform.s equal to or better than a11.

A potential problem inherent in a voxel-wise analysis, where each voxel ls treated individually, is the likelihood of Type I errors (false positive findings), due to the numerous simultaneous comparisons that are made. Brain volumes the size of the voxels employed in this study, however, are not likely to be functionally independent of each other; we expect that lesions will span many voxels. Nonetheless, we have take:n several steps to address and control for this issue. We controlled for Type I errors using the FDR measure (Benjamini and Hochberg, 1995), choosing a statistical threshold to ensure th.al the percentage of false positives relative to the total number of rejected hypotheses did not exœed 1%. Additionally, the clustering algorithm used in the final stagesof the analysis requires statistiœl significanœ not just at the voxel level, but a1so across a duster of a:mtiguous voxels. Finally, *we* discarded dusters comprising fewer than 100 voxels. These stringencies make us confident that our conclusions are based on an exl:remely conservative asses&-ment of the data, with the likelihood that white matter injury is even more widespread in mTBI assoclated with cognitive impainnent th.an we report here.

Differences in the brain-wide distribution of white matter FA in patients and controls further support the strength of our findings. The histogram analysis is entirely free from the

potential biases introduced by regio:nal analyses (ROI or voxel-wise) as all voxels are considered without regard for location. The main limitation of this approach is its lack of sensitivity; if few voxels differ between the groups, effects might not be detectable. Thus, the fact that we do detect group differences in the FA histogram that. are consistent with the voxeJ..wise and ROI analyses, further supports the validity of our findings.

Notably, even evaluation of single subjects revealed fod of lower PA than controls in eve.ty case. This finding was not expected beœuse a:nalysis of such a small patient sample (n = 1) should be highly underpowered to detect such effects. Nonetheless, the single subject findings suggest that the magnitude of effect seen using OTI may ultimately be arnenable to true diniœl application where measurements must be made in single suhjects.

Severa! additi.onal limitations of this study bear mention. The sample size is small and our findings must be confirmed in a larger group. Nonetheless, a conservative approach to data analysis was used and the study was powered to tect the effects reported. The patients studied all met cri ri for mTBI and had docum.ented cognitive impairment. However, due to the retrospective nature of the study, patients did not undergo standardized cognitive assessments on a standardized follow-upschedule. Our findings indicate that a prospective trial, in whlch standardized clinica1 and cognitive evaluations are administered on a strict timeline, is likely to be informative.

We have shown that OTI can identify abnormalities in patients cognitively impaired following mTBI. While the findings hold promise for identifying mTBI patients who have cognitive impainnent, they do not neœssarily imply that DTI can be used to identify such patients before the onset of neurobehavioral symptoms. That question is most important as its answer could facllitate early identification of the 15% or more of patients who are at risk for cognitive decline following mTBI (Alexander, 1995; Kushner, 1998). Such early identification could certainly be used to define prognosis, but more importantly might serve as a proxy endpoint in the study of novel treatments with potential for preempting late cognitive disability altogether.

Author DIsclosure Statement

No competing financial interests exist.

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White Matter Abnormalities in Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study

BACKGROUND AND *PURPOSE:* Traumatic axonal injury is a primary brain abnormality in head trauma and is characterized by reduètion of fraètional anlsotropy (FA) on diffusion tensor imaging !DTI). Our hypothesîs was that patients withmild traumatic brain injury ITBI) have widespread brain white matter ragions of reduced FA involving a variety of fiber bundles and show fiber disruptlon on fiber tracking in a minority of these ragions.

MATERIALS AND METHODS; Ethics committee approval andinformed consent were obtained. Twenty-one patients with mDd TBI were investigated lmen:women, 12:9; mean age ± SD, 32 ± 9 years). In a voxel-based comparison with 11 control subjects (men:women. 8:3; mean age,:r7 ± 9 years) usîng *z* score analysis, patient ragions with abnormally reduced FA were defined in brain white matter. MR imaging, DTI, and fiber tracking characteristics of these ragions were described and analyzed using Pearson correlation, linear regression analysis, or the 1' test when appropriate.

RESULTS: Patients had on average 9.1 ragions with reduced FA. with a mean region volume of 525 mm^3, predominantly found in cerebral lobar white matter, clngulum. and corpus callosum. These ragions mainly involved supratentorial projection fiber bundles, canosal fibers, and fronto-temporo-occipital association fiber bundles. Internai capsules and infratentorial white matter were relatively infrequently affected. Of all of the involved fiber bundles. 19.3% showed discontinuity on fiber tracking.

C0NCWS10N: Patients with mlld TBI have multiple ragions with reduced FA in various white matter locations and involving various flber bundles. A minority of these fiber bundles show discontinuity on hber tracking.

raumatic brain injury (TB!) is common in Western society, with an estimated incidence of 235 per 100.000! At least 80% of traumatic headinjuries co.nsist of mild head trauma.1.2 Many patients with mild TBI have long-term neurologie or neuropsychologie abnormalities.1.4 It has been suggested that the.se abnormalities may be caused by traumatic axonal injury that persists in a chronic stage.s.a

Predilection sites of trawnatic axonal injury include subcortical white matter, corpus callosum, fornix, internai capsules, and infratentorial white matter.'H² These sites have been identified through analysis of patients with relatively severe TBI, but in mild TBI, conventional radiologie imaging often shows no white matter injury.[13] Diffusion tensor imaging(DTI) bas emerged in recent years as a valuable additional technique to investigate traumatic axonal injury in mild-to-severe TBI.[11 12 14 15] D11 quantifies white matter architecture through an extensive description ofwater diffusion andallows for the reconstruction of white matter fibers in 3D through fiber tracking algorithms.[20 21] DTI parameters. such as fractional anisotropy (FA), descnbe microstructural anatomy and integrity. where FA reduction corresponds with local loss of structural integrity.[20] Predilection sites of traumatic axonal injury arecharacterized by reduced FA.[12 14 15 17 19]

ln mild TBI, FA reduction has been demonstrated in the corpus callosum, internai and externat capsules. and the centrum semiovale, both in an acute and chronic stage.[15,] Axonal injury is probably more widespread in mild TBI, asindicated by global decrease of white matter FA[22] However, it is unclear which white matter fi.bers may be affected. It may be suggested that similar predilection sites of traumatic axonal injury are involved in mild TBI, as are known from patients with more severe TBI.'"[12] ln addition, it is unclear whether areas of decreased FA in mild TBI correspond with fiber dismption. Our hypothesis in the present studywas that patients with mild TBI have widespread brain white matter regions of reduced FA, inv0Iving a varietyof.fiber bundles and showfiber disruption on fiber tracking in a minority of these regions.

Methods

Patients and Control Subjects

Thestudy wasapproved byour localethical ccmmittee, andsubjecu' informed consent was obtained. We investigatcd 21 patients with mildTBI (l2menand 9 women;mean age:!: SD,32 *:t* 9-years), which was defined as traumatic head injury with an initial Glasgow Coma Sade (GCS) score at or more than 13, Head injury was caused by a traffic crash in 14patients, byaggression-relatedblows to theheadin 4 patients, and by a fall in 3 patients. The median tune interval between injury and MR investigation was 5.5 months (minimum, 0.1 months; maximum, 109.3 months; first quartile. 0.5 months; third quartile, 31,5 months). In this tùneinterval, patients had norepeated episodes ofTB[. Our patient group was selected from 43 consecutive patients whoweretreferred toourneuroradiologydepartmentforDTI cvaluation ofTBI between June 2006 and May 2007 and who had no

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BRAIN

ORIGINAL RESEARCH

known history or MR imaging evidence of additional central ncrvous system disease. From thcsc 43 patients. wee xduded those with movement artifac:ts on the MR image *(n* = 7) and those with moderate or severe TBI (GCS, <13; n= 15). We investigated 11 controls subjects (8 men and 3 women; mean age± SD, 37 ± 9 years) for reference values. They were volunteers Crom our depanment and had no knowa history or MR imaging evidence of central nervous system disease.

MR Protocol

Investigations were perfonned on a 1.ST system (Sonata; Siemens, Erlangen, Gennany). Straight head positioning without tilt was aimed for in each patient and CQntrol subject. The MR protocol consisted of an axial 3DTl-weighted scan (TRJTE, 11/4 ms), an axial fluid-attenuated inversion recovery {FLAIR) sc:an (TRfrE/inversion rime, 9480/112/2390 ms), an axial n•-weighted gradient-echo (GE) scan *(TRI* TE. 1330/33 ms), and an axial echo-planar imaging DTI scan (TRII'E. 5700/llOms; FOV, 24 X 24 cm; image matrix, 128 X 128; 30 sections with 4--mm thickness; nominal voxel size, 1.875 X 1.875 X 4 mm; number of signal intensity averages, 3) wîth diffusion gradients set in 25 noncoilincer directions using 2 b-values (b = O and 1000 slmm2). The DTI scan took *1* minutes and 30 seconds.

D11 Data Processing

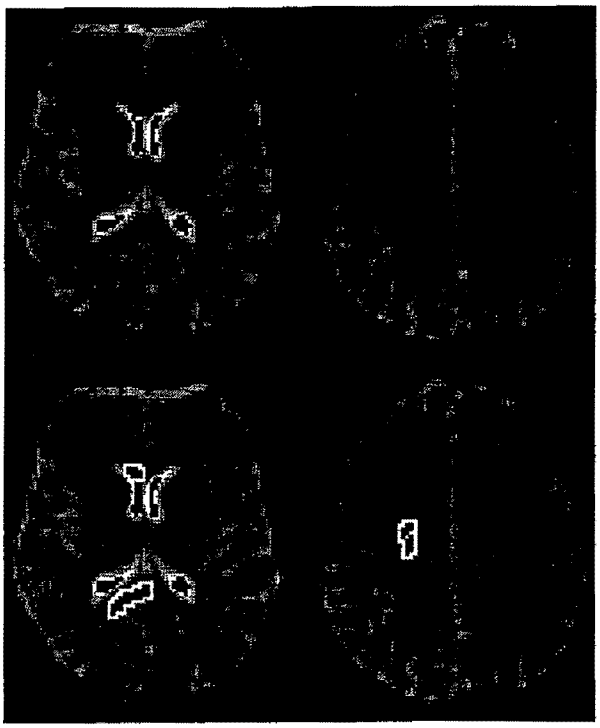
DTI data were processed on a voxel-by-voxel buis with dedicated software (DPTools, http://www.fmritools.org). A correction algorithm was applied to the Dlt dataset to account for distortions that were rdated to eddy currents induced by the large diffiision-sensitizing gradients. It relied on a 3-parameter distortion model including scale, shear, and linear translation in the phase-encoding direction.[23] The 25 elernents for each voxel. calculated from the images that were ohtained hy applying diffusion-sensitimiggradients in the 25 noncol• linear directions, in addition to a nondiffusion-weighted image, **were** diagonalized to compute the eigenvalues ($\mathbf{A_1}$, Al> and A_3) of the diffusion tensor matrix. The apparent diffusion coeffident (ADC) and FA were suhiequently calculated. FA values at approximately **l** are totally anisotropie, and FA values at approximately O are totally isotr pk.[24] FA values were visualized in 2D color maps.

Fiber Tracking

Ptber tracking was performed with dedicated software (MedlNRIA, http://www-sop.inria.fr/asclepios/software/Med1NRIA). White matter fiber tracts were created in 30 bued onsimi1 aritiesbetwec:nneighboring voxels in shape (quantitative diffusion anisotropy measures) and orientation (principal eigenvector map) of the diffusion ellipsoid and coregistered on the FA map using a special algorithm described previously.[25]. u The principal diffusion directions method: 16-[211] was used, where the eigenvector corresponding with the largest eigenvalue is extracted from the diffusion tensor field generated from the DTI datasets in the region where the diffusion **was** linear. The FA threshold value was 0.20, and the angulation threshold **was** 45° (to prevent fibers from sudden transition and to keep tracking based on the connectiv--ity of the neighborhood), as described elsewhere.[26,27] The 3D fiber reconstructions **were** color coded, where blue represented the superior-inferior, green the anteroposterior, and red the left-right direction.

Measurements

Measurements were performed blinded to the clinkal status of the patient using the software packages descn'bed in the previous paragraphs. Afier realignment and spatial norrnalization, FA values of



Rg 1. Selaclilllllofl!Ofs in a paliant wilb mikl TllL The top mw shows 2 of 30 sections of 11ta *ISC1111* map of fl'llCtlonal 8!1isotmpy. superimpose an, *b* = O an scan. Pixels 'M1h a z si:ora less than -1.98 ara high ilghllld in *purple.* Abnonmll nigions aie villibla îll llllll Sl)!enium and genu of llllll C!))IUa callosum [tep *'8fl miagel* ami ttie right sem ÎOl/llltl canter (tep *right* ROIII. Inçludjng these almrmal pixel$, weiil mammlly drawl, as illustrated in the lower *111N* of cornisponding images.

controls subjects were pooled on a voxel-by--voxel basis to derive mean and SD reference values for the control group. To identify voxels of abnormally reduced FA in each patient, the patlent's FA map was realigned, spatially normalized, and individually compared with the control group in a z score analysis. A $|z| > 1.96$ ($P < .05$) was considered to indicate abnormal voxels. which were automatically high·lighted on the zscore map (Fig 1). White matter region. sof voxels with reduced FA were manually outlined as illustrated in Fig l. For each of these regions of interest (ROIs) with reduced FA, visual comparison was made with the corresponding low b value diffusion, Tl, and FLAIR scam to confinn its locafuation in white matter. Particular care was taken to avoid inclusion of gray matter or CSF. For each region of interest, we calculated volume, FA, z score, and ADC and detennined the presence of FLAIR hyperintensities and T2" GE hypointensities indicative of microhemorrbage.

The ROI localization in brain white matter wa.s categorized according to the following classification: cerebral lobar white matter, dngulum and corpus callosum, anterior and posterior limb of the internai capsules, mesencephalon, brain stem, and cerebellum. Cere·brallobar white matter was subdivided in centrum semiovale, frontal lobe, parietal lobe, temporal lobe, and occipital lobe. If an ROI extended in more than 1 of these locations. ail of the involved locations were scored.:

Fiber tracking software allowed for reconstruction of merely the fiben that piwed through a given ROI. The number and length of individual through-passing libers were calculated for each ROI, and we determined the anatomie type of through•passing fiber bundle(s) 211 that was composed of the individual fibers. Finally, the recon-

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No. of Reghms with Reduced FA

Variable	Ali Patients .. ln = 211. n1%)	Per Patient, Mean:!: SD
Cerebral lobar white matter	118(61.81"	5.6:!::2.6"
Centium semiova!a	· if(14.11	1.3 ±1.3
Frontal lobe	42(21.9)	2.0 :!:1.3
Parietal lobe	31116.1}	1.5± 1.4
Temporal lobe	28(14.6}	1.3 :±: 1.1
Occipftal lobe	... 4(2.1)	0.2±0.4
	45(23.61	2.1± 1.0
lntemal capsules	11{5.7}	0.5 :!: 0.7
Cingulum/corpus callosum	211.0)	0.1 :±: 1.3
Posterior limb	9(4.7)	0.4 :t: O.S
Mesencephalon	7(3.7)	0.3 :t: 0.6
Brain stem	412.1)	01:!:0.4
Cerebellum	6(3.1)	D.3± 0.5
Total	1911lDOI	9.1 ±3.2

Note:—FA indicates fractional anisotropy.
*** The values of the 5 sublocations in cerebral lobar white matter fie, centrum semiovale to occipital lobe) add up to more than the value for cerebral lobar white matter as a whole because a given region with reduced FA could be scored in more than 1 sublocation.**

structed throughb-pu,ingfiher bundle wasvisually judged fordiscontinuityat thelevel of theROI.

Statistkal Analysis

The number ofROIswith reduced FA wu œlcu l ated III *n* (%) for the total of patients and asmean :!:SD to describe patient averages. ROI volurne,FA,zscore,AOC.andnumberandlengthofthrougb-passing fibers aregiven asmeanswith 95% confidence intervals. Pearson correlation wuœlculated between these parameters and the time interval after injury. White matter fiber bundles that were involved in regiom with reduœd FAaregiven as *n* (%) for thetotal of patients. A multiple linear regression analysis was applied to identify variables that were rdated to the presence of discontinuous libers in an ROI. Using the')(" test, the distribution of Rota among various white matter regions and the proportion of discontinuous fiber bundles were compared between patientswhowereinvestigatedlessthan 3 months and at or more than 3 monthsafter injury. ln ail of the analyses, data from the left and right sides of the brain were pooled, because we found no significant differences between bothsides of the brain. A *P* value less than.05 was considered to indiœte a statistkallysignifiant difference,

Resuhs

Tl-weighted, FLAIR, and n•-weighted MR imaging were normal in 17of2I patients. Four patientsshowed peripherally Iocated contusions. andoneofthesepatients alsohadan extra· axial hematoma. Weidentified 191 white matter regions with reduced FA in our patient group. Four of these regions contained FLAIR hyperintensities. whereas in none of the 191 regions signs of microbemorrhage were found on T2*-weighted GE ùnaging. Most regions with reduced FA were Iocated in cerebral lobar white matter (61.8%; Table I) or included thecingulumorcorpusc.allosum (23.6%).Thenumberof regions located incerebral lobar white matter wascomparable in the centrum semiovale, the parietal lobe, and the temporal lobe, whereas most Iobar white matter regions were found in thefrontal lobeand fewregions in theoccipital lobe. In the centrum semiovale 9 (33.3%) of27 regions were subcortic.ally located or had a subcorticalpart compared witb 14 (33.3%) of42 frontal lobe regions, 10 (32.3%) of31 parietal lobe regions, 16 (57.1%) of 28 temporal lobe regions, an 0 (0%) of 4 occipital lobe regions (P = .10, *Jè* test). The frequency of regions with reduœd FA in the internal capsules, mesencepbalon, brain stem. and cerebellum ranged from 5.7% to 2.1%. No regions with reduced FA were found in the externat capsules. On average, each patient had 9.1 regions with reduced FA, ofwhich 5.7 were located in cerebral lobar white matter, 2.1 in cingulwn/corpuscallosum, and at or less than 0.5 each ininternai capsules, mesencephalon,brain stem, and œrebellum. The distnôution of regions with reduœd FA among the white matter locations did not differ significantly between patients who were investigated less than 3 months after injury (n = 9) and those who were investigated more than 3 months after injwy (n = 12;*P* = .9S.*Jè* test).

Averagevolume, FA, *z*score, ADC.and number andlength of through-passing fibers of regions with reduced FA are shown in Table 2. None of these parameters showed a statistically significant correlation with thetimeinterval between in*jury* and MR investigation.

In 140 of the 191 regions with reduœd FA, 1 fiber bundle was identified on fiber tracking,, 2 were identified in 45 regions. 3 were identified in 5 regions, and 4 wereidentified in l region. Most of these 249 fiber bundles included supratentorial projection fiber bundles (27.7%; Table 3) and corpus callosum fibers (sum of genu, body, and splenium: 21.7%). Among association bundles. fronto-temporo-occipital fiber bundles were most often involved (19.3%). The fomix was identified in l patient. In the 249 white matter fiber bundles, wefound discontinuity in48 bundles (19.3%). Figures 2 and 3 show examples of fiber track:ing analysis, with discontinuous fibers found in 2 patients with mild TBI. Most of the discontinuous bundles were supratentorial projection tiber bundles (33.3%) or fronto-temporo-ocdpital fiber bundles (25.0%), but also fibers of the major forceps were discontinuous to a relatively frequent extent (14.6%}. In a multiplelinear regression analysis, the presence of discontinuous fibers in an ROI wa.s significantly related to FA of the ROI (b = - 7.303; *P* == .006) butnot tozscore,ADC, or volumeof the ROI,nor to the patient's age or the rune interval between injury and MR investigation. The proportion of discontinuous fiber bundles did not differ significantly between patients who were investi-

Table 2: Diffusion tensor imaging of brain white matter regions wit FA Ji .cha

Variable	Miki TBI In... 21). Mean 195% Confidence lntervall	rValue	PValue
Regions wi1h reduced FA			
Numher of reglons	a1(7.IH0.61	0.082	0.725
Volume, mm3	52?(453-597)	-0.085	D.240
FA	0.30 (OlfH).31)	0.349	0.121
zscore	-3.38f-3.50to-l261	0.100	0.6117
AOC,mnr/s	2.56 (2.47-2.661	-0.221	0.336
No. of throufl!-passing fibers .	371 (31&-423)	-0.118	0,611
l.ength of througfl.passing fibers, mm	82180-851.	0.155	0.503

Note:—TBI indicates mild traumatic brain injury; FA, fractional anisotropy; ADC, apparent diffusion coefficient.

Table 3: White matter fibers in regions with reduced FA

Variable	White Matter Fiber Bundles in Regions with Reduced FA: All Bundles, n (%)	White Matter Fiber Bundles in Regions with Reduced FA: Discontinuous Bundles, n (%)
Supratentorial projection fiber bundles		
Corticofugal and corticopetal fiber bundles	69 (27.7)	16 (33.3)
Association fiber bundles		
Fronto-temporo-occipital fiber bundles	48 (19.3)	12 (25.0)
Temporo-occipital fiber bundles	15 (6.0)	1 (2.1)
Fronto-temporal fiber bundles	41 (16.5)	1 (2.1)
Cingulum	14 (5.6)	1 (2.1)
Fornix	1 (0.4)	0 (0)
Commissural and forceps fiber bundles		
CC genu	17 (6.9)	1 (2.1)
CC body	23 (9.2)	2 (4.2)
CC splenium	14 (5.6)	1 (2.1)
Minor forceps	15 (6.0)	2 (4.2)
Major forceps	12 (4.8)	7 (14.5)
Infratentorial fiber bundles	17 (6.9)	2 (4.1)
Total	249 (100)	48 (100)

Note:-:-fA icaces ftaclimal anisotropy; CC. CC11JU$ r:allosum.

gated less than 3 months after injury and those who were investigated more than 3 months after injury (17 of 85 fiber bundles.versu.s 31 of 164 fi.ber bundles; $P = .84$, i^2 test).

Discussion

This study bas 3 major fmdings. First, compared with control subjects, patients with mild TBI had multiple white matter regions with reduced FA. predominantly invomng cerebral lobar white matter, cingulum, and corpus callosurn. Second, white matter fiber bundles that were frequent1y included in these regions were supratentorial projection fiber bundles, ca.llosal fibers, and fronto-temporo-occipital association fiber bundles; Thini, there was no significant relation of the time interval after injury with our DTI and fi.ber tracking findings.

Predilection sites for traumatic axonal injury include subcortical white matter, internai capsules, corpus callosum, fornix, and infratentorial white matter (hrain stem and cerebellum).[9-11] We found that.in mild TBI, predominantly cerebral lobar white matter, including subcortically located white matter, dngulum, and the corpus callosum were affected. It may besuggested that abnormalities in the intemal capsules, fornix, brain stem, and cerebellum are markers of more severe TBI, because these sites were infrequently involved in our patients with mild TBI. Traumatic axonal damage can vary Crom small focl to widespread axonal injury, depending on the severityof the initial trauma.[7] In thisregard, therelativevastness of affected fiber bundles in our patients seems not in proportion with their relatively mild initial trauma. However, even mild TBI patients show diffuse neuronal and axonal injury as evidenced by a reduction in whole brain N-acetylaspartat and a global decrease of white matter FA.[22] The diffuse characterofthese typesofinjuriesisin accordancewithourfinding of rather widespread affected fiber bundles. Our results are supportèd bya recentstudyin mild TBIs[1]. Although thatstudy found no difference between patients and control subjectsina whole-brain histogram analysis, ROI analysis in a few white matter regions {corpus callosum and intemal capsule) did show FA rednction both in asubacute and chronic stage. We found a considerably Jarger number and distn1mtion of abnormal regions. This may be explained by different methods. PoSSJblyour voxel-based analysis detected more subtle FA abnonnalities than a histogram analysis. Furthennore, ROI anafysis that islimited toafewwhite matterregions may Jeave other regions with reduced FA undetected. Among themultiple regions withreduced FA in our patients. weidentffiedonly 1 that involved the fornix,though thisstmctureisknown to be affectedinTBI.[12] Thefomixwaseithernot affected inmanyof our patients because of their relatively mild degree of head trauma or it was too small to be detected. Similarly, we may have underestimated the ment of injury in other small fiber bundles. such as the anterior and posterior commissure.

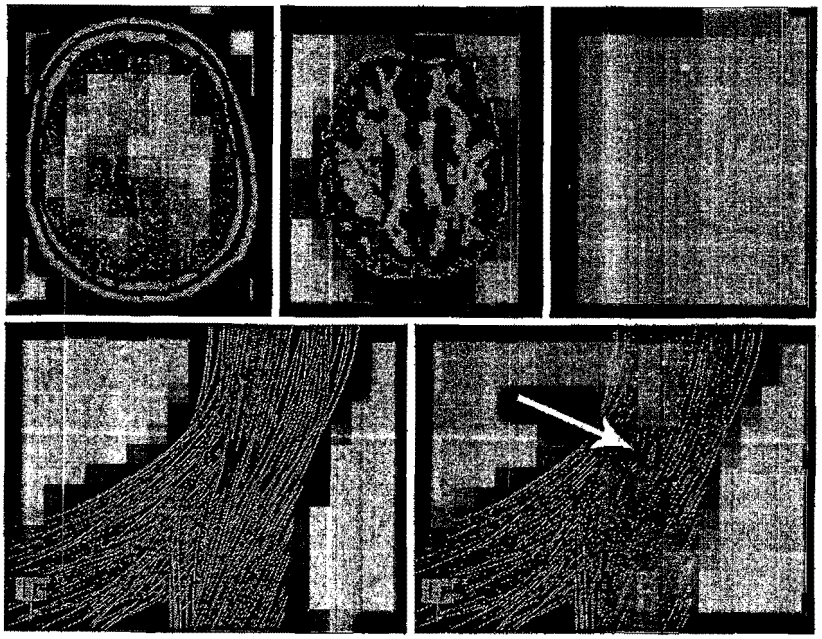
Ourstudyindicates that DTI and fiber tracking characteristics of regions with reduced FA remain unclumged during subacute andchronic stages ofmildTBI, becausewefound no significant change of these characteristics when correlated with the tiJne interval after injury and no signifiant differ-

or more than 3 months after injury. Our findings are sup-

ences between patients who were investigated less than 3 or at

ported by a previous study in patients with mild TBI who demonstrated FA reduction in thecorpus callosum andinterna} capsule.[1] These abnormalities were found to be present both in subacute and chronic patients. From this previous studyand our resultsit maybesuggested thatsubacuteorearly chronic DTIchangesareanindicator oflong-term DTIabnormalitiesin mild TBI. Longitudinal studiesareneeded to investigate this. It should be emphasized that our results do not necessarily apply to acute TBI, because we did not investigate patients within 24 hours after injury. The time course ofDTI and fiber tracking abnonnalities may bedifferent in acute patients because acute posttraumatic changes may evo1ve rapidly.

The cause of FA reduction in brain white matter in TBI is not Cully understood; Generally, it is attributed to a change in parenchymal structure.[1,2,i:1i, 1-1 9] This may include misalignment of fibers, edema, axonaJ degeneration, or fiber disruption. In the setting ofbrain trauma, it should be stressed that axonal degeneration ma:ybecausedbytraumatic axonalinjury but may also be induced by overlying brain contusions. Chronic contusions can bedifficult to appreciate on imaging, in particular if they are small and peripherally located. It is known that mild TBI can cause fiber disruption,:u but it is improbable that all of the regions with reduced FA in our patients represented in vivo fi.ber disruption, because fiber trackingshowed discontinuity in only a minority of fiber bundles. We hypothesize that most regions were related to fiber misalignment or edema or to degeneration in\ chronic patients. Where we found discontinuous fibers. it is not evident that these fi.bers were disrupted in vivo, because we had no histologie correlation. Discontinuity on fiber tracking may havebeencausedbythe presenceofsharplyangulated fibersin anROI,impedingfullfiberreconstruction,orbysmallareasof hemosiderin thatwerenotvisibleon MRimaging.These areas may have induced significant intervoxel variations of FA, which may have impeded full fiber reconstruction as well Nevertheless, it may besuggested that regions with discontinuous fibers on fiber tracking are more likely to include disrupted fibers in vivo than other regions. The clinical correla



F.19 2. R.AIR scan. FA 1111111, andliber trackingina palfent MIi TBI **YmO was** imaged 16 after tha initial trauma. The R.AIR image shows no abnolmalilies (rop *left* ÎIIIB/I8I. Alter analysls of lhe tolor.coded FA map lrop *midd1s* Il reglon MIi reduœd FA was idenlified inthalloilite manernfthe lelt flanlal loba This ROI, illuatrated in 1hetop lfght 12-weighted image, indllded folœps minor and fromo-œmporo-occlpiial fiben1botlan *lekimage.* superior oblique vlew; th8 ROI is rai and lœalBII CIIIltrany; the fib8rs !Ife superin!posed on an axial 12-welgilted scœnl. *At.*th8 llMII of tha ROI th8 libers are disccminUIIIIS1anow. *bel· tom tight image;* llle ROI is lelt OUI Ill lhis image).

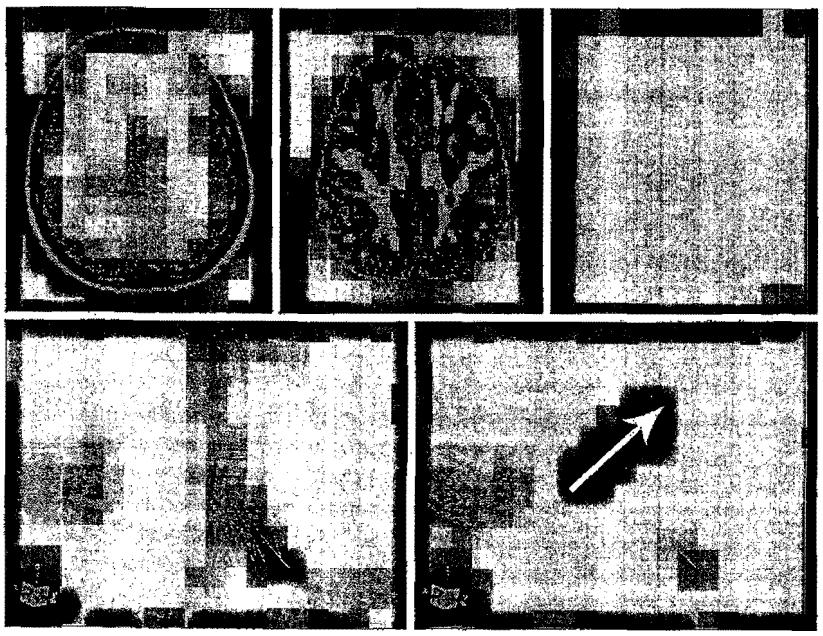


Fig 3.R.AIR scan. FA map. andliber tracking ina 311-year-ohl patient wilh TBI v.flo W8S imaged 2 W8lb after the initfat tra11111a. The RAIR image shows no abnormalilÎIIII in llle semioVale centels trop *18ft* imlgal. Alter analysls of lha color-cocfed FA map (top *midd1s* illagl,t. a reginn wilh re-dlmf fA **was** idm!ified iri tha right semiovale celller. This ROl lllustrated inllle *rop tight* 12-weiQhted image, incltJdad J)TojactlCII libln fbDtlom */eft image,* **)IIIrior** lllaw; 1h11 ROlismdand lŒalllld in lhe top lfght quarter of the imaga; 1h11 fibers ere superimposad **on** *a multiplanat* 12· weighted si:an that shows the lateral WIIIrides in wbitei At 1h11 level of the RO projectioo fibers are discontlnuous 1- *bottam right imagt,;* lha ROI is lelt outinlhia imaget

. tion of FA teductîon in mild TBJ remains to be elucidated. From patients with varions trauma severities, it is known that FA reduction is correlated with clinical admission and outcornescores.[17,18] Possibly, FA reduction in mild TBI gives evidence of axonal injury that is related to long-term neurologie or neuropsychologie abnormalities.3-6 Follow-up studies and neuropsychologiecorrelation are needed to investigate this.

To define regions with abnormally reduced FA, we compared patients with control subjects in a voxel-based *z* score analysis. This allows for a clear definition of abnormality that is independent of absolute FA values, which vary with white matter location. However, in periventricular regions, realignment and spatial normalization in relation to control subjects may be difficult, even with dedicated algorithms.[32] This may cause an overestimation oflesion size in these regions. Further limitations of our study were that no histo l ogk correlation of DTI findings was available and that no neuropsychologiemea· surements were performed. For obvious reasons it is difficult to obtain histologie confirmation, but we anticipate that fur. ther pathophysiologicirisight may be gained from future longitudinal studies and neuropsychologie correlations.

Conclusion

The present study shows that patients with mild TBI have multiple white matter regions with abnormally reduced FA, predominantly in cerebral lobar white matter, cingulum, and corpus callosum. These regions predominantly involve supratentorial projection fiber bundles, callosal fi.bers, and fronto-temporo-occipital association fiber bundles. A minority of these fi.ber bundles show discontinuity on fiber tracking. The

clinical and pathologie-anatomie correlation ofthese.findings remains to be elucidated, but possibly they are related to .chronic complaints or long-term axonal damage.

Acknowledgments

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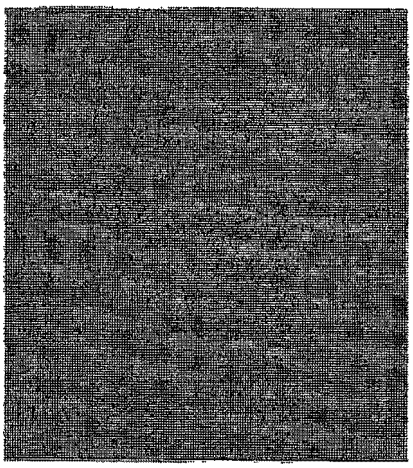

Diffusion-Tensor Imaging Implicates Prefrontal Axonal Injury in Executive Function Impairment Following Very Mild Traumatic Brain Injury[1]

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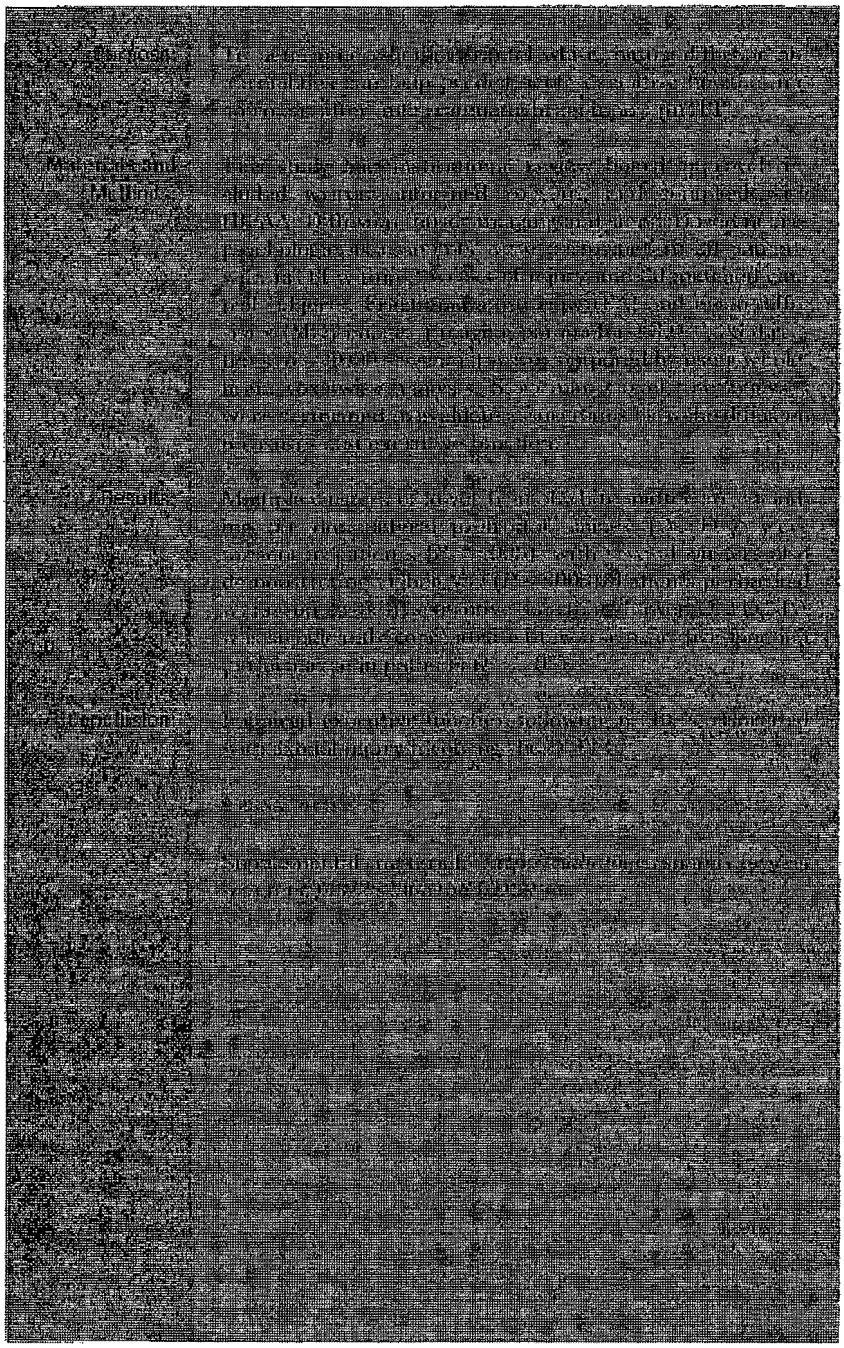

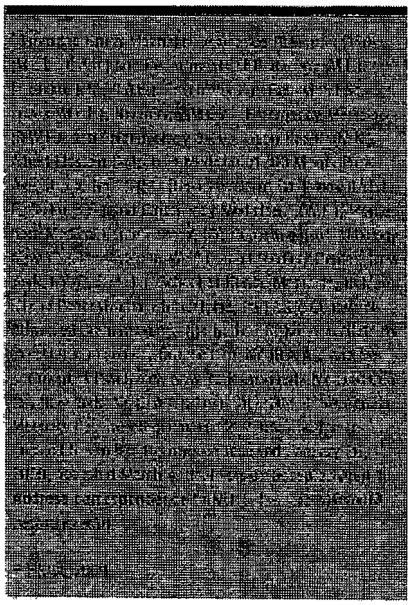

More than 1.t million cases of mild traumatic brain injury (mTBI) are reported annually in the United States (1). While most patients with rnTBI recover, as many as 30% or more will have permanent impairment and 20% of patients with mTBl are unable to return to work (2), costing $80 billion yearly in the United States (1).

mTBI is diagnosed on the basis of history and clinical examination; computed tomographie (CT) and magnetic resonance (MR) imaging results are typically normal (3,4). The Glasgow Coma Scale assesses brain injury severity on the basis of clinicàl criteria; à Glasgow score of 13-15 is mild. Additional criteria used to diagnose mTBI include loss of consciousness not exceeding 20 minutes, posttraumatic amnesia not exceeding 24 hours, and the absence of abnormalities at conventional imaging (5).

Patients with mTBI exhibit nonspecific symptoms, including headache, dizziness, and behavioral abnormalities (2). Neuropsychologie dysfonction is known to occur after mTBI (6), particularly for execuûve function and motor control impairment (7,8). Executive function impairment in mTBI likely re-Rects frontal lobe injury; dorsolateral prefrontal cortex {DLPFC) is essentiol for normal executive function (9,10) and susceptible to injury in mTBI (11,12).

While the shear forces exerted during mTBI may not be sufficient to cause frank tissue laceration and hemorrhage, two autopsy reports have shown pathologie evidence of injury **(13,14),** and animal studies have shown ultrastructural axonal abnormalities, such as neurofilament misalignment and impairment of axoplasmic transport after mTBI (15). Animal studies a1so indicate that iajured axons undergo progressive changes with evolution offrank ax disrupt.ion during the weeks following injury (16-18).

While evidence suggests neuropathology tbat results from mTBI, to oor knowledge, no diagnostic test. is present!y available to confirm the presencœ of injury invivo. Diffusion tensor (DT) imaging has recently been used to characteri7..e axonal changes seen in traumatic brain iqjury (19,20). While DT imaging seema to show brain abnormalities after mTBI (21,22) asaociated with outcomes (23-25), the ahility of DT imaging to identify specific pathologie changes that predict specific functional impairment remains less ciear. Previous stuc.lies (23-26) have examined the relationship between DT imaging and cognitive :function in mTBI but have not directly linked specific acute impairment to evidence of pathologie changes at a specific brain site. Our study was designed to determine wheLher frontal white matter dîflùsion abnormalities help predict acute executive function hnpairment after mTBI.

Materials and Methods

Study SUbjects

This study was institutional review board approved and Health Insurance Portability and Accountability Act compliant. Subjects were prospectively enrolled, and written informed consent was obtained. Study procedures were distinct from routine clinical ce.re.

Patients with mTI1I.-Twenty consecutive patients with mTBl meeting inclusion and exclusion criteria (Table 1) were recruited from one hospital emergency department between August 2006 and February 2008. Patients presented following mild head injury owing to motor vehicle accidents (n = 18) or falls (n = 2) and were evaluated to rule out brain injury.

Ail mTBI subjects underwent CT imaging of the brain during their evaluation in the eme.rgency depnrtment as part of clinical care.

Control subjects.-Twenty control subjects matched for age and sex were recruited. Control subjects underwent the same MR imaging protocol and cognitive evaluation as did the patient sample group. Similarity of the patient and control groups was confirmed with *')(′* (sex) and Student *t* (age) tests. Control exclusion criteria included *(a)* history of head injury, *(b)* history of neurologie or

Advances in Knowledge

- Multifocal frontal white matter axonal injury is detectable in the acute period following mild traumatic brain injury (mTBI).
- Dorsolateral prefrontal cortex (DLPFC) white matter anisotropy correlates with performance on tasks of executive function.
- In patients with mTBI, executive dysfunction correlates with low white matter anisotropy in the DLPFC.

Implications for Patient Care

- Diffusion tensor (DT) imaging provides objective evidence of brain injury related to impairment following mTBI, even in the setting of otherwise normal imaging.
- DT imaging evidence of injury correlates with important functional measures that are known to be adversely affected in mTBI.
- DT imaging shows potential as a diagnostic tool to assess injury and impairment in patients with mTBI.

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Abbreviations:
CPT = Continuous Performance Task
DLPFC = dorsolateral prefrontal cortex
DT = diffusion tensor
FA = fractional anisotropy
MD = mean diffusivity
MP-RAGE = magnetization-prepared rapid acquisition gradient echo
mTBI = mild traumatic brain injury

Author contributions:
Guarantor of integrity of entire study, M.L.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.L.L., E.Gulko, E.Gellella; clinical studies, M.L.L., E.Gulko, M.L.Z., B.W.F., E.Gellella, T.G., K.S.; statistical analysis, M.L.L., E.Gulko, M.K., D.A.A., C.A.B.; and manuscript editing, M.L.L., E.Gulko, M.L.Z., B.W.F., M.K., E.Gellella, T.G., K.S., C.A.B.

Authors stated no financial relationship to disclose.

psychiatrie disease, and *(c)* history of illicit drug use.

Data Acqulsftkm

Following discharge from the emergency department, patients returned 2-14 days after the injury to complete cognitive testing and brain imaging.

Demographics and beha.vioral moo-*sures.-AD* study subjects completed the .Brain Resource Persona! History Questionnaire (Brain Resource Company, Sydney, Australia) to asœrtain age, sex, educational attainment, substance use, anxiety, depression, stress, and Ien. or right handedness (26).

Neuropsychologie assessment.-hlteg· Neuro (Brain Resourœ Company) was used to quantify executive function. hJ.teg-Neuro is a computer-hased test with established reliability across ail cognitive domains (27;28). Two tests of executive function were selected for use in this study, the Continuous Performance Task (CP:r) and the Executive Maze Task (M.E.Z., witb 12 years neuropsychologie testing experience).

hl the *CPT,* a series .ofletters (B, C, D, or G) are presented on a computer touch screen for 200 msec separated by 2.5 seconds. When a letter is presented twiœ in a row, the participant is asked to press a target button with both index fingers. hi total, 125 stimuli are presented, 85 nont.arget letters and 20 target letters. The nwnber of errors of omission and commission were recorded as dependent variables.

The Executive Maze Test is a computerized adaptation of the Austin Maze Task (29). Participants are presented with an 8 x 8 roatrix of circles on a computer touch screen. The objective is to find a hidden path through the grid by means of trial and error. A tone and a red cross are used to indicate an incorrect move.. Adifferent tone and a gl'een è.heckmark are shown to inmcatè a correct move. Twenty-four consecutive correct moves are required t9 transverse the niaze. The task ends 11.fter the partïcipànt completes the maze twice with:out errors or after 10 minutes, whichèver cornes . first. The number of trials and the time to mnze. completiou wete recorded as dependent variables.

Image acquisition.-Imaging was performed (M.L.L, with 18 years MR inlag· ing experience) with a 3.0-T imager (Achieva; Philips Medical Systems, Best, the Netherlands) by using an eight-cbanne1 head coi! (Sense Head Coll; Philips Medical Systems). Tl-weighted whole-head structural imaging was per· formed. by using sagituù three-dinlensional magnetization-prepared rapid acquisition gradient echo (MP-RAGE) imaging {repetition tinte msec/echo time msec, 9.9/4.6; .fieldof view, 240 mm; matri,c, 240 X 240; and section thlckness, 1 mm). T2·weighted whole-bead imaging was performed by using axial two-dimensionalturbo spin-echo (4000/100; :field of view, 240 mm; matrix, 384 X 512; and section thlckness, 4.5 mm) and axial two-dimensional lluid-attenuatedinversion recovery turbo spin-echo (1100/120; inversion tinte, 2800 msec; field of view, 240 mm; matrlx, 384 x 512; section tbick· ness, 4.5 mm: and average number of signais acquired, one) imaging. DT imaging was performed by using single-shot echo-planar imaging (3800/88; field of view, 240 mm; matrix, 112 x 89; section thickness, 4.5 mm; independent diffusion sensitizing directions, 32; and b = 1000 sec/mm2).

Data Analysis

Neuroradiolosic image assessment.-TwoAmericœn Board ofRadiology (with a Certificate of Added Qualification} certified neuroradiologists (M.L..L. and K..S., with 12 and 8 years experience, respectively) independently reviewed CT and MR images of all subjects (patients and control subjects) in random sequence during a single session. This review was performed to identify structural abnormalities, including assessment for evidence ofhemorrhage. Review took place after completion of alldata collection. Reviewers were blinded to all clinicaJ information and group membershlp {patient o:r control). Reviewer assessments were concordant in all cases **(100%)** that no abnormalities were visua.li7.ed on conventional images. For subject safety, attending neuroradiologistswho were Americar1 Board of Radiology (M.LL and nonauthors, each with a Certfficate of Added Qualification}-cerû.fied performed a clinical review of each examination contemporaneous witb its acquisition but this assessment was not part of the study.

Calculation of diflhsion parameter imases.-The 33dilfusion-weighted. inlage sets (32 diffusion sensitizing directions and the b = 0 sec/mm^2 image) were con-ected fOI" head motion and eddy current effects by using an affine registration algorithm (T.G.; with 2 years exparience in image analysis). Fractiomù anisotropy (FA) and mean di.fiusivity (MD) diffusion measures were derived from a DT modeJ at eacb voxel by using the FMRIB Dilfusion Toolbox function (30).

Image analysis.-Quantitative image analysis was perl'ormed as foUows:

Skull stripping: Nonbrain voxe.ls were removed from the MP-RAGE and turbo spin-echo inlages by using FMRIB-FSL software (31). F.a.ch brain volume wasinspected section·by-sectîon, tl!ld residual nonbrain voxels were removed manually.

Echo-planer imaging distortion correction: Turbo spin-echo inlages were acquired with similar section position and orientation as were DT images. Distortion correction was accomplished by using a nonlinear deformation algorithm to

Table 1

Criteria for Study Participants

Inclusion Criteria	Exclusion Criteria
8F 50 years of age	Hospitalization owing to the injury
Witnessed closed-head trauma	Abnormal conventional brain imaging
Glasgow Coma Scale score ≥13	History of prior head trauma
Loss of consciousness < 20 minutes	Cognitive impairment before injury
Posttraumatic amnesia < 24 hours	History of neurologic or psychiatric disease
No focal neurologic deficit	History of illicit drug use
English or Spanish proficiency	Limitation related to the injury

match the echo-planar imaging to the turbo spin-echo volumes (32).

Intermediate rigid-body registration: Bach subject's turbo spin-echo images were registered to their three-dimensional MP-RAGE images by using the Automated Registration Toolbox three-dimensional (33) rigid-body **approach (34).**

Registration to standard space: The nonlinear registration module of the Automated Registration Toolbox was used to register each subject's three-dimensional MP-RAGE volume to a standard T1-weighted template (Montreal Neurological Institute atlas) (35).

Transformation of DTI images to standard space: By using the Automated Registration Toolbox, distortion correction, intermediate rigid-body registration, and standard space registration were applied to the calculated FA and MD maps by using a single reslicing operation. Final cubic voxel size was 1 mm^3, masked to exclude nonbrain voxels from the analysis.

Segmentation: The fast automated segmentation tool in the FMRIB-FSL software (31) was used to generate a white matter mask for the three-dimensional MP-RAGE template brain images and restrict subsequent statistical analysis of FA to white matter voxels.

Voxelwise statistical analysis: The Automated Registration Toolbox was used to perform a Student *t* test analysis comparing patient versus control FA at each voxel, covarying for age and sex. Type I errors (false-positive errors) were controlled for by using the false discovery rate measurement in FSL (36). The false discovery rate is the expected proportion of rejected hypotheses that are false-positive results. A false discovery rate of 0.1 corresponded to a *P* value of .01. Thus, we selected a *P* value threshold level of .01 for our analyses to ensure a false discovery rate of less than 0.01 (1%). As an additional safeguard against false-positive results, we only retained clusters that were greater than 100 voxels (100 mm^3) in size.

Statistical images representing significant group differences in FA are displayed as color overlays superimposed on T1-weighted images from the Montreal Neurological Institute template.

Statistical analysis.—Statistical analyses were performed by using software (SAS, version 9.1; SAS Institute, Cary, NC) by a biostatistician (M.K., with 18 years experience).

Bivariate associations of FA and MD with tests of executive function were evaluated by using the Spearman rank correlation coefficient. Multivariate analyses were performed by using linear regression models on the rank-transformed data. The following predictor variables were considered: FA and MD in each region, age, education, sex, depression, stress, anxiety, tobacco use, and alcohol use. The final multivariate model was determined by using a forward selection procedure. Correlations were considered significant for a *P* value of less than .05.

Table 2

Mean	25.9 ± 6.8 (19–40)	30.1 ± 6.5 (21–40)	.04
Total	32.4 ± 8.3 (19–49)	34.2 ± 9.3 (19–49)	.77
Education (y)	13.9 ± 2.7	15.5 ± 2.9	.11
Stress	6.4 ± 7.9	2.9 ± 3.7	.02
Left handedness*	4 (22)	0 (0)	.05

Table 3

Executive Function Impairment

Function	Patients	Controls	*P* value
CPT errors of omission	3.21 ± 2.91	1.12 ± 2.39	.03
No. of maze trials	17.25 ± 9.94	9.95 ± 6.24	.008
Maze time (sec)	399 ± 200	278 ± 185	.053

Note.—Data are the mean ± standard deviation.

Results

Eighteen patients sustained their head injury during a motor vehicle accident and two as a result of a fall. The patient and control populations did not differ with respect to age, sex, or education (Table 2). Patients had significantly higher levels of depression ($P = .02$), stress ($P = .02$), and anxiety ($P = .01$) than did control subjects.

Patients performed significantly worse on tests of executive function (Table 3). CPT errors of omission and executive maze number of trials were significantly higher ($P < .05$) in the patient group. Patients tended to take longer to complete the executive maze, although significance was not found ($P = .053$).

Voxelwise analysis of FA images helped detect 15 clusters of lower white matter FA ($P < .005$) in 11 patients compared with control subjects, five of which were located in the frontal lobe (Fig 1 and Fig E1 *[http://radiology.rsna.org/cgi/content/full/252/3/819/DC1]*). Mean FA was lower and MD was higher in patients at each of these locations (Table 4).

Scatterplots (Fig 2 and Fig E2 *[http://radiology.rsna.org/cgi/content/*

Figure 1

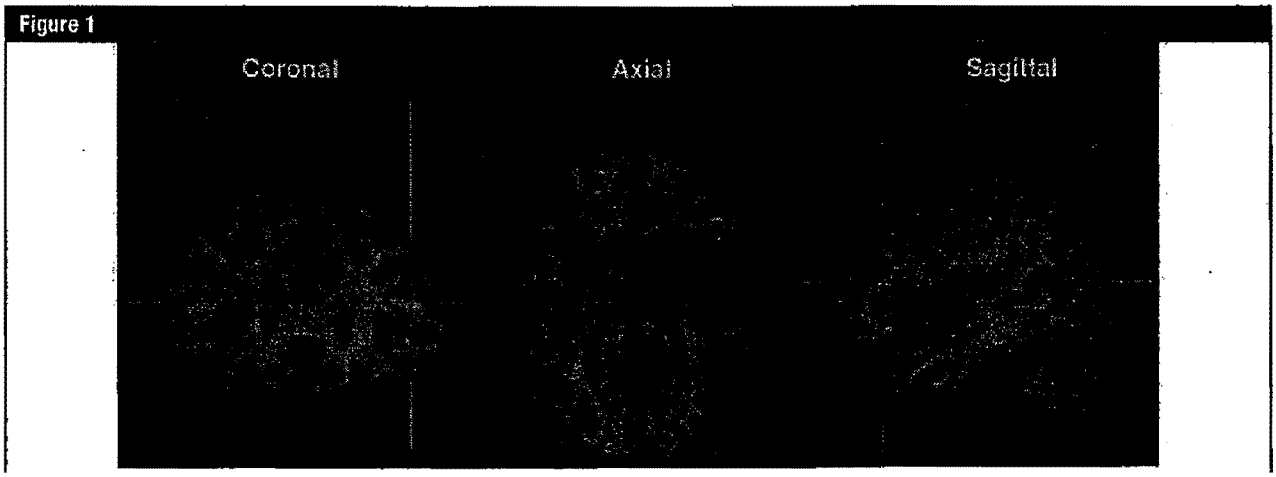

Figure1: Fronlal lobe whitemattef deffclts ln mTBI. Color overlayson template brain imagesshow reglon1wherefrontal whitematter FAislower ln pallent group (P<.01

ful1/2S23081S84/DC1]) demonstrate group dilîerences in FA and executive function between patients and control subjecf.s. The inverse relationship between FA and scores on executive func-, tion tasks indicates that lower FA is as· sociated with poorer executive f\mction performance.

Spearman ranlc correlations demon· strate lrignificant relationships between threeof the frontal FA measurements and tasks of executive function (Table 5). The most strongly COITelated regions are in the white matter subjacent to the Dl.PFC on the left. Although not reaching signifl-cance, the trend at ail locations was for lower FA associated with greater impair· ment. Results or multivariate analyses in-dicate that DLPFC FA predicts CPT er-- rorsofomission and executive maze num-ber of trials (P = .02) as well as Executive Maze time to completion {P = .05). Fur· ther correlation analyses covarying for age, sex, education, substance use, de-- pression, stress, and amrlety in our mul-tivariate analyses were not found to con-fowid the association between dilîusion measures and executive function.

Table 4

	MD	7.69 ± 0.89	7.19 ± 0.20	.007
	MD	8.12 ± 0.58	7.59 ± 0.64	.0015
	MD	6.77 ± 0.36	6.36 ± 0.35	.0011
	MD	7.33 ± 0.49	6.95 ± 0.30	.0048
	MD	8.53 ± 0.91	8.11 ± 0.88	.16

Discussion

Detection of ultrastructuraJ damage by using DT irnaging is a major advance in diagnostic imaging. Severa! studies have supported the capability of FA t.o help identify white matter abnormalities in pa· tients with traumatic brain injury (19,37,38), including mTBI (21-23). As confirmed by our findings, abnormal FA is detected even in the absence of other imaging abnormalities. ConceptuaJly, Joss of anisotropy would be· expected follow-ing injury to axons, ond elegant studies of DT imaging in an optic nerve injury mode! (39) provide a pathologie basis for the inference thàllower anisotropy in. mTBI reflects axonal injury. However, linking 1,-uch evidence of stJ'Uctural damaga 1.0 rel· evant functional consequenœs of mTBI remains the essential link in detennining the diagnostic utility of DT imaging an,d its capability to help select and monitor pa· tients for response to conventional and newer treatments. Onty by bridging structure and function can DT imaging maximaily contribute toward improved outcomes.

Our cohort sustained mild head in-jury. While ail patients had wilnessed closed-head trauma, only two cases had loss of consciousness (or only a few min· utes each). No patients had any gross brain abnormality, including microhem-olThages. Oμr cohort was also carefully spreened to exclude confounding vari-ables. Our findings underscore the fact that real brain in.jury occurs fffter mild trauma and that it is accompanied by brain dysfonction. DT imaging allowed us to_demonstrate the brain's pathologie fea-

tures and coWiect it to functional impair-- ment. It will be important to evaluate these findings longiludinally t.o determine their utility in forecasting long-term impairmenL

Our study demonstrates a structure-function relationship between an important out.corne measure and source ofrnorbidity in mTBJ and aspe· cific brain region. Executive Cunction underpins many of the common tasks necessary for normal functioning at work and in daily life (40). Executive Cunction, whicb is largely depende t on the DLPFC (9,10), is commonly im• paired after mTBI and is a major contribut.or to consequent disability (11,41-43). Our findings identify multiple sites of white malter injury after mTBI but most importandy show association of DLPFC .injury with impaired executive function.

To our knowledge, in the literature, only two reports of patients witb mTBI have assessed a quantitative cognitive measure in coucet't with DT imaging. Kra.us et al (24) found an association of lower FA with impainneut across many cognitive domains, but in a mixed population of mild, moderate, and severe injury and in the chronic phase. More recently, Niogi et al (25) examined a cohort of patients 1-65 months after iqjury. Jm.. portandy, one-third of the subjects hsd œrebral hemorrhage, indicating a degree of injury severity. Impai:red choiœ reaction time was associated with the nmnbe1· relatively large brain ragions. Thefindings of ahnormal brain regions. Both studies employed region-of-interest analyses to of Kraus et al and Niogi et al implicate a relationship hetween cognitive perfor• manœ and FA, but in more severely injured chronic patients with insufficient spatial specificity to identify specific sites of iajury that explain performance deficits.

Patients with mTBl are known to have excess stress, amriety, and depression. Our group also found signif· ioral domains in our mTBI group icant excess morbidity on tbese behav·.

While multivariate analyses did not supporL an independent effect of behavioral deficits on the association of DT imaging abnormalities and injury, such an association cannot be entirely ruled out. However, even the presence of such an unrecognized effecl would uot underroine our inference that frontal white malter injury indexed by using DT imaging is related ioral disturbanœs likely resiùt from io funotional sequelae ofmTBI; behav• brain injury and would thus represent

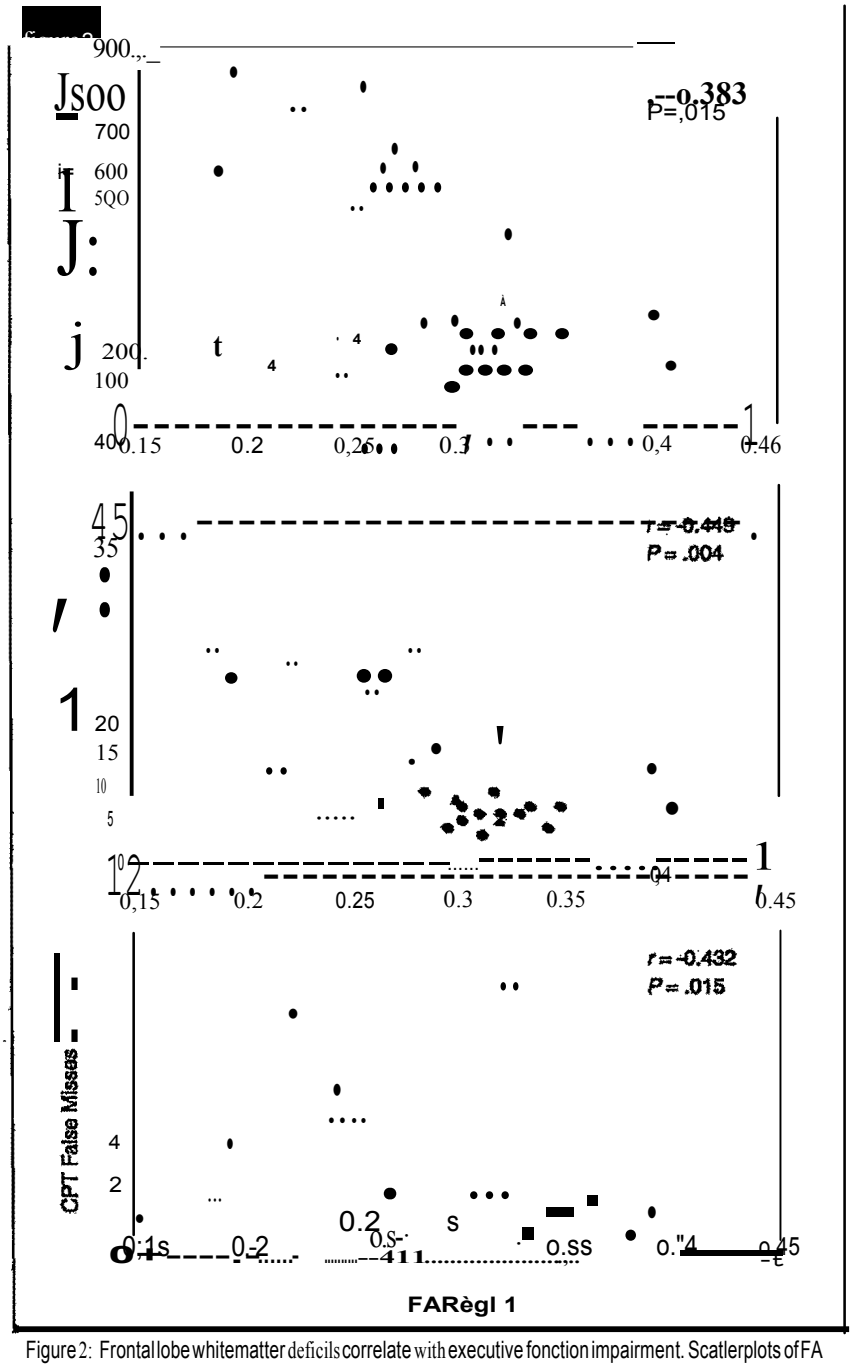

Figure 2: Frontal lobe whitematter deficils correlate with executive fonction impairment. Scatlerplots of FA and executive functlonscores are shown for same frontal lobe location (region 1) asshown in Rgure t HIgher scores on each task indicate decreased performance. Patients (triangles) are compared with contrai subjects (clrcles), indicating lower

FAandworseexecutlve funcUon performance.

an additional functional consequence of pathologie features of mTBl. Further investigation focused on the behavioral outcomes ns primary end points could further clarify their rela·

tionship to DT imaging evidence of pathologie features.

Two major approaches are employed for the interrogation of DT imaging data sets. We used a vo:x.elwise analysis tbat bas heen tested and val·idated in our lahoratory (44). The rationale for this choice is to eliminate observer hies and ma:x.imize sensitivity to small abnormalities that, given pathologie studies, are known to be the primary lesion of mTBI (15,45). Region-of-interest analyses, in contrast, may be biased during region-of-interest drawing or placement and as a result of partial volume effects.

To minimize the drawbacks of mannal region-of-interest placement, voxelwise approaches and many region-of-interest approaches (including that ofl<raus et al [24]) employ coreg·istration of subject images. This approach provides a powerful means for making automated and objective inter-subject and întergroup comparisons, but may still introduce error. This is especially true if distortion is present in the original diffusion-weighted im·ages owing to eddy current or mag·netic suscept.ibility-related effects. Our images were corrected for the effects of eddy currents, and we em·ployed a valideted method to correct for distortion prior to image analysis. To ensure that registration ofdifferent image types (DT and MP-RAGE images) and registration of images from individual subjects would be as accurate aspossible, we l'egistered each sub·ject's eddy current and motion-coITeCted DT images to their own T2·weighted turbo spin-echo images, which were sub·sequently registered to thcir own high-resolution Tl-weighted images and, finally, to a high-resolution Tl-weighted template (the Montreal Neurological Institute brain atlas}. This approach minimizes the potentiel for error in intermodality intersubject registrntion. The approach we employed has heen compared wilh several other methods, including automatic image registretion (AIR), analysis of functional neuroimages (AFNI), and statistical parametric mapping (SPM), and perfonns equal to or better than all (33,34).

Table 5

Correlation of Diffusion Measures with Executive Function

		CPT Omissions		Maze Errors		Maze Time	
Region	Diffusion Measure	r Value	P Value	r Value	P Value	r Value	P Value
1	FA	−0.432	.015*	−0.449	.004*	−.383	.015*
	MD	0.227	.219	0.229	.156	0.174	.282
2	FA	−0.271	.141	−0.142	.382	0.69	.672
	MD	0.008	.965	0.00	>.99	0.036	.825
3	FA	−0.255	.261	−0.397	.033*	0.311	.051
	MD	0.304	.097	0.237	.141	0.223	.167
4	FA	0.269	.143	−0.215	.183	−0.151	.354
	MD	0.99	.598	0.131	.419	0.116	.477
5	FA	−0.395	.027*	−0.346	.029*	0.260	.101
	MD	0.012	.950	0.023	.888	0.020	.904

*Significant correlations (P < .05).

When performing numerous multiple comparisous in a voxelwise anal**ysis** of this magnitude, an important consideration is the occurrence of type I errol'S (false-positive results). To minimize the likelihood of type I error, we computed the false discovery rate (36). This procedure determines the Pvalue at whlch tbe number of !aise-positive results eneountered would be Jess than 1%. Additionally, we required significance at the. voxel level as well as between voxels within a cluster, and we only retained clus·ters of at least 100 voxels in size. These conservative approaches make us confident that our flndings represent true abnormalities.

Our study had limitations. We included patients with common forms of mTBI, but other mechanisms, sùch as a combat-related blast injury might lead to different manifestations of in·jury. We evaluated patients only during the acute phase after injury. Evidence suggests that the Iesions of mTBI develop during the weeks following injury. Thus, our findings may not fûlly reflect Lhe final extent of in·jury. Alternatively, just as most patients with mTBI will recover function over time, abnormalities detccted by using DT imaging mighl evenlually regress owing to regression of aeute abnormalities, such as small amount.s of edema or repair of cytoskeletal injury. Longitudinal studies are required to determine the fate of acute DT imag·ing ahnormalities and tbeir relationship to long-tenn funct.ion. Finally, the nature of the voxelwise analysis approach we employed could possibly introduce bias. As described ahove, **we** think. that we have mitigated Lhis possibility to the greatest extent possible and that our approach is Iikely to be more sensitive and specific than oth·ers.

The imaging diagnosis ofbrain injury at the time of injury am serve two important purposes. F'U"St, it would allow us to document iqjury with an objective mes.-sure and truly ascertain who actually sustains brain mjury following trauma. This could ailow discrimination of true iqjury from other disorders presenting withsim·üar nonspecific symptoms aB well as from malingering symptoms.

The second potential role for DT imaging is to facilitate early initiation of treatment. Although most patients with mTBJ recover function during the months following their injury, as many as 30% retain persistent impairment thatleads to substantial disahility (2). The deficits of mTBl are often not clinically overt at the time of injury and only attract attention weeks or months later (6). lt may be that d ficits are simply not noticed initially, . are misattributed, or are ignored, but an-imal models of mTBI suggest that the pathologie features actually evolve over time (46). On the basis ofthese evolving pathologie features, early intervention ma.y be essentiel to limit.final injury sever-ity. For example. in detecting the pres·

ence ofbrain iajury at the time ofinjury, DT imaging would ellow selection of the subset of patients most likely to bene.lit from cognitive rehabilite.tion therapies. Furthermore, DT imaging could be used as a biomarker in clinicœl trials of nove! therapeuticœ.

In conclusion, we found that lower DLPFC white mat.ter FA in acute mTBI helps predict impaired executive function in these patients. It reroains to be determined, given larger longitudinal studies, whether the DT imaging lindings at the time of injury are in fact predictive oflong-term outcome.

Al.-knowlodgment: The authol'll wish to aeknowledge the thoughtful insights and reeom• mendations of Dr. Anthony Marmarou.

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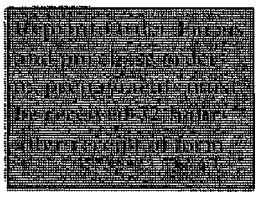

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ORIGINAL ÀRTICLE

Diffusion Tensor Imaging Abnormalities in Patients With Mild Traumatic Brain Injury and Neurocognitive Impairment

Calvin Lo, MD, Kdvan Shifteh, MD,* Tamar Gold, BA,* Jacqueline A. Bello, MD,* and Michael L Lipton, MD; PhD*t:t*

Objective: To determine if diftùsion llm50r imaginz can diffi:cntiate patients with dlronic cognitive impaimtent after mild traumatic brain injury (TBI) from normal controls.

Methods: Ten pa1i1mts with pemistentcognilive hnpairment aftermild TBI wete evaluated at leut 2 yem after injury. FractiOllllll anisolropy (FA) and apparent diffilllion coeffieient (ADC) were measuml at white malter regio!lll susceptl"ble to axonal injury after TBI. Cœnparison was made to 10 nonnaJ controla.

Results: Fractional anisotxopy wa11 significantly lower (4.5%; P''' 0.01} and AOC higher(7.1%; P-0.04) in patiems at the let\ side of the genu of the cmpus callosum. The mild TBI gmup also demonstrated **a s.ig**-nificant increase in FA within the posterior limb of the intemal capsule bilaterally (left, 5.1%; $P =$ 0.03; right,. 1 .9%; $P =$ 0.04).

Conclusions: These results dCIJIODSll'ate low ·FA and higb AOC in the geuu of the corpus callosum of mild TBI palients with persistent cognitive impainnent, suggesting tbat pemument white malter ultm-stradul'al damage OCCUI'll in mild TBI, and tbat sucb damage ,may be associated witb persistent cognitive disability. Further longitudinal studies are WBillllllted to elucidate the full importance of the findings.

Key Words: traumatic bnûn !ajury, diftùsion lmlsor imaging, cognitive impairmcnt

(J Comput Assist 'lbmogr 2009-,33: 293-297)

Traumatic brain injm:y (1131) is a major cause of morbidity and mortality in the United States. An estimated J.*S* million Americans sustain TBI each year, and 80,000 to 90,000 of tbem will experience long-term disability.[1] The US Centers for Disease Control defines mild TBI asa head ûtjuty resulting ftom blunt trauma or acceletation or decœleration forces where there is transient impaired consciousness, dysfintction of memory, or neuropsychological dysfunction. Reports indicate tbat mild injuries account for as muchas 7S% ofall TBL1.2 However, the prevalence of TBI is likely to be much higher; patienls ma.y not seek medicaI attention because the injury is *so* mild, and initial symptoms are few and nonspecific. Prior studies have demonstrated that 3 months isan accepted tirne frame for the resolution of mild TBI-related symptomsM Nonetheless, a signfficant number of mild TBI patients will develop persistent cognitive impainnent in themonths and years after injury. Prior studies of mild TBI have estimated that up to 30% of patients will suffer long-term cognitive, psychiatrie, or behavioral impairment.,._,, Despite the significant number of patients who will have long· tenn cognitive impairment, there is currently no method to identify th.ose at risk for a poor outcome. Barly identification is crucial because it bas been .shown that early rehabilitation after TBI ma.y improve clinical outcome.[9 10]

Alth.ough conventional computed tomography (CI') and magnetic resonanœ imaging (MRI) can detect inlracamia.l hematoma andpetec:hial hemorrhar, after mildTBI, most often. conventional imaging &; normal.1 Such normal imaging find. ings are discordant with. histological 81.Udies whete axonal dmmure is a common finding after mild, moderate, and severe TBt [1]l. [13] Ditlùsion-weighted MRI is a technique that quantifies motion of water molecules. The role of diftùsion-weighted MRI in TBI bas been studied, but results have been noospecific. Both increases and decreases in diffusivity, measured as the apparent diffusion coefficient (ADC), have been reported at locations known to be affected by diffuse axonal injury.[14] ! This variability bas been a.ttnbuted tovasogenic and cytoxic edema in the acute and subacute phases of injury.16 In the chronic phase of repeated head injury, increases in the average bmin ADC have been reported in professional boxeis.[17]

Diffusion tensor imaging (DTI) is a relatively new technique used to detect white matter abnormalities that may not be discœrruôle on conventional MRI. Diffusion tensor imaging chaxacterizes the dilection of movement of water molecules. In white matter, the parallel arrangement of axons and fibers leads topreferentiat diffusion parallel to the long axiso of the fiber. with restriction of diftùsion across the fiber. After injury, alteralion or disruption of the axonal tnicroarchitecture removes the anatomical feature conferring a preferential direction of diffusion.. As a result, more random direction ofdiffusion will bedetected atthe siteofinjury. Fractional anisotropy (FA) quantifies the degree to which the diffusion of water is unidirectional. High values of FA indicate unidirectional diffusion typical of normal white matter structure. Low values of FA indicate random direction of dillùsion, consistent with white matter injury. Previous studies have demonstrated Iow white mat.ter FA after TBu [h]u However, most of these studies assessed patients with moderate or severe TBI durlng the acute phase of injury.[11]19

Our objective was to study a group of patients with persistent cognitive impairment in the chronic phase of mild TBI to detennine if DTI oan differentiate these patients from normal subjects. We hypothesized that decreases in FA and increases in ADC would be present in TBI patients withln white matter regions known to be susceptible to a:xonal injury after TBI.

METHODS

Subjects and Design

The study comprised a review of MRI scans perfonned in 10 mild TBr patients (Table l} and 10 control subjects. Ali

and Une Cen1er for Advanced Brain Imaglng, Tue Nathan S. Kline lnstitute From the •0epartments of Radiology, tPsycbiatty and Bebavloral Sciences, Monœfiore Medical Centerand Albert Bwtem Collcgc of Medicine, Bl'Ollll, for Psyçbiatric Researcb, Orangeburg, NY.

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TABLE 1. Patient Characteristics and Neuropsychological Deficits

Demographlcs (at Jnjury)				Tüne From lnjury, yrs		Neoropsychological Domains				
Subject	Sex	Age	**Mechanism**	Neuropsycbology	MRI	Language	Memory	Attendon	Executive	**Sensorimotor**
	M	46.3	Fall	7.5	10.2	XX	XX	**XX**	**XX**	X
2	F	20.2	MVA	1.2	6.7	Intact	Intact	X	**X**	Intact
3	M	34.6	**MVA**	3.3	3.8	X	XX	XXX	XXX	Intact
4	F	51.2	**MVA**	8.5	9.3	Intact	XX	XX	XX	Intact
5	F	45.8	**MVA**	7.8	10.1	Intact	XX	XX	**XXX**	Intact
6	M	41.4	MVA	9.3	10.8	Intact	XX	XX	**XX**	**X**
7	F	37.0	**MVA**	3.5	6.1	Intact	XX	XXX	XXX	Intact
8	F	38.6	Fall	1.6	2.6	Intact	X	XX	**XX**	Intact
9	M	28.2	**MVA**	5.8	8.1	Intact	XX	XXX	XXX	Intact
10	**M**	38.3	**MVA**	6.0	6.1	**X**	XX	X	**X**	Intact

Demographic chaec:teristic:sof the patient groupatthe tüneof injuxy and thetünefrom injuty to neuropsychologicalevaluation and MRIareshown. Deficits on each of the *5* major neuropsychological domains are shown, graded as mild (X), mode:rate (XX), severe (XXX), or intact. based on the impression of the evaluating nemopsychologist

F indicates tèmale; M, male; MVA, motor vehicle accident.

institutional review board. Mild TBI patients were referred for aspects of the study were approved and supervised by the local M1U by a treating physician to evaluate for structural brain abnormalities that might ex plain symptomatic cognitive impairments due to falls and motor vehicle accidents. All patients were evaluated by a physician, and each patient demonstrated a Glasgow Coma Scale score of 13 or higher at the time of injury. None of the patients required hospitalization at the time of injury. Of the patients who had CT and/or conventional MRI at the time of injury, the results were normal. Ail patients developed pexsi stent cognitive impairment several months after the injury, with deficits including memory, attention, impulsivity, executive function, and personality changes. The diagnosis of cognitive impairment due to mild TBI was made during a clinjcal neuropsycbological examination in each case. The neuropsychological examinations were not standardized because patients were evaluated in the comse oftheir clinjcal workup by different neuropsychologists; patients were not administered the same test components in each case. Nevertheless, impairments were determined based on 2 or more standard deviations less than the mean (based on the normalized *z* scores for each impairment and classified each subject's impairment on eacb of the *5* major neuropsychological domains (verbal memory, attention, executive function, and sensorimotor) as intact, mildly impaired, moderately impaired, or severely impaired. Patients were referred for imaging more tban 1 year after the injury due to their persistent neurocognitive impairmenl Time from injury to neuropsychological evaluation and MRI is shown in Table 1. Ten age- and sex-matcbed control subjects (5 men, *5* women; mean age, 44 yeals; range, 18-54 years; SD = 10.9) were recruited for the study. The controls were patients referred for MR1 due to headache and had no history of head trauma.

Image Acquisition

Magnetic resonance imaging was performed on a 1.5-T system (Signa Excite MR/i; GE Medical Systems, Milwaukee, Wis). Pulse sequences included a 3-plane localizer (excitations, l; 22 x 22-cm field ofview [FOV]; 256 x *256* imaging matrix; 4-mm section thickness with a 1-mm gap), sagittal 3-dimensional fast spoiled gradient ecbo (repetition time [TR], 7.6 ms; time to echo [TE], 4.2 ms; excitations, 2; 30-degree flip angle; 26 x 26-cm FOV; 256 x 256 ima ging matrix; 1-mm section thickness), sagittal fast spin echo (TR, 550 ms; TE, 20 ms; excitations, 1; ecbo train, 3; FOV, 24 x 24 cm; *256* x 224 imaging matrix;: 5-mm section thickness with a l-mm gap), axial fast recovery fast spin ecbo (TR, 4350 ms; TE, 120 ms; excitations, 1; echo train, 16; FOV, 26 x 26 cm; *256* x 192 imaging matrix; contiguous 5-mm sections), axial fluid-attenuated inversion recovery (TR, 800 ms; TE, 120 ms; excitations, 1; delay time, 2250 ms; FOV, 22 x 22 cm, 256 x 224 imaging matrix; 5-mm section thickness with a 1-mm gap), axial gradient echo (TR, 750 ms; TE, 17 ms; excitations, 2; 15-degree flip angle; FOV, 22 x 22 cm; 256 x 192 imaging matrix; 5-mm section thickness with a 1-mm gap), and coronal fast spin echo (TR, 3155 ms; TE, 104 ms; excitations, 2; echo train, 17; FOY, 23 x 23 cm; 512 x 224 imaging matrix; 5-mm section thickness with a 1-mm gap).

Whole brain diflùsion tensor echoplanar imaging was performed using 25 noncolinear directions and *ab* value 1000 s/mrri2. Echoplanar imaging parameters were TR, 8700 ms; TE, 89 ms; excitations, 1; FOV, 26 x 26 cm; 128 x 128 imaging matrix; contiguous 5-mm sections.

Image Analysis

In ail patients, cçnventional MR1 as well as FA and ADC images were reviewed by 2 Certificate of Added Qualification-certified neuroradiologists to identify hemorrhage or other evidence of gross brain pathology. Any discrepancy between the 2 intexpretations was resolved by consensus.

Images were analyzed off-line on a LINUX workstation running the Functional Magnetic Resonance Imaging of the Brain (FSE) software package. Two investigators blind to the group assignment (patient or control) drew regions of interest (ROis) on the BO images using the FSLview module of FSL. Polygonal ROis were placed in the genu and splenium of the coxpus callosum, posterior limb of the intemal capsule, and in the pontine tegmentum. Region of interest placement was supervised by 2 Certificate of Added Qualification-certified neuroradiologists. For eacb structure, ROis were placed on both rigbt and left. Semples of the locations of Rot placement are shown in Figure 1. Anatomical landmarks determined the shape and size of the polygonal region of interest in each case. Care was taken to exclude adjacent gray matter and cerebral spinal

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FICUR.E 1. Reglon of Interest placement on an **FA** Image: ROI markets (white wlth black outline) were placed in the genu and splenlum of the corpus callosum and the posterior llmb of the Internai capsule. Region of interest markers were also placed In the pons (not shown). For darlty, the **ROIs** are shown superimposed on an FA Image but were actually drawn on the BO Image.

fluid. Average FA and ADC were computed for each ROI using the AVWmatbs module of FSL

Statistical Analysls

Student *t* test for nonpaired data was used to compare mean FA and ADC extracted fi:om eacb ROI between subject and control groups.

RESULTS

Table l reports demographic features of the patient group. lime fi:om injury to neuropsychologicalevaluation, and MRland severlty of neuropsychological impairment On theconventional **MRI** sequences, suggestion of a small focal area of lobar gliosis was present in l of the subjects. No other abnonnality and, specifically, no evidence of hemorrbage were found in the remaining subjects. V ISual assessment of the FA and ADC images disclosed no abnormality. lntergroup differences between the controls and subjects in mean FA and ADC for each ROI are summarized in Tables 2 and 3, respectively. The TBI group demonstrated a 4.2% absolute reduction in FA within the left side of the genu of the corpus callosum compared with the control group. This finding was statistically significant ($P = 0.04$). The corresponding mean ADC of the TBI group at this toca. tion demonstmted a *6:r/4* increase when compared with the control group, wbich was statistically significant ($P = 0.03$). The mild TBI group also demonstrated a significant increase in **FA** within the posterior limb of the internai capsule bilaterally (left, 5.1%; $P'''' 0.03$; and rigbt, 1.9%; $P = 0.04$).

TABLE 2. Fractlorial Anisotropy (Mean ± SD) for Miki TBI Patients and Controls

Location	Patients	ControJs	*p*
Genu(L)	0.737 ± 0.086	O.772 ± 0.045	0.01
Genu (R)	0.743 ± 0.114	0.743 ± 0.054	0.41
Internai Capsule (L)	0.700 ± 0.094	0.666 ± 0.032	0.03
Intemal Capsule (R)	0.687 ± 0.088	0.666 ± 0.032	0.04
Splenium (L)	0.800±0.091	0.780±0.056	0.23
Splenium (R)	0.811 ± 0.097	0.796±0.065	O:J.7
Pons(L)	0.524 ± 0.112	0.532 ± 0.074	0.39
Pons (R)	0.514±0.117	0.515 ± 0.065	**0.48**

L indicates left: R, right.

DISCUSSION

Our results demonstrate a significant decrease in FAwithin the genu of the corpus callosurn in patients with persistent cognitive impainnent after mild TBI. Although expert visual assessment of FA and ADC images (Fig. 2) revealed no qualitative diff'erence between the control and trauma patients, highly significant quantitative intergroup differences are present. These results agree with previous studies showing low FA after TBI.[1] [1;23] However, onlv 2 of the pubtished studies evaluated subjects with mild TBI.[1'o,2t] Additionally, those studies that did include subjects with mild TBI included patients with s!ructural bt'ain abnormalities on CT or MRI consistent witb TBI or diffuse axonal injury. The prevalence of these gross abnormalities inprior studies. including peteclùal hemonbage, contusion, or hematoma. suggests that thepatients studied had moresevere TBI than our study population. The extremely mild degree of TBI in oursample may bewhy significant reduetions in FA were not in other areas known to be susceptible to DAI.[24,25]

Persistent cognitive, psychiatrie, and behavioral dysfunction after TBI bas been we1l descrlbed in the literature. Nonspecific and variable sympto:ms reported bypatients after trauma are often categorized as postconcussion syndrome. The subjective and nonspecific nature of the symptoms bave led some authors to question whether mild TBI is in fact a real cognitive disorder.[2,6,;l,7] However, ex.isting evidence strongly indicates that up to 30% of patients ex.periencing mild TBI develop neurocognitive impsinnent related to the initial injury. Although acute and subacute changes in FA after TBI have been studied, our study is the first to address the important problem of chronic cognitive impairment after mild TBI. Our study shows tbat DTI

TABLE 3. Apparent Diffusion Coefficient (Mean ± SD, $10^{-5} cm^2/s$) for Mild TBI Patients and Controls

Location	Patients	Controls	*p*
Genu(L)	0.673 :t 0.100	0.614 ± 0.059	0.04
Genu(R)	0.618 ± 0.106	0.()36 ± 0.061	0.22
Intemal Capsule(L)	0.541 ± 0.720	0.535 ± 0.019	0.31
Intemal Capsule(R)	0.526 :t 0.069	0.583±0.012	0.44
Splenium (L)	0.577 ± 0.090	0.600 ± 0.052	0.17
Splenium (R)	0.584 ± 0.089	0.583 ± 0.060	0.48
Pons (L)	0.547 ± 0.067	0.555 ± 0.052	0.33
Pons	0.554 ± 0.064	0.560 ± 0.043	0.39

L indicates Jeft: R, right

can be used to detect differences between patients with cognitive impahment after mild TBI and controls.

It is generally established that reductions in FA·in anatomical ragions prone to TBI are due to changes in the microarchitecture that restricts movement of water molecules across white mat:ter tracts. However, in our study of patients with chronic TBI, it is unclear why a persistent reduction of FA in the genu of the corpus callosum in pa.rticular was identified, whereas other regions also known to be susceptible to axonal injury such as the splenium of the corpus callosum, intemal capsule, and pons did not demonstrate a statistically significant remJci:ion. One possible explanation is that, in some ragions. FA nonnalized during the time between initial injury and the DT1 examination. Using an animal impact-acceletation model, B8lZO et al[16] reported nonnalization of AOC 4 weeks after TBI. However, the mecbanisms relevant to our study may be different because the initial changes in ADC in the study of Barzo et al of moderaœ/severe TBl were due to vasogenic and cytoxic edema. In our study, however, subjects were imaged well beyond the acure phase of injury wben edema would be present. Altematively, due to the small sample size and the inherent limitations of ROI analysis, our study may not have been powered to detect a significant effect in the other anatomical regions prone to TBL

Interestingly, FA was bigher in patients than in controls in the internai capsules. No associated abnonnality of ADC was fuund in this region. Although the mechanism leading to increases in FA beyond that found in normals is not entirely clear, such findings bave been descrlbed in other white matter disorders; an inerease in FA greater than normal may be a manifes.. tation of recovery Crom injury.211.29 Altematively, with loss of a subset of corticospinal tract fibers, but preservation of other fibers such as in Wallerian degeneration due to lesions in the cerebral hemisphere, FA might be enhanced.. In such a scenario, the extmcellular space would be increased but with preserva.tion of a linear arrangement of cellular structure (remaining axons) and consequent greater facilitation of diffusion along the direction of the liber. Measun:ment of the component eigenvalues of the diffusion teusor might shed light on this possfüility. Finally, it is plausible that the increase in FA retlects a compensa.tory altetation related to reduced FA in the left side.of the genu of the corpus cal l osum. A longitudinal study may be helpful in addressing these possibilities.

A linûtation of this study is its small sample size. Our findings need to be replicated in a larger group. In addition, the study sampJ.e is somewbat heterogenous with ditferent mecbanisms of TBI, varying time intervals between injury and the DTI examination, and varying degrees of cognitive iropairment Nonetheless, the fact that we did detect significant group differences, despite these limitations, suggests that signi:licant abnormalities are lilœ1y to be found in a future study of a larger and more homogeneous patient group.

The ROI analysis method used in this study is similar to ROI analyses that bave been described inail prior reports of DTI in TBL lt is important to reeognize that the ROI approach canies several limitations. Placement of the ROI, even by a trained and blinded observer as in our study, inevitably introduces observer bias. Furt:hermore, due to the low resolution of the FA images, it is extremely diflicult to be sure that ROis are placed precisely. Finally, partial volume effects are inevitable whenever an ROI is placed. Given the very small sû:e of TBI lesions, one important consequence of such partial volume effects isa Jossofsensitivity to small lesions. Although we were extremely careful to exclude adjacent CSF and gray matter, partial volume effects can sti1l bias the mean FA within the ROI. We used a relatively large ROI based on the appeaxance of the anatomy on the BO images. This approach facilitates standar<lization of ROI placement and avoids the potential for bias if ROls were dtawn on the FA and ADC images. The ROI metbod, however, may decrease

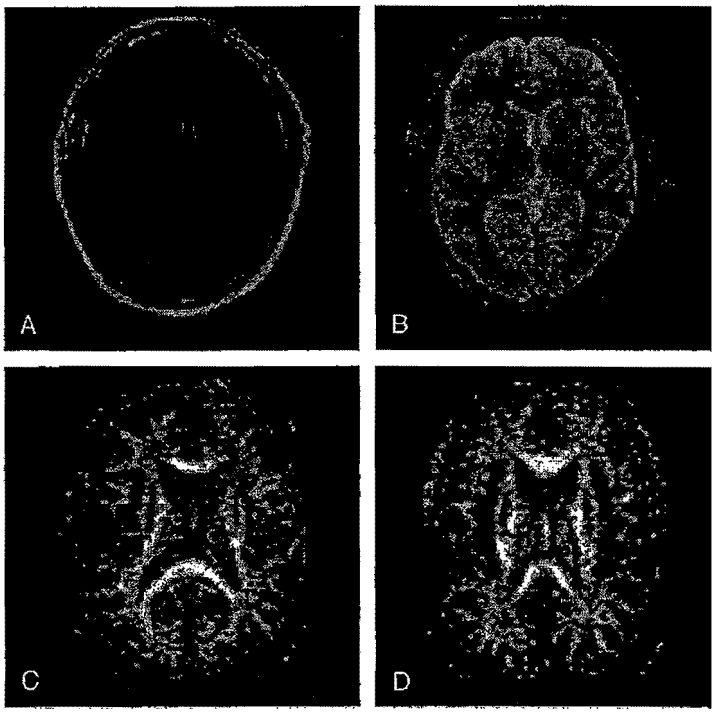

FIGURE 2. Image appearance ln mild TBI (A-C} and controls (D): Fluld-attenuated Inversion recovery lmaging (A) and gradient echo (B) image from a mild TBI patient show no signal abnormallty (D) are quantitatively similar, with no visual orevidence of hemorrhage. Fractional anisotropy Images in the mild TBI patient (C) and contrai evidence of white matter lesions.

sensitivity to small lesions even where tbere is a significant diffe.rence between groups. Voxel-based analyses may be more sensitive and can help better delineate the full extent of injmy.

Finally, a prospective longitudinal atudy with standardized neurocognitive testing and imaging at the time of injury and at set intervals post injmy is needed to chamcterize temporal change inFA and its relationship to neurocognitive impairment. Sueh a design may separate subgroups of TBJ patients who develop pemistent neurocognitive impainnent and those who recover and remain symptom-free. The resultll of the pœsent study indicate that sueh a longitudinal study is lilœly to be informative.

CONCLUSIONS

The patient group with persistent cognitive impairment after mild TBI was distinguished fmm matched controls by evaluating themeanFA and ADC within regionsprone toaxonaJ injury after ttaurna. Tbese results build on prior studies demonstrating FA n:duction in sirnilar regions immediately after trauma. The present findings are important in that they addn:ss a serious adverse outcome of a very common disorder. cognitive impainnent due to mild TBL Longitudinal studies will be mquired to confirm and elucidate the full importa'nce of our findings. which suggest that pennanent white ttraUer ultrastructural damage occurs inmildTBI, and that such damagemaybe a substrate of persistent cognitive disability.

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CONTINUED

Diffusion tensor unaging

A biornarker for mild traumatic brain injury?

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Erin O. Bigler, PhD
Jeffrey J. Bazarian, MD, MPH

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The most common yet most conuoversial neurologie injury is mild tmumatic brain injury (mTBI), which may have an anni.uù incidence rate as high as 653/ 100,000.[1] Most mTBI cases have a po.,itive outcome; the controversy exists in whether lasting sequelae occur. Typically, the neurologie eramination is negative other than subde cognitlvè complaints and subjective symptoms (e.g., headache, dizziness), as is conventioruù brain imaging. After head injury, the absence of definicive findings and a Glàsgow Coma Score at or above 13 is the standard thar defines mTBI.

There bas been an active search for biomarkers of mTBI for dinical or research plll'p(ISeS. Conventloruù neuroimaging may reveal contuSion or hemorrhage--referred to as complicated mTBI--'however, such 6nd.ings occur in fewer than 20% of mTBI cases evaiuated in an emergency depamnènt,l minimizing its ucility. CNS-related serwn proteins have been identified *in* mTBI, but have proven unsuccesi;.. fulas bîornarketS. Variablessuch as loss ofconsclousness (LOC) and duratlon of pœttraumatic arnnesia. (PT.A) are important in assemng mTBI and its outcome, but outside ofaresearch *setting,* LOCand PTA are difficult roidentify and verify. The ahove-mentioned physical or neurocogni.tive symptoms amiociated with mTBI are nondescript, so t:hey too Jack specificity as objective markets. Without an aœurate and reliable biomarker of injury, itbas been dlfficult fur cllnicians and reseatche.cs to dearlydefine mTBI, study itseffi:as, and empirically address the controveœy.

In this issue of *Neuro* , Mayer et al.' present diffusion tensor imaging (DTI) find as a potential MRl biomarker in mTBI patients with otherwise normal i.maging, Dn is partlcularly sensitive in as--sessing white matter (WM) microstructure, even in parenchyma deemed normal. The sensitiviry of on for WM injwy makes it especially important in understa.nding mTBI, given the general absence of imaging ahnorma.litles and the susœptibility of WM injuiy from trauma. There are severa l common DTI mettics, with &actional anisotropy (FA) being the most &equently reported. FA ranges from O to 1, where O represeins maximal· isotropie difmsion of water (e.g., free diffusion in perfect sphere) and 1 represenm maximal anisotropie diffusion, i.e., diffu. .sion of water in single direction. Diffusion anisotropy varies across WM regi.on&, likely reflectlng differences in œllular membrane integrity, fi.ber mydinatlon, fiber diameter, and directionality. Elevated or reduced FA vàlues likely reflect different types of WM ahnormalities. For example, devated FA be--yond normal values in rnTBI may reflect an inflammatory response such as axonal swelling or cytotoxic ec l ema.•.s In contrast, lower FA may indicate axoruù degradation and discontinuitles with exœss water be-r:ween rracts or in perivascular spaces, which may also occur in mTBI.[6] In their mTBI sample, Mayer et al. observed elevated FA, inrerpreted as a result ofsub-acute cytotoxic eclema, which normalized over 3-5 months. Since conventioruù imaging was negative, the observed FA changes were nota result of visible rraumatic lesions. lmporrantly, the normalization of FA was associated with the l of mTBI symptoms, matching a typical recovety cimefram.e. From a pathologie perspective, subde mTBI induced WM changes, in the absence of macroscopic lesions, malœs sense as a mechanism associated with symptoms. Traumarie axonal injuries evolve and may result in avarietyofchanges in axoruù integrity ranging ftom full restoration to cell death.7 on appears to be sensitive to this range of porentia! axonal pathologies.

The newness of the 01 1 approach indic.ares the need for more research. While Mayer etal. identi6ed focal areas of potential axonal swelling. they dîd not apply tractography specifically to assess affected tractll and their cortical projections. Ukewise. longer· term prospective DTI studies from the day of injury

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are needed ro help answer questions about restoration or degene.ration of neural funcrion and how DTI findings re1aœ ro mTBI symptoms and recovcry and to other functional neuroimaging fmdings. A recent study8 demonstrated the use of acuœ pe:fusion *CT* in assessing mTBI outcome at *6* months, aiso in mTBI pariencs with negative conventional Cr. Indeed, the teehnology now exists to use DTI techniques integrated with other neuroimaging methods to examine entire neural networksand their inœgrity in mTBI. Could normal early DTI 6.ndings in mTBI be a marker fur good recovcry?

The Mayer et al.3 study also demonstraœs that traditional neuropsychological measures poorly differentiate mTBI patients from conttols. In a companion artid Mayer et aJ,[9] used functional MRI (fMRI) methods to show difierences in processing speed and allocation of attentional fucus in mTB! paclem:s. EvenMelated fMRI differenœs in the mTBI group occurred as CqJ:)y as 200 msec after stimulus onset, a tlmefuune that cmnot be captured by traditional neuropsychological resring, which measures function in seconds to minutes. Such a lag in measured response time may render aspects of the neuropsychological examination inerfective in differentiating mTBI patients from controls,b although traditionalneuropsychological techniques clearly dif.. ferentiate TBI patients with moderate to severe injuries. If the stibtleties of cognitive impairment assoclated with mTBI cannot be reliably derect<:d by such traditional methods, then neuroimaging modalities, induding functional neuroimaging integrated with D'TI, may be more suitable to detect neurophysiologie differences, including cognitive processing and the outcomes from mTBI.

DTI holds considemble promise as a potential bi omarker of injury that may·assist in classification and tracking of mTBI and its drect:s. The integmtion of functional neuroimaging techniques with DTI will likely add powerful new insights to inform the controversy over mTBI and its sequelae, enhanœ our understanding of its ndiropathologic basis, and provide new insigb.ts into its diagnosis, care, and management.

DISCLOSURE

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A prospective diffusion tensor i aging :study in mild traumatic brain injury

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ABS:TRACT

Objec:tmst Only a hendful of studies e Investlgated thé nature, functional significance,.and course of white matter abnoonalitiasnsociated Withmildtraumaticbraininjury (mTBI) during the serni·acute.stage of Injury. The present study used diffusion tensor imaging (DTI) to Investigate whlté matter integrity and.compared the accuracy of treditlonal anatomie sc:ans,neuropsycholog-ical.testlng, and DTI for objectively classifyingmTBlpatients fromcontrols.

Methods: Twenty·two patients wlth semi-acute mTBI (mean = 12 days postinjuryJ, 21 matched healthy controls, anda larger sample{n = 32) of healthy controls were studied with an extensive imaging and clinical battary. **A** subset of participants was examined longitudinally 3-5 months after their initial visit.

Results1 mTBlpatients didnot differ fromcontrols onclinical imaging scans or neuropsychological performance, although eff.ectslzés were consistent with literature values. In contrast, mTBl pa-tients demonstrated signiflcantlygrèater fràctlo al anlsotropy asaresult of reduced radial dlffu-slvlty in the corpus calfosum and several lèft hemisphere tracts. DTI measures were more accuratethan tredltlonial olinioel measures in clessifylng patients from controls. Longitudinal data provided prellminary evldence of partial normalizatlon of DTI values in several white.matter tracts.

Condusiowu Cun:ent findings of wRitematter abnormalities suggast that cytotoxic edema maybe present.dtJringthe semi•acut phase of mildtraumat!c braln injury (mTBI). Initial mechanical dam-age·to axons dlstupts ionic homeostasis and the ratio of intracellular and extracellular water, primarily affecting diffusion perp ndicu r to axons. Diffusion tensor imaging measurement may have utility for ebjectiVl!lty.classif.yll'lQ mTBI, and may serve as a potential b!omarker of recovery.

Neurology® 2010;74:643-650

GLOSSARY

AOC apparent diffusion cuefflcîent; CC.. oorpus IOSiJl'l'I; CC!., cortical Impact injury JJ;@I; CR"' corona radlata; DTJ = diffusion tensor imagtng; l:C = ellternal capsule, **FA**= fractlo!11ll anisotropy; FPI "'fluld percussion injury mode!; HC = healthy controls; IC "" internai capsule; JHU ., .Jôh!'l& Hopkins Unlvarslty; **MANCOVA** = multivariate analysls of covariance; mTBI = mild traumatic braln"11UrY; **RD**"' radia!diffl.!IMty; **ROI**'" rOOion of Interest; SCR = super1or corona rad'iata; **SLF** = superior longltudlnal fa11elculus; UF.. uncmate l8eclculus.

Complex cognitive processes such as attention, executive functions, and memory depend on intact white matter tracrs among frontal, parietal, and media! temporal lobes,1 which are likelr disrupted following mild traumatic brain injury (mTBI). Histologie evidenœ of white man changes have been observed in both human autopsyl and animal[4] srudies of mTBI. Although traditional neuroimaging sequences (i.e., T1 and T2 weighted imaging) are typically insensi-dve to d1ese puta.tive white mattet changes, diffusion rensor imaging (DTI) .is capable of measuring white matter pathology with histologic correlates in animal models of injury.

The majoriiy of hwnan mTBI studies have been cross-sectional in nature. examining se-lected patients (i.e., those with persistent complaints) during the chronic (e.g., after severaJ

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Supplemental dataat

From Th Mind Re$ean:h Newrork (A.R.M.,J.L, M.V,I\f., C.G.. J.P.P., R.i\.Y.J. Albuquerque, NM: and ,menu ofNeurology (A.R.M., J,P.P.), Emcrgency M<diclne (D.D,). Pisydtology (C.G., lU.Y.), and Pathology (R.R,), Univonity ofN""Mexico School of Medicine, .Albuquerque,

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months or years) injury pbase.6-9 This can be problematic *as* the majority (80%-95%) of mTBl patients fully recover from their injuries within 6 months.io.n An initial DTI study on *5* unselected patients (i.e., all eligible patients) œported reduced fractional anisotropy (FA) in the corpus caUosum {CC), interna) capsule (lC), and exremal capsule {EC) within 24 hours ofil!jury. ri More reœnt studies focusing on unselected patients in semi-acute phase of injury have reported mixed findings. with 2 adult studies reporting reduced FA[3,14] whereàs other adolescent[15] and adult[16] studies have reported increased FA. Inglesc et al.[13] reported reduced FA in the CC and IC at approximately 5 years postinjury in an adult sample, with nosignificant **FA** di.fferenœs between chronic and semi-acutely injured patients, suggesting limited recovery. At1other study examining mTBI patients longitudinally (2 out of 5 patients srudied) reported evidence of partial FA normali7.ation at 1 month.[12]

Addicionally, few studies have exatnined potential differences in axial diffusivity or radial diffusivity (RD) following roTBI in cither selected or unselected populations.[1,2,15,17] The distinction between axial diffusivity and RD is critical given t:hat FA is determined from these measurements. and each is putatively assodated witb different pathologies. Specifically, animal models of retinal ischemia suggest t:hat axial diffusivity corresponds to axonal pathology whereas RD measures myelin pathology.[18] Mouse models of TBI indicate tbat axonal pathology (reduced axial diffusivity) is more pronounced in the arute phase of in*jury,* foUowed by both pseudonorrnalization ofaxial diffusivity values and increased involvement ofdemyelinatingprocesses (RD) and edema.[19]

The present srudy examined FA, axial diffusivity, and RD prospecrivdy in an unselect:ed sample of mTBI patients. Based 011 previous dinical studies, we predicted t:hat FA and axial diffusivity would be reduced in the CC, IC, superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), and corona radiata (CR} in mTBI patients compare<! to controls in the semi-ocut:e phase of injury (21 days postinjwy) with increased findings in tenus of myelin inœgrity (RD) during the more chronic injurystages.

Table1 Mlld traumatlc braln111,lurypatlentinformation

Age	l.ender	Mecof lii)u1f	.ÀAN	υay,,	
32	Male	CoÛlsk>n/sports	Ill	3	5
24	Female	MVA	ïlr	.20.,.	·..?:0..
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2:1	F81'11ak,	',<	lil	15	14.
24	l'emal!!	Aiî1lault		7	5
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24	Male	Fall	Ill	13	1.3
25	Female	MVA	Ill	19	19
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33	Male	Fall	Ill	20	19
		MVA	lll	14.	11/
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24	Male		IU	10	i<t.
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23	Male	Fall	Ill	17	. .-
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S1	Male	'FallIngobject	Ill	16	is
20	Female	MVA	Ill	14	14

Abbreviatlons: AAN Amerk:an Acaclemy of Neurology; MVA e motor vehide accident; NP - neuropsychologicaltesting.

METH0D$

Partldpants. Twemy-two pam:nts (recruiœd from the University Emei:gency Department) with mTBl and 21 se:c-, age-, and educatio1Ml'lIltched c;controls participaœd in an ongoing study. DT!dam from an independenc sample ofhealthy conuob (HC) were also collected.

AU p;uienlll experie11ced a cll)se(j head injury dting in an :tlteradon in mental starus (sec table l} and were ev,,luared days posoinjury; imaging examinatiou '" 12.50 -'- 5.40 da:., within 21 days ofinjury (dmical examination = 11.75 ..t: 4.97 postlnjttry), The majority (85%} of patients complered the imag·ingandclinical prococols wirhin 3 d2ysofeadtother. Inclusion criteria for the rnTBI group were based on th American Con·gress of Rehabilitation Medicine {Glasgow Coma Score of 13-15, I05S of consciousnw <30 minures, posttraumotic amnesia <24 hou.rs). mTBI partlclpanœ and controls wrn:: exduded if there was additional history of head injuries with more than 5 minutes loss ofa,nsciousness or any head injury wirhin the last year, learning disorder, attention deficir hyperacrivity disorder, or a history ofsubstanœ or alcohol abuse,

Standard protocol approvaù, regiurations, and patient c::omen._. Infurmed consent was obtained from all participants according to iru.tltutional guldelines at the University of New Mexico.

Clinical assessment. Similar to previous studies,"' composite indices were œlcub.ted fur attention, working memory, proœss-

\.

Table2	Demographlc and cllnlcal mea8Ul'ell forvWt:1					
	Mllîf :.					
	br		Heei		p Value	Cohen's d[a]
		7.39	26.81	6.68	0.77	0.09
Age	27.MI..	2.46	13.95	2.67	0.30	0.32
..	...:i:'..;;f/t jJ\	37.92	82.84	35.83	0.71	0.12
HQ	'713.l>&.					
:'	;:..}t:iù#iiŒ),:			5.20	0.29	0.35
Attention;	50.éi	-J5.20	52,73			
	'.°: if ?'.%	:f(:5	/\jfj.f(		;;	ô.s!t...
Memor/	49.às	a.:	48-16	s.99	o,13	0.12
PS	\ff. .4	"1 ;				04
l;f'	45.83	5.47	47.91	SAS	0,26	0.34
J'ITAR".	48.25	8.87	53.95	8.34		0.ê7
TOMM				12.4.1	0.77	0,09
Emotlc,{<	Mo	9.i;o•		6..8	0.01	o:éà:
r.àsi-'.}/			.//i{! :}JilJ	i';tr	-0.000	
NBSl..()og"	8,00	6.0		.2(26	P,001	1.14

Abbrevlations: *EF* = executlve fuootlon; HQ"' handedness quotient; NBSl·Som = Neurobehevloral S)'.mi>tô!fl lnventory Somatlc cotnplafnts (Cog "' cognitive compfaints}; PS = processlng speed; TOMM = Test of Memory Malingerlng; **WM** = worklng memory; WTAR = Weclieler Test.of Adult Réading.

° Cohen's disan stlmate of affect size.

bMeens, standard devlatlons, and e:ffect slzes for neuropsychologica! Indices reported follówlng correction for WTAR as covarlate at 51.03.

"Denotes slgniflcant result,

ing speed, cxccutlve function, n1emory, and cmoùonal statm based on pmicipanrs' mean *t* score in eadt of the dotnllins (appendlx e-l on the *Ntmro!ogy®* Web site at www.neurology.org}. Somatic and cognitive (;l)Jnf'lalncs were aJso -ed along with estimai:es of ovcrall premorbid cogni«ivc funccioning and effort (nppendix e-l).

MRI and analyses. Tl, T2, and DT! imageit were colkcrcd on a 3-Tesla Siemens Trio scanner (appenàix c-1). nie AFNI software package2 was used ta process and analy.te DTI d.ua ducœd on the genu, spblium, and body of the:CC, ns wdl ns the {appendix e-1). Region of interes1 (ROI) analyses were con- SLF, rheCR, die superior corona mdiara (SCR), the UF, anrl the IC fur both hemispheres based on heJohns Hopkins Unl\'el'$îty and FA) werecalculated for each ROI, as were measures of inter- (JHU) white matter allas." Scaktr mffils (axial diffüsivity, RD, bemispheric variability beiween homologous ldi and right ROI (righr ROI - left ROI)/({riglu ROI + l n ROl]/2) to invesrigace increased asymmeuy *as* a 1ruu-ker of injury. M ulcivariace analyses were used whenever possible ro reduce the number of multiple comparisoos. E!fect mes (Coherîs *d'*, are also reponed as a measnre of diniœl & ignifu:anœ,'

RESUL TS Neuropsychological and clinical measures. A compilation of ail major neuropsrchological and dinical indices is presented in table 2. Resuks indicated an inaease in emotional ($r_{1.!}$ = -3.11; $p <$ 0.05; mTBI > HC), cognitive ($t_{1,...}$ = -4.20; $p <$ 0.001), and somatic ($t_{1.3a}$ = -3.62: $p <$ 0.005) complaintS for mTB! patients compared. to conttols. Estimares of premorbid intellecrual functioning were lower in mTBI patients ($t_{1,37}$ = 2.09; $p <$ 0.05) despite educational matching.

A multivariate anal of covariance (MANCOVA) examining di!ferences in neuropsychological testing using premorbid intelligence as a covariate wa.s not sign.iflcant for group di!fer:enœs. However, effect sizes (table 2) in the clomains of attention, executlve functioning, and memory Wtte of similar magnitude to those reported. in rcœnt meta-analyses on cogni rive deficits in mTBI.

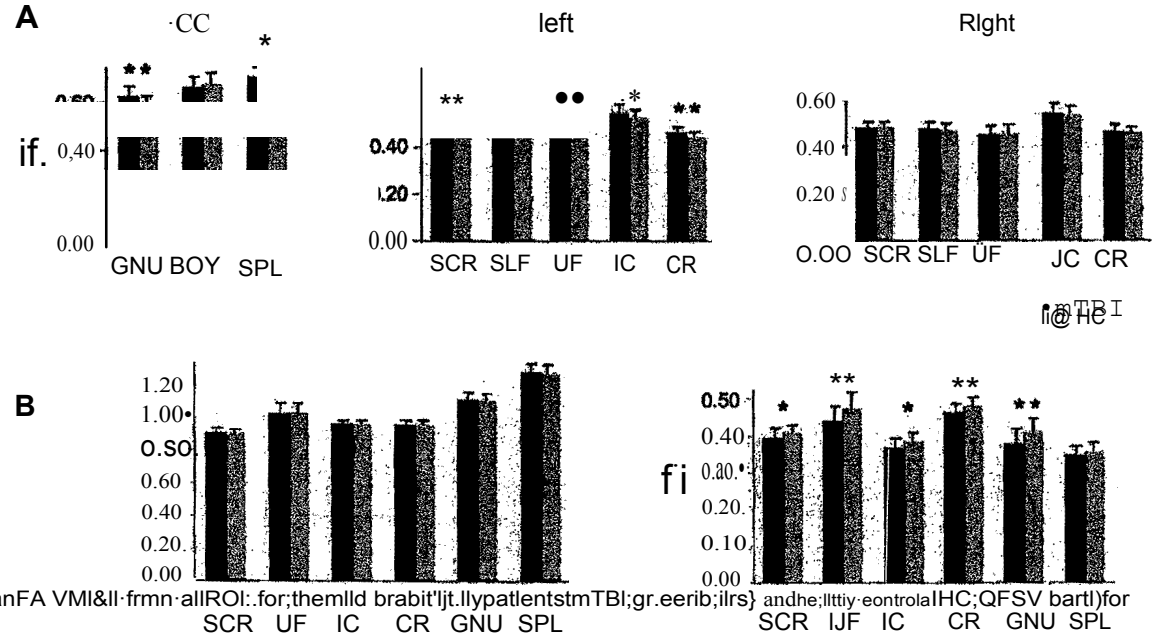
Stmctu.ral imaging data. Anatomie images were limi.ted to Tl· and T2-weighted images. Thcse were fourui to be free of pathology fur both *groups* of subjects *by* a board-a:rtified neuro.radiologist (i.e., ail mTBI patients were classified as being noncompliated).

ROI analyses. Three MANCOV.As were conducted to examine group differences (mTBI patients vs matched controls) in FA values within the corpus callosum and left and right hemisphere ROI (figure lA) with estimates of premorbid intellectual functioning as a covariate. Resulrs indicated. a multivariate effect of group fur both. tµe CC (*Fa,311* = 3.81; $p <$ O.o5) and the left ($F_{5.)4}$ = 2.70; $p <$ 0.05) but not rlght ($p >$ 0.10) hemisphere. Follow-up univatiate t:esrs indicated that mTBI patients had hlgher FA withi11 the genu ($F_{1.38}$ = 7.52; $p <$ 0.01, d = -0.91), left SCR $CF_{1.,;s}$ = 5.54; $p <$ O.o5, d = -0.77}, left CR ($F_{1,38}$ "" 5.47; $p <$ 0.05, d = -0.74), and left UF ($F_{1.38}$ = 6.67; $p <$ 0.05, d = -0.84). Trends were observed for the left IC ($F_{1.->11}$ = 3.69; p = 0.062, d =-J).62) and the splenium {$P_{1,38}$ = 2.9); p = 0.094, d =:: -OS}) with mTBI patients agiùn edlibîting higher FA values th.in HC(li(!('; figure e-l fur oormalized FA histogt.uns).

HC were then compared with a larger normative sample. However, there were no multivariate effects of group for al!: multivariate analyses of variance ($p >$ 0. FO), suggesting that our control group *was* statistically similar to the larger normative sample in te= ofFA.

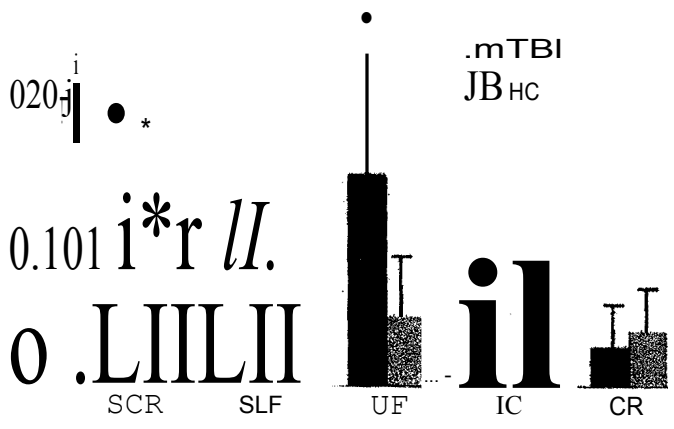
Next, we compared. axial diffusivity and RD values for the 6 ROI that exhibîted significant or trend differences in FA using one-way analyses of covaria11ce (figure IB). There were no signifi.cant diffei.·· ences between patients and controls in œrms of axial diffusivity. In cont111St, RD was lower in mTBJ patients within the genu $CE_{1,...}$ "" 5.09; $p <$ 0.05, d = 0.74), rhe left UF ($F_{1...8}$ = 5.67; $p <$ 0.05, d = 0.77), and the left CR ($F_{1,8}$ = 4.42; $p <$ 0.05, d = 0.66), with trends present in the Ieft SCR ($F_{1,313}$ = 3.58; p = 0.06, d """ 0.59) and !di: IC ($F_{i,38}$ =

f Pfgure1 Fractional anlsotropy (PA) valuelJ nomail reglona of lnterest (ROI)



This themeanFA VMl&ll·frmn·allROl:.for;themlld brabit'ljt.llypatlentstmTBI;gr.eerib;ilrs} andhe;lttiy·eontrolalHC;QFSV bartl)for v1$1t 1,(1') aorrected for dlffJn.prel'i'l(ltbld m.tall!Qence eetlmatelli·QGl:iMkufedthâ,SJeJ'lll,lGNlJ}, b'ôdy.lBOYt aAd splenlum lSJ;!lJ of the (CC), the COl'Oriln'l'làlata(Sœ). thallllf)eflor1 fJijc!iMUIJ(SLF),,theuneil'laté {l:JF},thecoi'.'onamdlata ICRl.80\fthe intemal cçsule lièl..Signlfleal'll:effeèts are·dèooted wltll<loubl& statlètleal:trl!!'ldswlth allll'tgkî CE11 dlffûàivlty lAOI and.radial dlffuslvlfylRDJ .-formTBIpattlimtè aAdHCfornglonsexhlblting. !caldlffé!'e1''1t:&ln FA.For.'thé y,axla, the,unltllofFA eredlimmslonlee,Whereas aidal'Cllffuslvltvand.RDareequlvalent to mm &.

Var!ablllty ln mean fractlonal anlsotrppy fFA) between rlgfrt and Jeft hemisphare ragions of lnterast {ROI}



A measurement of variability in mean FA values between right and left hemispheric homologue ROI for the mlld traurnat!c braln lnJury patienta (mlBI; gl'Mn bars) end hulthy cootrols (HC: g,ay bars} eorrected for dlffumnces in premorbld lntell!ganœ llfltlmatea. ROI radlsta(CR) and the internaicapsule(IC). Sif1'1'1iflc1mteffectsaredénotedwlth doubleasterisks, statlstical trends with a single asterisk.

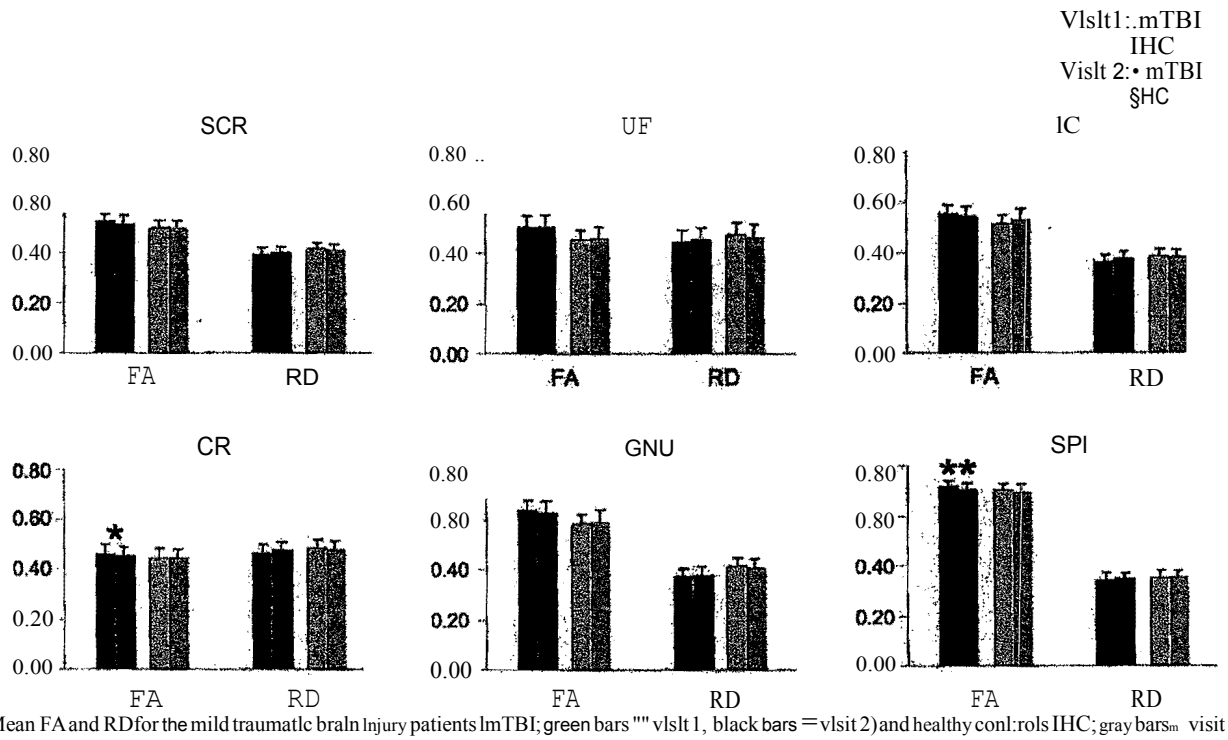
3.')9; $p = 0.053$, $d = 0.66$). Histograms fur the normali7.ed RD data are presented in figure e-2.

Fmally, a MANCOVA (figure 2) comparing variability in FA measurements between right and *left* hemisphere homologue ROI (SFL, IC, UF, SCR, and CR) revealed a groun effect ($F_{5,34} = 4.53$; $p < 0.005$), with univariate tests indicating increased SCR ($F_{1,38} = 15.06$; $p < 0.001$. $d = -1.21$), with variability in patients compared to controls for the a trc11d fur the UF ($F_{1,38} = 3.82$, $p = 0.058$; $d = -0.63$}.

on and clinicat measures. Hierarchical multiple regress.ions were performed on the 6 clinical measm-es with the largest effect si'l.CS (attention, memory, executive functions, cognitive complaints, soma.tic complaints, and emotional complaints) using **FA** from independent variables and premorbid intelligence as the CC and right and left hemisphere ROI as the a covariate. Although premorbid intelligence a<:-counted for significant variancœ in tenus of both attentional and executive functioning, only FA levels in the right hemisphete ($F:i_{,18} = 6.84$; $p < 0.01$) predicred variance in attentional deficits (positive relationship) for the mTBI group.

Next we determined which of our objective measures of deficits **(FA** or neuropsychological tc.$ting) premorbid intelligence were entered înto both modwould more accurately classify mTBI patients and HC using binary logistical regres.üon. Estimates of els as it discriminated (Wald $= 4.16$; $p < 0.05$} be--

Figure 3 Fraetlonal anlsotropy (FA) andradialdlffuslvlty (RD) valll8$at bothvlalta



Mean FA and RDfor the mild traumatlc braln lnjury patients lmTBI; green bars "" vlslt 1, black bars = vlsit 2) and healthy conl:rols IHC; gray barsm visit 1, brown bars= vislt 21. Analyses werellmlted to ROI that dlsplayed slgnificent affectsat visit1, and included the left superlor corona radlata (SCR). the left unclnate fascluulus (UF), the left Internai capsula OC), the left corooa radlata {CRI, thegenu(GNU). andthesplenlum (SPLJ. Forthey-axis, theunitsof FA are dlmensionles&, whereas RDis equfvalent to mm²/s.

tween HC (65% accuracy) and mTBI patientS (66.7%) at slightly above chance levels. Ttaditional neuropsychological measures (attention, memory, and c:xecutlve:xecutlve functionfunction) didid notnot significamlysignificamly improveimprove nificant differences in FA values w the2 60%, mTBI = 71.4%). In contrast, results from the classification accuracy in the fim mode! (HC = second mode! indicated that both the left (Wald = 7.73;p < 0.05) and right (Wald= S.66;p < 0.05} racy (HC = 70o/o; mTBI = 81%), with,a trend behemisphere FA indices improved classification ac:cuing noted for the CC(Wald = 3.59; p 0.059). A out methodology confirmed the generality (HC = support vector machine analysis with the leave-one-65%; mTBl=81%} ofthe classification findings.

V'isit 2 data. To date, 10 out of 17 (59%) eligible mTBI patients and 15 out of 16 (94%) eligible HC participants have returned for their 3,- to 5-month follow-up visit (see appendix e-1). lntradass correlation coefficient values for FA were highly reliable {ail ROI= 0.65 < r_i > .93; p < 0.01) in rhe HCsa mple; however, reliabiiity of homologue measures was much more variable(SCR r_{14} = 0.64,p < 0.01; SLF r_{14} = 0.81,p < 0.001; UF r_{14} == 0.22,p > 0.10; CR r_{14} = 0.71;p < 0.01; IC r_{14} = -0.26. p > O.iO).

There were no signifia.nt differenccs for al1 clinical rneasui:es for mTBI patients who returned and those who did not. Addirionally, t!tere were no significamly improve hemisphere).

groups across the 3 setS of ROI (CC, right and lefi:

Change scores in dinical measures were calculated (visit 2 - visit l data) for those measurements thar were most suggestive (i.e., based on sign.ificance or effect si? eS) of group differences at visit 1 (attention, memory, executive funccions, emotional distress, so-matic and cognitive comp!aincs) as.ing premorbid intelligence as a covariare. Although there were no significant group effects, effect mes suggesred that memory scores improved (d = -0.52) and cognitive complaints decreased (d = 0.79) for the returning mTBI group compared to their matched comrols at visit2.

Differences in visit 1 and 2 FA and RD mea.surements were compared sepatate.ly across the 2 groups with paired samples t tests to maximîze power (see figure 3). Tests were again limited to those ROI that exhiblted significant or trend differences in mcan FA and RD (genu, splenium, left SCR, le.fi: IC, left UF,

and left CR) ac visit 1. In HC. here were no sîgnifl-cant differences for either FA or RD across the 2 visits. In contrast, partial normalization (i.e., decrease) in FA values was evident in the splenium ($t_8 = 4.17, p < 0.005$) and CR ($t_8 = 1.89, p => 0.09$) at visit 2 for mTBI patients. Although none of the RD effects reached statistical levels of significanœ, visual examination of the data suggests that RD differences may have parti.ally normali?:ed at visit 2 as well.

DISCUSSION The types of abnormalities seen in of total water in white marter compartments, a re-human neuropathologystudiesof mTBI2.3 are poorly duction in this percentage would theoretically also revealed by neuroimaging techniques, limicing detec- decrease cliffusiviry perpendiculâr to the axon.'° cion of potential white matter pathologies, and pre- At a more basic level, there may·be qualitative diction of cognitive impairment and functional differences in neuropathologie proœsses among ap-omcome.2" Hence, c:onvencional imaging modalities propriately diagnosed mTBI patients as illusuated by cannot provide an objective measure of injury fur the a reœnc srudyM comparing the fluid percussion (FPl) difficulc differential diagnoses that most clinicians and cortical impact (CCI) injury mooels. Injttred an-face when confronœd with mTBI patients.[10] Con- imals from both groups differed from shams in œnns trary to our initial hypothesis, mTBI patients dem- of T2 values and apparent diffusion coefficients onstrated increased FA and reduced RD within the (ADC), but in·opposite directions. The FPI injury, genu and several left hembphere white matter tracts which might be a better model for mTBI injuries compared to age- and education-matched controls caused by motor vehicle accidents, showed decreased during the semr-acute phase of injury. T2 and AOC, while the CCI injury, ptrhaps a better

Animal research indicares that i:here are several model fur falls or :tssauh:s, showed increased AOC morphologie changes, metabolic processes, and·in- and elevared T2. Both groups showed evidenœ of flammatory rC$pon..'ICS that follow mTBI.[25,26] There- increased immunoreacrivity.

fore. a definicive mechanistic explanaùon fur current Magnetic resonance spectroscopy also captures results is challenging at best given the many con- unique information about white matter pathology straints of an in vivo human clinical irnaging study. that may elucidate potential mechanis.ms of pathol-With tlm caveat in mind, perhaps the 2 most plausi- ogy. Increased créatine-phosphocreatine concentra-ble explanations for the cum:nt and previous[15,16] ob- tions in supraventriculat white matter and in the servacions of increased diffusion anisotropy following splenium have been observed in mTBI, perhaps re• tenr within the myeli1 1sheath. The mechanical forces for repair.3, 'Though such metabolic derangements mTBl are cytotoxic edema or changes in water con- lated to an incteased need for energy resources CATP) of mTBI typically result in the stretching of axons may follow a different recovery course than DTI ab-and related supporting structures such as oligoden- normalities,[36] they likely represent an important drocytes,[17] alrering the funcuon of gated ion chan- component of the suite of pathologie proceilSCS. A nels and resulting in an increase in intraœllular water 1:ematìve hypothesis linking the 2 imaging modaliûes and a decrcase in extracellular w.:uer.'.111 The decrease suggests that disruption of ionic homeosta$Is causes in extracellular warer leads toa dectease in diffusivity increased imracellular water, simultaneously redue• perpendicular to the axon (second and third eigen· ing RD and increasing ATP de.mai-id so as to upregu values; RD), secondary to more tightly compacted late membrane pumps and restore ionic homeostasis.. axons and poten:tial differences in the tortuoslty of Currem results also suggest that DTI results are intraœllular and extracellular water.[28-29] Mooeling more accurate in objeccively cl ifyi1 1g mTBI pa-studies suggest that even small deparrures from the dents from carefully matched HC. Although limited normal distribution of imraœllular and extracellular in nature, our anatomie protocol was completely in-water can lead ro dramatic changes in perpendicular sensitive (e.g., all mTBI and HC scans were inter-diffusion coeffu:ients.[30] preced as rrauma-free) to the putative underlying

A central role for cytotoxic edema is also partiaHy pathology following trauma. Second, although our supported by animal mooels of both ischemic stroke mTBI patients exhibited cognitive deficits on several and TBI, in which perilesional white matter shows neuropsychoiogical domains (attention, memory, a reduction in FA and RD &om 4 to 120 hours magnitude wich previous meta-analyses[37] these defi-postinjury.[25,26] Of note, the timeline from these an- cits did not substanrially improve classification accu-

'

racy even though neuropsychological testing bas traditionally seivcd as the gold standard for diffi:rencial diagnosis.[1fl.H] In contra$t, classification accuracy improved to *75%* with data derived from DTI images. Future &tUdies should examine the classification accuracy ofDTI and neuropsyc:hological measures in orthopedically injurep patients or similar populations38 to better control for nonspecific effects of trauma.

Similarly, longitudinal scudies with larger samples spanning the acute to chtonic rime frame are also ne to chan the evolving nature of mTBI, which has been docwnented in studies employing animal models.[19] FA measurcmenœ appear to be relatlvely stable.over month-long intervals in HC, rendering it an ideal mechanism for monitoring potential changes associated with recovery of fonction. Our preliminary longitudinal data suggest a partial normaliz.ation of FA {i.e., a decrease toward levels observed in HC) within several ROI in our mTBI group. Although others have examincd more severely injured populations,® we cxamincd longitudinal DTI changes in mTBI. Consistent with patients' self-report of continucd cognitive and somatic symp--roms at visic 2, not all of our ROI demonstratcd significant changes as a fonction of time, suggesring that a more extensive postimaging interval may be necessary to track recovery.

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DISCLOSURE

Dr. Mliycr hos tcœwed/reœives , .ruppori r.•om rl,c NfH (1 P20 RR02J958-0l [Co-1, Projcct Pl], IUINS064464 !Pl], R24HD050836 [J>l], Clinlœl LRP []>fJ, 1 RD DA0224:l5·D1AI [Pl], and R03 DA022435-01Al [J>IJ).]. Ling and M.V. Mnnncn rcpmt no c&cloources. Dr. Gaspatovic: bas re,:,,iv«!Jr=iw,s r=rclt $Uppo11 !rom the NJH (IU!NS064464 [Co-1], !ROI NS052305-0l [Co-lJ, R01-NS:l5708-04 [Co-ll, 11UIAA017313-0l [C.,.JJ, •nd NCRR 11'20RR0219:18..0l [Co-IJ), Dr, l'billips!<lp(>rtsoodi$clo,ures. Dr. Doct.cma reuivtt,....rd, support from the Nlli (R21NS06.f464 (Sub-<0ntract P!J). Dr. Rei<:hard reports no dùc!osun:s. *Dt.* Yco""""""on the editorial ndviso,y boards of Ltums/;ty:md *Fmuin:,In N-imr,*.

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CDC, AAN to Health Care Professionals: Monitor Patients for GBS

The Cenrers for Disease Control and·Prevention (CDC) and the Americœn Acade.my of Neurology (AAN) collabom.ted to reach ont to neurologists 11cross the US to monitor and report any possible new cases of Guillain-Barré syndrome (GBS) following 2009 H1N1 flu vaccination.

Neurologists and health care profcssionals nationwide who diagnose patients with vac:cine- associru:ed GBS should use the CDC and FDA Vaccine Adverse Event Reporting System (VAERS) to report their observations.

In addition, neurologists and all health pracrltione.rs in the 10 Emerging Infections Program (EIP) states-Califomia, Connecticut. Maryland, Minnesota, New Mexico, New York, Colorado, Ore- gon, Gcorgia, and Tennessee-are asked ro report ail new cases of GBS, regardless of vaccination status, to their state's surveillance officer.

The MN hosted a series of webinars providing an in-depth look at H1NI vaccination and how ir may pose a risk for GBS and information about the vaccination monitoring campaign.

For addicionaJ information about the moniroring campaign, or tO watch the webinars or download VAERS form and information on reporting to surveillance offiœrs in your state, visit the AAN's GBS roollcit page, *www.agn.com/viewlgbstoolkit.*

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Multivariate analysis of diffusion·tensor imaging data improves the detèction of microstructural damage in young professional boxers

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Abstract

In tbis study, we piesent two different metbods of multivariate ana1ysis of voxel-based diflùsion tensor imaging (DTI) data, using as an exam:ple data derived from 59 prof'essional boxeni and 12 age-matched conttoJs. Conventional mîvw.iate analysis ignores much of the diffusion infonnation conlained in the tensor. Our first multivariate method uses the Hotelling's '14 statlstic and lbe second uses linear discriminant aœ1ysis to gene:rate the linear discriminant function at each voxel to form a *separabUity merrlc.* Both multivmiate methods confirm the findings from the individua1 metrics of large-scal e changes in the bilateral inferior temporal gyri of the boxers, but they also reveal greater sensitivity as well as idemifying major subcortical changes .that bad not been evident in the univariate analyses. Linear discriminant analysis bas the added slrength of providing a quantitative measm-e of the relative contribution of each metric to any diffi:i:ences between the two subject groups. This novel adaptation of statistical and mathematical techniques to neuroimaging analysis is important for two reasons. Clinicall y, lt develons the fmdings of a previous mt'ld head iJtjury study, and, metbodologically, ît coutd equally wellbe apptied to multivariate studies of other pathologies.

//(eywonb: Multivariate analysis; Voxel-ba$ed ana1yllis; Linear disc:rimiwmt aMlysis; Dülùsion 11111sor ilnaging; Sepamhilil.y icetrie; Mild n:petitive lwad injury; Hotelling's 2 statis1ifo

1. IntroducCion

fonned by Statistical Pammetric Mapping (SPM) [1 J

Conventional neuroimaging analysis sucb as that per-employs univariate statistics. Multivariate metbodology using multiple biomar.kers may improve the sensitivity of significance testing between groups of subjects and controJs to provide a more sensitive indication of regions of btain damage. To test this hypothesis, two multivariate methods from professional boxers who bad experienced chronic mild, closed head injury, for which the results from standard were applied to diftùsion tensor imaging (DTI) dataobtained univariate analysis have been published elsewhere [2].

DTI is a valuable tool to identify microscopic changes in brain tissue resulting from damage ordisease [2-6]. The 3><3 symmetric tensor that models the diffusion of water in the b min ca;n be represented geometrically by an ellipsoid [7]. The tensor contains information about the ellipsoid's axes lengths and spatial orientation. The axis lengths are proportional to the square roots of the three tensor eigenvalues, ..t1 1 2 ..t2 0. If the ellipsoid's three orthogonal axes are aligned with the reference axes, the tensor is diagonal, if the ellipsoid is rotated with respect to the reference axes, the tensor contains symmetric off-diagonal elements to account for the rotation. Several tensor derivatives are unaffected by any rotation of the tensor, and these are the quantities used to calculate quantitative values of the diffusion process (8-1O]. Such derivatives tbat are potentially usetùl for imaging can bee Jassified into tbree groupings: *apparent diffusion coefficients,* which measure

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the "magnitude.. of the diftùsion; *dijfu.,ion anisotropy* the con1rol dataset. This statistic is the multivariate counia"' *indices.,* which measure the directional preferences of the part of Student•s *t-statistic,* while the cenuoid is the multi-ditlùsion; and the *apparent propagation measures,* which variate coonterpa:rt of the mea:n.

quantify whether the geometry of the diftùsivity is more linear (l 12!Â.2l':::ll 3). spberical (Â.1l::ll 2 l 3) or planar (l1 l22!l3). Dü:lùsion following a single fibre bundle shows linear ditlùsivity, while regions of crossing fibres, identification, along witbany sheet·like structures. show planar diftùsivity data [15] and·anotber [11]. Since these three groupings are measuring diffèrent spectroscopie and convmtional MRI physical properties of ditlùsion, it is concei.vahle that they aim of the approach used in tbis report was might be sensitive to different microstmctural changes. To employ LDA at every single voxel to geoerate a new diftùsion metric to subsume independent MD, analysis. risks losing important infonnation about sucb changes.

tbis study. mean diffusivity (MD) was used as the apparent diftùsion coefficient; Jhrotional anisotropy (FA) as the diftùsion ànisotropy index; and mode as the apparent propagation measure. In tenns of the tensor eigenvalues, these are given by:

$$MD = \frac{1}{3}(\lambda_1 + \lambda_2 + \lambda_3) \quad (1)$$

$$FA = \sqrt{\frac{3}{2}\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (2)$$

$$\text{Mode} = \frac{\hat{A}.1\hat{A}.2\hat{A}.3}{[(\hat{A}.1 - MD)^2 + (\hat{A}.2 - MD)^2 + (\hat{A}.3 - MD)^2]^{3/2}} \cdot 2 \quad (3)$$

Voxel-based analysis ofbrain structure, such as that done by SPM. leaves the choiœ of the variable of interest to the individual researcher. The analysis is. however, restricted to being univariate. Commenting on tbis aspect of the metbodology in their paper on voxel-based lllOIPhometry (using grey matter concentration as the variable of interest). Ashbmner and Friston {12) said, ..A possfùly more powerfùl procedu:re would be to use some furm of voxel-wise multivariate approacb...The Hotelling's T^2 test could be used to perform simple comparisons between two groups. However, for more complex models, the more general multivariate analysis of covariance would be necessmy." This study picks up this suggestion fiom lllOIPhometry and applies it to the investigation of microstructural integrity, using the same underlying methodology. Herc. instead of using grey matter concentration asin mo:rphometric analysis, we use the diffusion tensor derivatives MD, FA and mode. To our knowledge, it is the first time that microstructural integrity bas been interrogated using multivariate metbods with voxel-based DTI parametas.

Our first multivariate method entailed evaluating the Hotelling's T^2 statistic {13,14] at each voxel to test the null bypothesis that the centroid (the vector ofmeans of the three metrics) of the boxer dataset was the same as the centroid of

OUr second metbod was a novel application of linear discriminant analysîs (LDA) at the voxel leveL Other studies bave used LDA to investigate brain structure,. but they focused on using LDA to perform group using multimodal MR data [16). The aim of the approach used in tbis report was to ignore two of the tbree groupings, as is necessary in 11'.lOde measures, to maximise the diftèrentiation between the group of boxers and their ccntrols at the level of each In voxel. We called this new metric the *separobility metric.* The feature of this approach compared witb other multi-variate analyses is that it is voxel based, generating this new sepambility metric at each voxel. The advantages of a voxel-based approach ovcr operator-dependentregionselec-tion are well documented (see, ••[17D. In this way, itam identify those where the separability metric of the boxers is be used to investigate every voxel, and to objectively

statistically significantly different from the controls. To do this, the new metric was used in a standanl voxel-based analysis of the brain using SPM2 (http://www.fiLion.ucLac.uk/spm/). The difference between tbis approacb and standard SPM analysis is that instead ofusing MD, FA or mode individua.Ily in the analysis, the separability metric has, at each voxel, incorpomted information from alt three diftùsion metrics to ensure optimal separability between the two groups of subjects. Extending the improved power

of multivariate analysis to DTI data at the voxel level is likely to have pote:ot.ial value in studying many clinicat disorders that involve diftùse and/or multisystem altera- tions or damage.

2. Materials and methods

In vivo data were acquired from *S9* professional male boxers and 12 male control subjects (aged ftom 22 to 31 yea:rs) in the same age range. The control subjects were free ftom neurologicat disease md bad no boxing histmy. Informed consent was obtained from all participants. Jmaging protocols wereapproved by the institutiona1 review board. Thebrain imaging waspartofascreening programme to monitor professional boxexs; those in tbis study did not show clinicat signs of neurological damage. Conventional MR imaging of these subjects produced negative or nonspecific tindings, including cavum septum pellucldum, subcortical white matter disease and periventricular white matter disease.

2.J. MR Data acqui.,ition

Scans were perfunned on two GE 1.5-T MRI scanners (General Electric Medicat Systems, Milwaukee, Wl, USA}

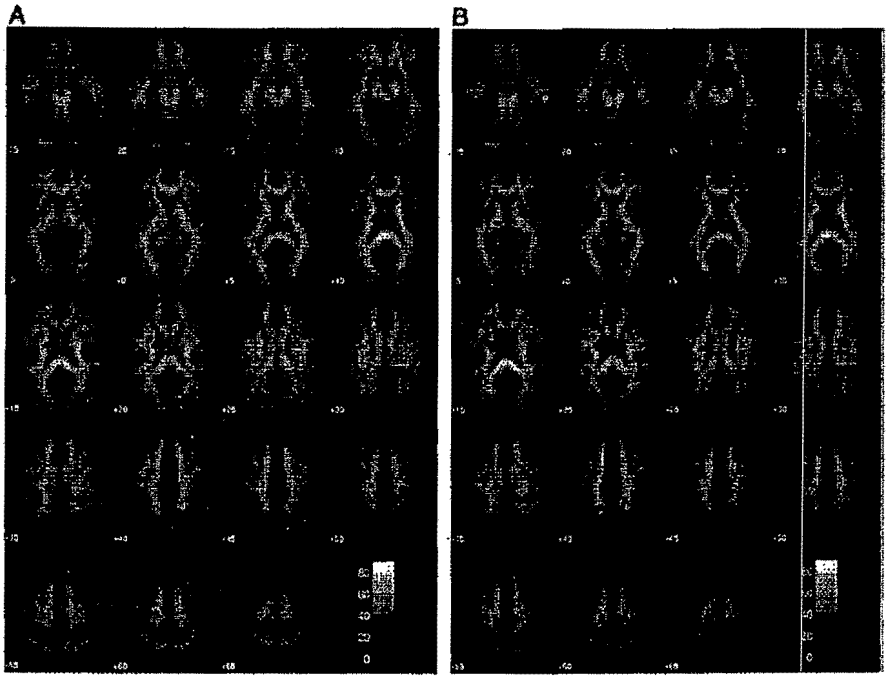


Fig. 1. Comparison of the effects of different smoothing filters. Statistical group comparisons and all used in each case were identical, except for the isotropic filter width of (A) 4 mm and (B) 8 mm FWHM.

with 22 mT/m gradient strength. A quadrature head coil was used, and in all cases the section thickness was 5 mm, with no intersection gaps. A 20 spin-echo EPI acquisition was used with TE/TR=100 ms/12 s. An acquisition matrix of 128×128×30 and 1.7×1.7×5 mm^3 voxels in 26 gradient directions with direction-dependent b values between 815 and 1152 s/mm^2 and six acquisitions with no diffusion weighting, was used. The total acquisition time was 6 min 24 s. No subjects, whether boxers or controls, were excluded from the analysis.

SPM2 was used to preprocess the data. The images were firstly spatially normalized to the Montreal Neurological Institute's (MNI) EPI template using SPM's nonrigid body transformations. The source image used to obtain the normalization parameters for each subject was the subject's T2-weighted (b=0 s/mm^2) image which was fitted to an MNI template image with similar contrast. These parameters were applied to the MD, FA and mode images. The resulting normalized images were then smoothed. The selection of the matched filter theorem, which states that the filter width smoothing filter width should ideally be driven by the should match the expected size of the differences being investigated [18,19]. In practice, however, this a priori information is seldom available. However, as traumatic head injury is known to manifest itself as diffuse axonal injury {20,21], we started with a 4-mm full-width at half-maximum (FWHM) filter and compared it with an 8-mm one (Fig. 1). also an intermediate width in the range of 10–16 mm reported in the literature [18].

The pre-processed, normalized, smoothed images became the input data for an three analysis methods: conventional univariate testing, Hotelling's T^2 statistic and the LDA. Multiple comparison correction algorithms, such as false discovery rate and random field theory corrections have not yet been written for the Hotelling's algorithm. To facilitate comparison of the different methods, we therefore addressed the problem of multiple comparisons by using a level of significance for the two-tailed t tests of <0.001, and by requiring a cluster size of at least k=8 voxels before the cluster was accepted. A flowchart outlining the analysis methods used is shown in Fig. 2

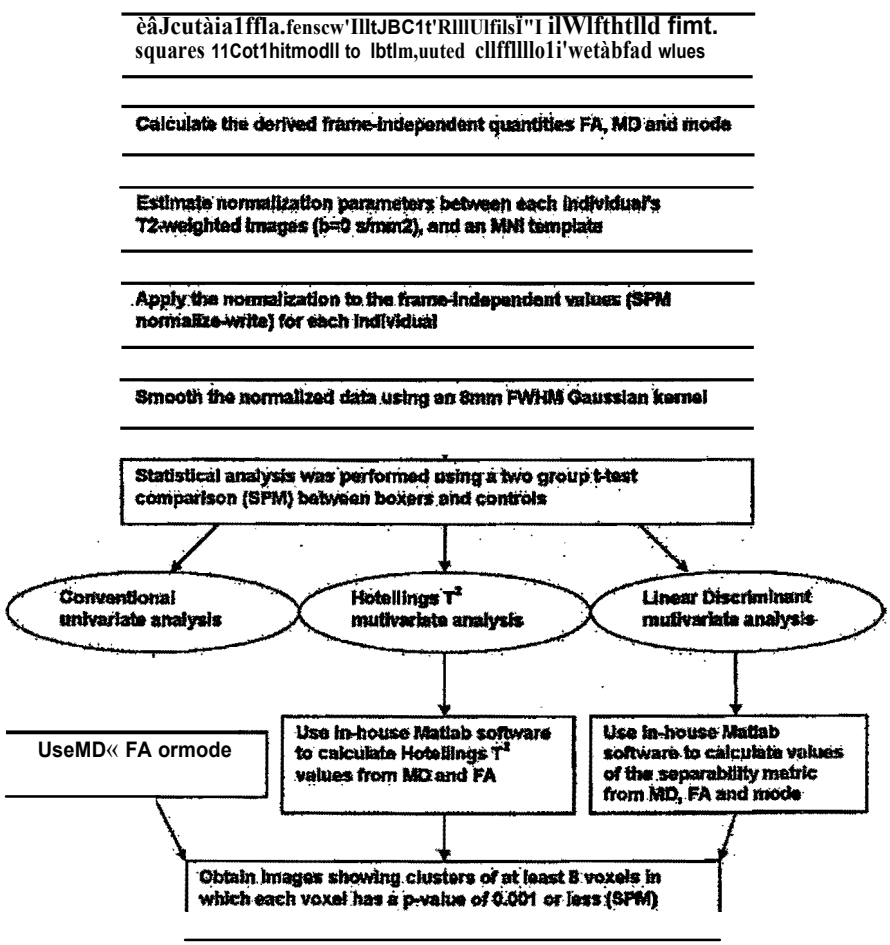
2.2. Hotelling's multivariate tests

We used Hotelling's T^2 statistic to perform multivariate hypothesis tests of the data (see Johnson and Wichem [22] for the relevant equations). With this methodology, an unbalance in the strengths of the contributing metrics tends to reduce the power of the final test compared to the strongest individual metric. In this study, including the weak metric mode was found to noticeably reduce the power of the analysis. We therefore opted to use just MD and FA in the Hotelling's analyses in this study.

2.3. Linear discriminant analysis

This visual comparison showed the 8-mm filter was more sensitive and was thus used in ail remaining analyses. It is

Linea:r discriminant analysis (see [23,24D investigates the extent to wbich two or more groups of subjects can be



I'"ig. 2. Flowchart outlinmg the analysis proœss Cromusing the 011 data to find the tensor at each voxcl lhrougb to obtaÏiJmg i1'llages of statilll:ieal diffittence between thesubject and oontrol groups.

separated, based on the measurements of several different variables foreach subject.It does thisby maximizing the ratio of the between-group variance to the within-group variance - i.e., the distance between the groups is rnaximized while the distance within the groups is minimized. The resulting "separating" function is called the *linear discriminant fonction.* Unlike Hotelling's analysis,. IDAdoes not penalise strong metrics if weaker ones are included in the analysis. This is because it finds the weighted combination of the metrics that best separates the two groups. Any metric that contn'butes littleornothingtothediscriminatingpowerofthe analysis is simply down- or zero-weighted.

If X_i are the univariate metrics being used (in this study MD, FA and mode), the linear discriminant function (L)can be written as

$$L = a_0 + a_1 x_1 + a_i x_2 + \cdots + a_n x_n, \quad (4)$$

The weighting parameters a_i aredetermined insuch away that thediscrimination between thegroups ismaximised. The linear discriminant tin;lction is the single linear function in MD, FA and mode that provides a mathematically derived optimal discrimination between the boxer and control groups. This is the justification for using the evaluated linear discriminant function fur each subject at each voxel as the new multivariate metric to test for ditferences between boxers and controls. and to test whetber it is more sensitive than any of the contn'buting univariate metrics.

We used the Fisher's Linear Discriminant function in the Matlab Statistical Pattern Recognition toolbox[1] to perform the LDA. Its identification of the function that best discrimina at between the groups is based on the Rayleigh quotient as the measure of separabfüty (25).

The novelty of this study is in applying LDA to eacb and every voxel. and thus generating a diffèrent linear discriminant function at each voxel. This provides two important pieces of information about that voxel Firstly, it

[1] http://cmp.felk.cvut.cz/~xfrancv/stp:tool/.

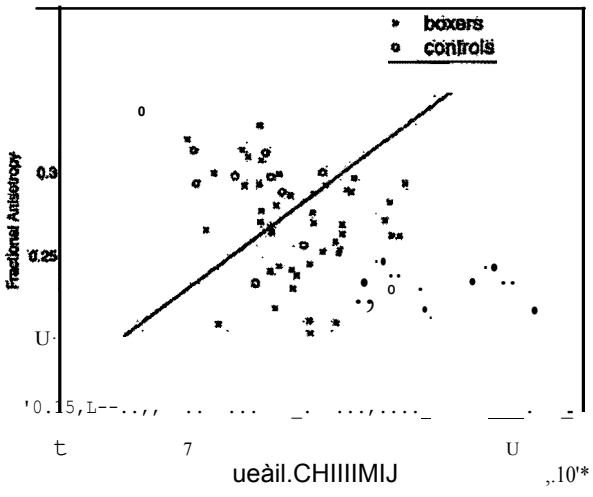


Fig. 3. Scalterplot ofFA vs. MD for -1 with MNI coordinares (36-16 12) In the îllllUlar cortex. The lineardlscrimi.namfùndion using the FA llllld MD llll!Irics (the "separator lme") issuperimposed. For easeof dlsplay and visualisation. Ibis result waa produœd usina OD!y two of die three llllllXïl:S, wi1h an auendant reduclion in succssfùJly categOrlsing each Sllbject ftom 90%to 72%.

finds.the linear discriminant function L, which is the linear combination of the three metrics tbat best separates boxers from controls at tbatvoxeL This gives aquantitative measure of the discriminating ability of the different conlributing metrics at tbat voxel - i.e., whichmetrics contribute most to the separation. This property is the motivation for the novel use of LDA in this study: that a *separability metrlc* c.an be genemted at each voxel of each subject. This is done by the voxel-wise evaluation of L for each subject. These separ•

Table l

A p!WI-Wise compacisonofthesensilivityoil'tbediftmentmelbods.**wheni** the numberof"significaut"vœels oonimon ta bolh melhod!l 11!1a pmpotlion of the total.numherofvoxelsinthebrainisrecorded(Fotex.ample. thenumher of voxels 1hat we.t11 idenlified as significant by both œivariate MD and by Hotelling's r2 comprised 1.8% of the brain)

	Univariate MD .	Hotelling's 'f2	Linear dlscrimi.nam analysis .
Univariate MD	0.040	O.OJS	0.023
Hotelling's 'r	O.OJS	0.050	0.031
Lineardiscrimiaallt llOldysi, 0.1)23		0.031	0.126

ability metric values for each Slllbject were then u.sed in signilica:nce testing to find voxels where the boxers• and controls' values were different.

An exâmple of the xesultsofLDA at a single vox.el in the insular cortex region [witb MNI coordinates (36-16 12)) is shown in Fig. 3. This scatteJplot shows the expected pattern that with mikl head injury MD increases and FA decreases [26,27}. With the difiùsion metric val1;1es statistically nonnalized to a mean ofO and standard deviation of 1, the discriminant function (Eq. (4)) for this voxel was:

$$L = 0.0265+0.0116 \times MD_z - 0.0042 \times FA_z - 0.038 \times mode_z$$

wbere the z subscript refers to normalized values. The coefficients show that at this voxel mode is the strongest metric, followed by MD, with FA the weakest. This is nnusua1. as mode is typically a weak discriminator (see Results and discussion section below) whicb is not used in univariate analysis. However, in the rare voxels such as this one where it makes an important contnbution to the

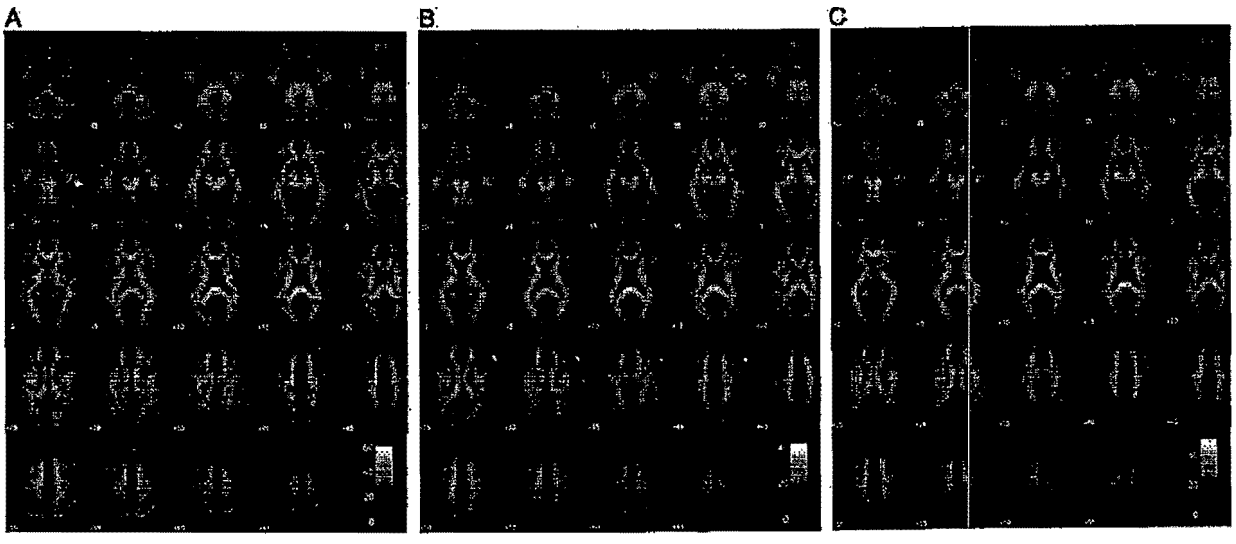
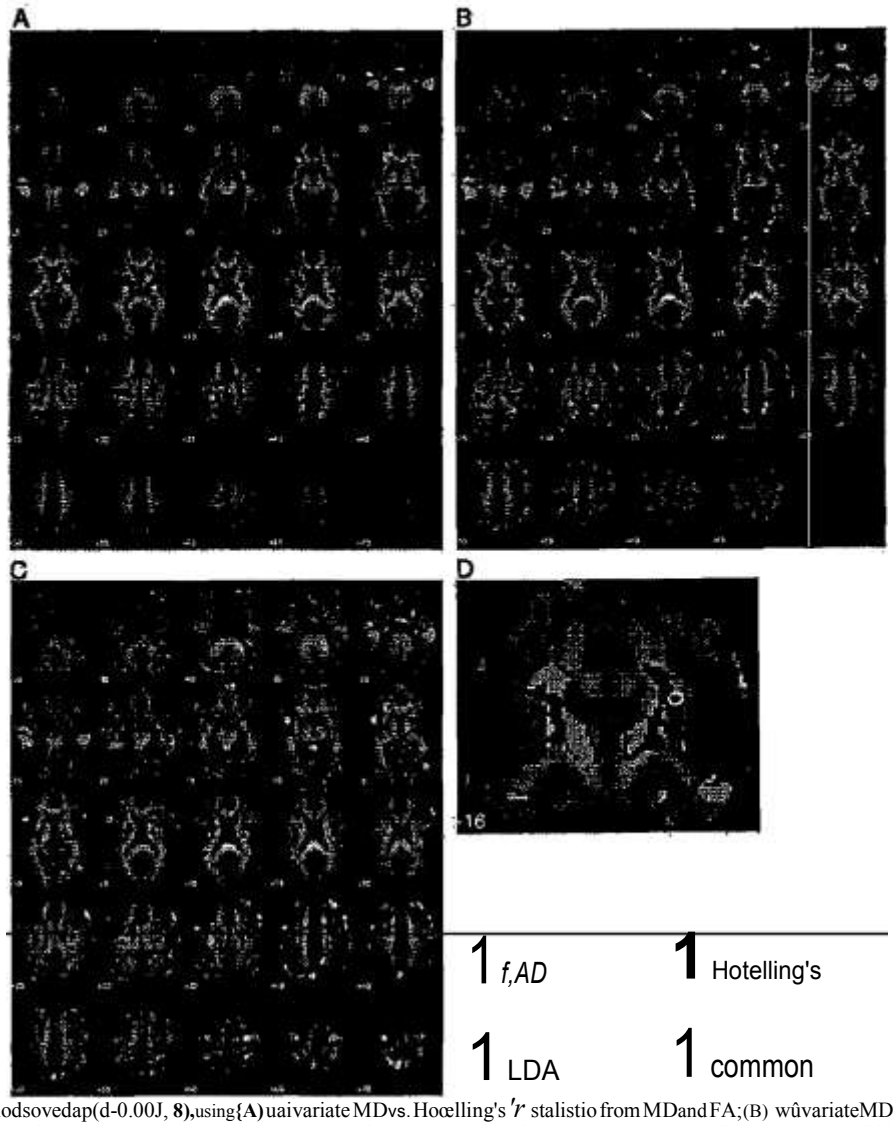


Fig. 4. Coloured regions showing V<rolls where the boxers are s1atistically significantly diffèrent from the controls (<r'0.001, l.=8). These regions are superimposed on an average FA map of ll()nnnlized, llllldamaged bmin.. The œivariate analyses wied are (A) MD. (B} FA and (C) mode.



andwhecthe twomethodsovedap(d-0.00J, **8),**using{**A**)uaivariate MDvs. Hocelling's *'r* stalistio fromMDandFA;(B) wûvariateMD vs. LDA's measure *Yig.S.*Co.loun:d regiol!Sshowiog paif-wisecomparisoDSofw}m,ecch method identifies theboxmsas bemgstatisw:ally sipifiC11111ydifti:rmtfrom the llOJllli:>ls,

using MD,FAandmode; (C) HoteUing's *T* StatlSuC f'o.111. MD and FA, vs. LDA's measureusing MD, FA and mode; and(D) ac:oronal si ction ofthe main . damage identi.fied **by** both Hotelling sandLDA metbods. These regio111are superimposedonan avexage FA niapofnormalized. uodamaged bœln. Theci.tcled

mgi0111(CandD)cantain voxel.(36-16 12) **C-** afsoFig.3), **whose**acelysisil discussed in the11:Xt.

ability to discriminate between the two groups. LDA is able to include this information and so increase the power of the test This illustrates the importance of the linear discriminant function as a separator, optimally incorporating as it does, separation information from all three metiics a.t evr:ry voxeL

3. Results and discussion

Beloœ utilising multivariate analyses, it is important to understand the behaviour of the three univariate metiics separa.tely. Fig. .4 displays standard two-sample two-tailed *t-test* results for each metric. ViSUa.l inspection shows that overall there is one strong metric (MD) and two weak ones (FA and mode) in identifying differences between the professional boxer brains and the control brams. This quantifies the çxtent of the :regions identified as being different between boxers and controls by the diffèrent methods. From the table, it is apparent that LDA is 2.5 times as sensitive as MD. The Hotelling's linear discriminant pa.iring

The compatative sensitivities ofHotelling's, LDA and the univariate MD methods in this study are shown in Table J. as sensitive as Hotelling's, whfob itself is 1.35 times as sensitive as MD. The Hotelling's linear discriminant pa.iring

bas the greatest overlap, i.e., the greatest number of "significant" voxels in common. with Hotelling's sbming 600./4 of its significant voxels witb IDA.

Fig; 5 shows the pair-wise comparisons of the œgions of differcnce unique to each method, and the regions common to. both. Fig. *SA* shows that Hotelling's *r2* confirms the main problem area identified by MD: bilaterat damage to the region of the infèrior tempoml gyrus. In addition. however, the Hotelling's approach identifies major subcortical damage in the sttiatum and thalamus that was not detected by MD. By contrast. Hotelling's did not dctect some of the diffuse white matter damage shown byMD.

Fig. *SB* and C shows that LDA appears to provide an · optimal multivariate approach. LDA supports the main . damage identffied by both the univmiate MD analysis and the multivariate (MD and FA) Hotelling's analysis, although theextent ofsubcortical damage inthestria:tum andthalamus is Jess evident. An additiooal feature of the LDA analysisis that it reveals more diffùse mkrostructura1 damage than theother methods.. Fig. 5Disa coronal viewofthedamage to thesubcortical and intçma]. capsule regions. showing thatthe . subcortical damage in boxers appears most prominent at the level of the posterior limb of the intemal capsule when analysed witb Hotelling's and IDA multivariate methadol· ogies. This finding, notapparent from the univariate analysis of these data, is in agreement with results of another boxers study [28).

4. Conclusions

In tbis study. wehave presented twodifferent metbods for. analysing and displaying differences in brain structùre between two subject groups using multivariate statistics. The two methods are the voxel-wise evaluation of Hotelling's *r2* tests of multivariate dat.a. and Studcnt's· *t* tests of LDA's. separability metric that optimises group differences a.t individual voxels.

In this study, LDA w more sensitive and provided more detail of the mîcrostructural damage in the boxers, while Hotelling's statistic revealed fewe.r, more consolidated bcortical clusters. LDA in addition reflects the diffuse nature of themild, repetitive, closed head injury. Hotelling's and LDA methods complement each other, mn,roving the power and thereby extending the findings of sepamte univariate analyses.

LDA is robust to changes in the relative strengths f the contnôuting metrics, since if one metric is weak at a particular voxel, it is down-weighted there without penalis-ing the others. This is a strengtb it has over the Hotelling's method which loses power when a weak metric is included. We have demonstrated LDA's flexibility in tbis regard. showing how it can capture the discriminating information from a metric that is weak in most voxeJs but is nevertheless 8 strong separator ln a few.

A weakness of this retrœpective study isthe low number of control subjects, which consid!embly reduces the power of the analyses. Despite tbis Jimiîation, these new methods enabled us to i major subcortical damage in the mains of the professional boxers dlat was not evident using univa.riate analysis.

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Vol. 25, No. 1, pp. 31-42

Serial Changes in Diffusion Tensor lmaging Metrics o Corp s C losum in Moderat Traumat1c Brain lnJury Patients and Their Colrelation With Neuropsychometric Tests: A 2-Year Follow-up Study

Raj Kurnar, MSc; Sona Saksena, MSc; Mazhar Husain, MCh; Arti Srivastava, MA; Ram K. S. Rathore, PhD; Shruti Agarwal, MSc; Rakesh K. Gupta, MD

Objective; To assess longitudinally the sevcrity of diffuse axonal injury in the cotpus callosum in patients with moderate traumatfo brain injury (TBI) through quantitative diffusion tensor imaging and to con:elate these changes with neuropsy· cbometric tests (NPT)at 6 and 24 monthsafter injury. **Design;**Prospective longitudinal study. **Parddpants:** Sixteen patients with TBI and 17 age/sex-matcbed healthy c:ontrols. **Methods:** Patients undc:nvent magnetic resonance imaging at *3* time points: within 2 weeks (range= 5-14 days), 6 months, and 24 months aftcr injury. NPT could be performcd only at 6 and 24 months. **Results:** In patients with TBI, a significant increase in &actional anisotropy (FA) values in genu as wel1 as an insignificant decre.ase in radial diffusivity (RD) and mcan diffusivity values in genu and splenium wcre observed ovcr time, n:spectively. FA. RD, and mean diffusivity values continucd to be abnormal in patients compared with controls at the end of 2 yeai:s. Although some NPT scores improved over time in these patients, these were still significantly impaired comparcd with controls. **Conclusions:** FA and RD indices appear to be surrogate markcrs of microsttucturalalterations in patients over time and correlate significantly with some of the NPT scores. The recovery in these indices associated with recovery in neurocognitive deficits suggests that these indices may be used as an objective marlœr for residual injury in these patients.
Keywords: *œrp,u cafloSN111, diffose axtmalinjury; diffesion temOT imaging,.fractionrJl.anisotropy. M'IITOpsyd,ologiml test, radial tlfffiaiuî!Y, tTamnatic brain mj,try*

TRAUMATIC BRAIN INJURY (IBI) is the most common brain disorder amongyoung and middle-aged adults, exceeding the incidence of epilepsy, tumors, and stroke.[1] It is most commonly associated with transportation-related accidents, assaults, falls, and sports-related injury.[2,3] Severa! pathophysiologic sequelae such as location and severity of injury, diffuse effects, and secondary mechanisms of injury affect the neurobehavioral outcome in TBI. Contusions are common and may directly disrupt function in both cortical and subcortical regions. Disruption of function can also result from diffuse damage to white matter tracts that are particularly susceptible to the shearing forces that often occur with TBI.[4] Such diffuse a:xonal injury (DAI) can disrupt cortical-subcortical pathways and lead to widespread cognitive dysfunction.[5] DAI may result directly from the trauma orsecondarily due toIschemia.

It has been shown that DAI is primarily responsible for transient deficits in cognitive performance in domains such as processing speed, working memory, and attention in patients with mild to moderate TBI.' Fork et al[7] reported that patients with probable DAI had long-lasting neuropsychological impairments dominated by

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C-,-Jing Alllhor: RnhsbK G•pta, MD, DepartmmtofRadiotlifJ/t wsis, Sanjtg Gandhi Post Grfl8l'1l/e Institute of Medical Scimas, LIICknD'lll 226014, UP, India (rgupta@sgpgi.ac.in).

executive ànd memory dysfunctions. A previous study has shown that patients with TBI have worse performance than a matched control group in a broad spectrum ofcognitive domains at 1 year postinjury.[8]

Accurate diagnosis and assessment of the distribution and severity of DAI is a major challenge, since computed tomography and conventional magnetic resonance imaging(MRI) are known to underestimate theextent ofDAI and corrdate poorly with final outcome.[9,10] Recently, diffusion tensor imaging(DTI) has been shown to be a valuable technique for in vivo quantification of white matter microstructuralalterations following TBI.[11] .Noninvasivdy, un provides information about the degree and directionality of tissue water diffusion.[12] Currently, the most commonly used scalar invariants in un are fractional anisotropy (FA) and mean diffusivity (MD).[12] Other un measures include axial diffusivity (AD), which represents the water diffusivity parallel to the axonal fibers, and radial diffitsivity (RD} represents water diffusivities perpendicular to the axonal .fibers.[13] Previous DTI studies of TBI have found reduced FA valuesinsevera1 white matter areas, both within lesions and in tissue appearing normal on conventional Mru.[1+-16]

Several DTI studies have investigated the corpus callosum (CC) in patients with head trauma.[14,17-19] The extent of traumatic axonal injury in the CC and *its* relation to trauma severity are not clear from these studies, as they investigated only the genu and/or splenium rather than genu, body, and splenium[14,18,19] and included only patients with mild orsevere TBI instead of a range of trauma severities.[14,17,18] Rutgers et al[16] demonstrated that there are local differences in DTI characteristics within the CC related to the dinical severity of head trauma. Mild TBI was associated with DTI abnormalities (reduced FA values and increased MD values) in thegenu less than 3 months posttrauma[1.6] In patients with moderate and severe TBI, ail investigated less than 3 months posttrauma, both the genu (reduced FA values and increased MD values) and splenium (reduced FA values without significant change in MD values) were affected.[16] DTI showed different types of microstructural injuries within the corpus callosum, suggesting a larger contribution of vasogenic edema in the genu than in the spleniuro.[16]

The CC is the largest commissural fiber bundle in the brain and has been considered especially vulnerable to TBI due to its unique location and composition. Longterrn follow-up studies in TBI have shown diffuse atrophy of CC.[20] lnjury to CC is a concem in TBI because ofitsimportant role in interhernispheric functional integration, communicating perceptual, cognitive, leamed, andvolitional infonnation.[21]

We conducted longitudinal DTI studies to assess the severity of DAI in the various regions of CC in patients with moderate TBI in the early period (5-14 days) and after 6 months and 24 months. We have also attempted to correlate the changes in the DTI metrics (FA, MD, AD, and RD) with performance on neuropsycbolo·cal tests (NP1) at 6 months and 24 months following ne-')t

.METHODS

Participants

Our study included 16 patients with TBI (8 men and 8 women, mean ± SD = 35.25 ± 10.28; range = 18-55 years} admitted to the Neurosurgery Emergency and Trauma Centre of Chhatrapati Shahuji Maharaj Medical University, Lucknow, India. The causes of TBI in these patients were motorvehicle accidents (n = 11) and fall from height (*n* = 5). These patients sustained moderate closed head injury with demonsttable computed tomographie findings at the time of injury. The mean Glasgow Coma Scale score was 10.8 (range = 9-13).[16] Ail patients had a history of loss of consciousness immediately following trauma, but no abnormality was seen in CC on conventional MRI. Patients with visible abnormality in CCwere excluded from thestudy. None ofthe patients in thisstudy had a history suggestive of TBI, hypertension, diabetes, orstroke. Of the 16 patients, 5 had vorniting, 8 had severe·headache and confusion, 6 had vertigo, 2 had bleeding from ear and nose, 1 had a third nerve palsy, and 1 gave history of early posttraumatic seizures (within 24 hours after injury}. None of these patients experienced late posttraumatic epilepsy when interrogated at the time of follow-up at 6 months and 24 months following injury. Patients underwent MRI at 3 time points: within 2 weeks (range = 5-14 days). 6 months, and 24 months of injury. Seventeen healthy age- and sex-matched controls (10 men and 7 women, mean ± SD = 37.35 ± 9.34; range= 18-55 years) were investigated during the study period by using the same MRI protocol at3 different time points comparable wi!11 that of patients. None of the healthy controls had history ofTBI, drug abuse, alcoholic, and neurocognitive disord.ers. The study protocol was approved by an institutional ethics committee, and written informed consent was obtained from each subject or the nearest kin.

Con.ventioual MRI acquisition

Both patients and controls underwent both conventional MRI and DTI on a 1.5-T General Electric MRI scanner (GE Medical System, Milwaukee, WISconsin) by using a quadrature birdcage receive and transmit head coil. The conventional **MRI** protocol included T2-weighted fast spin echo (repetition time [TR]/ echo time [TEJ/number of excitations [NEX] = 6000 milliseconds/85 mitliseconds/3),Tl•weighted spin echo (fR/fE/NEX = 625 milliseconds/14 milliseconds/ 2), T2-weighted FLAIR (TR/TE/inversion time/

milliseconds/1], and T2* gradient recalled echo sequence (TJ.VI'E/NEX/flip angle= 500 milliseconds/15 milliseconds/1/200). In all sequences, 36 sections were acquired in the axial plane with 3-mm slice thickness. 256 x 192 matrix, and 240 mm x 240 mm field of view, with no intersliœ gap.

NEX = 9000 milliseconds/120 milliseconds/2200

DTI acquisition

Diffusion tensor imaging was acquired with a single-shot echo planar dual spin-écho sequence with ramp sampling.[13] The dual spin-edio sequenœ reduces image distortions in the diffusion-weighted images by compensating for the effect of eddy currents.[22] The sequence used a spectral selective 90° pulse for fat suppression. The number of diffusion gradient pulses in the dual spin-ecbo sequence was 4. The durations of these gradient pulses were 81 = *84* = 6 milliseconds and *82* = *83* = *11* miUiseconds. The effective diffusion time was approximately 50 milliseconds (TE/2). The b-factor was settoOand I000 s/mm^2; TR= 8seconds, TE= lOOmilliseconds, and NEX = 8. A total of 36 axial sections were acquired with a slice thickness of 3 mm, no intersliœ gap, field of view of 240 mm x 240 mm. The acquisition matrix was 128 x 80, and a homodyne algorithm was used to reconstruct to 128 x 128. This was zerofilled to reconstruct an image matrix of 256 x 256. A balanced and rotationally invariant diffusion..encoding scheme with 10 noncollinear directions over the unit sphere was used for generating the DTI data." To enhanœ the signal-to-noise ratio, the data were temporally averaged.

DTI data were processed and evaluated by using JAVA-oased program as described in detail elsewhere.[24] For region-of..interest(s) placement. the CC was divided into 7 segments: rostrum (CCI), genu (CC2). anterior rostral midbody (CC3). anterior midbody (CC4), posterior midbody (CC5), isthmus (CC6), and splenium (CC7) (Fig 1) by using the scheme proposed by Witelson.[25] The FA, MD. AD. and RD values in di.fferent regions of CC were averaged for statistical analysis in both patients and controls (CCl and CC2 for genu; CC3, CC4, and CC5 for midbody; and CC6 and CC7 for splenium). The size of the region of interests varied from 5 x *5* pixels to 7 x 7 pixels. To obtain the volume of di.fferent regions of CC, the data were interpolated along the *x-*, y-, and z-axis (voxel size, 1 x 1 x 1 mm^3); the number of pixels counted in each segment of CC was multiplied with slice thickness.

Nemopsychological tests

NPT were administered to controls and patients at 6 and 24 months following injury, not at the time of 6.rst study as the pain associated with trauma in the initial phase of IBI is known to influence the NPT results.[26]

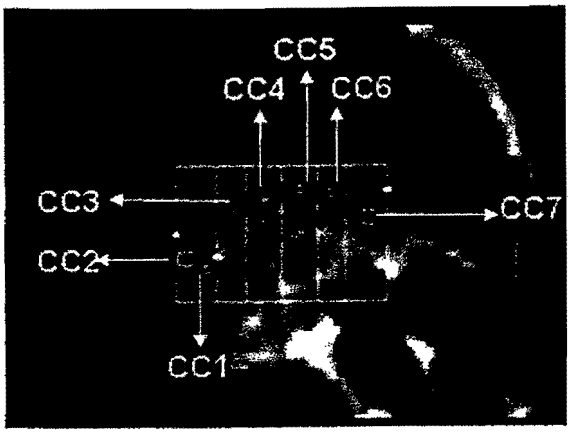


Figure 1. Gray scale fractional anisotropy **(FA)** map superimposed on the mean diffusi.vity (MD) map showi.ng region of interest placed in corpus collosum (CC) in patients with traumatic brain in jury and controls at the level of massa intermedia. The eut-off value for the FA map was kept at 0.2 thresholds.

All patients underwent a series of psychometric tests, which included number connection tests (NCT A and NCT B) if literate; figure connection tests (FCT A and FCT B)27 if illiterate; and selected performance subtests of modified Wechsler Adult Intelligence Scale (WAIS-P, modified for Indian population),[28] which included picture completlon test (PCf), digit symbol test (DST), and block design test (BD1).[29]

Number connection test is a derivative of the Trait Making Test:311 and evaluates visuospatial orientation, motor speed, concentration, and attention.[31].3[2] NCT A consists of 25 circles consecutively numbered from 1 to 25 on a sheet of paper. The patient is required to connect the circles in numerical sequence as quickly as possible. After completion of NCT A, NCT Bis administered. In NCT B, circles are marked either by letters or by numbers, and the patient has to altemate between numerical and alphabetlcal sequences (1-A-2-S..3 ... L-13). FCT is a universally applicable test for assessment of mental state, which transcends the barriers of illiteracy and linguistic di.fferences. In prindple, the FCT *is* sirnilar to the NCT, except that numbers are replaced by figures. In FCT, each cirde bas 1 to *5* motifs (designs), thus giving the required 25 figures. In FCT A, the patient is required to connect ail cirdes with the same motif in order of increasing numbers of motifs and insequences specified in the chart; while in FCT B, ail circles with the same motif are widely scattered in the chart and the patient is asked to connect these circles as quickly as possible.[27] The test score is the time required to complete the test, induding the time needed to correct any errors. On NCT and FCT, a low score indicates better performance. NCT and FCT carry the same interpretation except that in FCT numbers are replaced by figures so that the test can therefore

be perfonned by people who are illiterate. Both FCT A and FCT B evaluate visuospatial orientation, motor speed, concentration, and attention. However, in FCT B, the circles with the same motif are widely scattered on the page and therefore more visuospatial orientation, motor speed, concentration, and attention are required to connect these circles, compared with FCT A.

On WAIS-P, the PCT is done for the accuracy of perception. The DST is a measure ofmotor speed, accuracy, and shorHenn visual memory. The BDT is a construction test and measures visµal-spàtial motor function. It describes theability toconstrllct designsorpatternsfrom pictorial models. In WAIS-P, a highscore reprèsents better performance. The clinical significance of these tests has bèen evaluated in patients with TBI.[33 35] These tests have been validated and usedinsevèral otherstudies.[36,37] The duration for perfonning NPT ranged from 45 to 60 minutes in patients and 35 to 45 minutes in controls.

Statisakalanalysis

The DTI metrics (FA. MD, AD, and RD) and volume in diffcrent regions of CC were quantified within 2 weeks, 6 months, and 24 months following TBI. Multiple comparisons using Bonferroni post hoc test was perfunned to study the changes in FA, MD, AD, and RD values; volume; and NPT scores among contrais and patients with TBI. To study the relations between NPT scores and FA, MD, AD, and RD values on follow-upimaging, Pearson's correlatîon coefficients were computed. A Pvalue .05 was considered tobe significant. Ninety-five percent confidence interval ofthe estimated parameters was a1so computed wherever applicable. All statistical data computations were performed using the Statistical Package for Social Sciences (SPSS, Version 15.0, SPSS, Inc, Chicago, Illinois).

RESULTS

Convenûonal MRI 6udings

The location of brain in.jury on conventional MRI was frontal (*n* = 8), frontotemporal (*n* = 3), multifocal (n = 2), parietotemporal (n = 1), temporal (n = 1), and occipital (n = 1). These patients showed hemonhagic DAI (R DAI, *n* = 8), nonhemorrhagic DAI (Nh DAI, *n* = 3), and noapparent DAIon conventional MRI (NA DAI, *n* = 5). Both H DAI and Nh DAI lesions were scattered in the white matter (frontal, parietal, temporal, and occipital) and deep gray matter (basal ganglia and thalamus). No visible abnormality was seen in the CC in any patient on initial or follow-up study at 6 months and 24 months. None of these patients bad any motor defidt.

Q!iantitative DTI6udings

The mean FA. MD, AD, and RD values from the different regions of CC in controls as well as in patients

lbN!W• *Summaryof DTImetrics fromthe different regions of CCincontrols and patients with TBI at different time pointsa*

Region	Control (M ± SD)			Patients [M ± SD)		
	1ststudy	2ndstudy	3rdstudy	4ststudy	2ndstudy	3rdstudy
FA						
Genu	0.57 ± 0.02	0.57±0.02	0.57 ±0.02	0.46 ±0.01	0.52 ±0.01	0.51 ±0.01
Midbody	0.43 ±0.0t	0.43 ± 0.01	0.43±0.02	0.43 ±0.01	0.40± 0.01	0.39±0.01
Splenium	0.63 ±0.02	0.62 ± 0.02	0.62 ± 0.02	0.58±0.03	0.57 ±0.02	0.56± 0.01
MD x10-^{3} mm^2/s						
Genu	0.78±0.05	0.78±0.05	0.78 ±0.04	0.83 ±0.07	0.80 ±0.04	0.80±0.04
Midbody	0.79±0.04	0.79±0.04	0.79±0.04	0.84±0.09	0.85±0.05	0.88±0.06
Splenium	0.76±0.07	0.75±0.05	0.76± 0.05	0.84±0.06	0.79±0.04	0.76 ±0.04
AD x10-^{3} mm^2/s						
Genu	1.36±0.09	1.35±0.10	1.35±0.09	1.32 ± 0.14	1.34 ± 0.08	1.34±0.09
Midbody	1.27 ± 0.15	1.28 ± 0.15	1.27 ± 0.14	1.22 ± 0.12	1.28::!::0.09	1.30 ± 0.10
Splenium	1. ±0.13	1.38 ±0.12	1.40 ± 0.15	1.32 ±0.10	1.38 ±0.08	1.30::!::0.08
RD x10- ^{3} mm^2/s						
Genu	0.50±0.06	0.50 ±0.09	0.52 ±0.08	0.57 ±0.06	0.53±0.04	0.53 ±0.03
Midbody	0.58± 0.08	0.58±0.08	0.60±0.09	0.64 ±0.04	0.64±0.05	0.67 ±0.05
Splenium	0.44±0.06	0.43± 0.09	0.45± 0.07	0.64±0.08	0.49 ±0.04	0.48::!::0.03

Abbreviatîons: AD. axial diffusivity; CC. corpus callosum; DTJ, diffusion tensor imaging; FA. fractional anisotropy; MD, mean dIffusivity; RD, radial diffusivity; TBI, traumatic brain injury.

aFirst study"" within 2 weeks, Second study = 6 months, third study = 24 months.

IM=J!#J *Multiple comparisons using Bonferroni test for FA, MD, and RD values from different regions of CC in controls and patients with TB/ at different time pointsa*

DTI metrics	Region.	Group	Group	Mean difference	Standard error	p	95%CI LB	95%CI UB
	Genu	Control vs	1ststudy	0.111	0.005	.000	0.096	0.126
			2ndstudy	o:053	0.005	.000	0.038	0.068
			3rd study	0.057	0.005	.000	0.042	0.073
		1st studyvs	2nd study	-0.057	0.006	.000	-0.075	-0.040
			3rd study	-0.053	0.006	.000	-0.071	-0.035
FA	Midbody	Controlvs	2ndstudy	0.024	0.002	.000	0.017	0.030
			3rd study	0.034	0.002	.000	0.028	0.041
		1st study vs	2nd study	0.024	0.002	.000	0.016	0.031
			3rd study	0.034	0.002	.000	0.026	0.042
		2nd studyvs	3rdstudy	0.010	0.002	.002	0.002	0.018
	Splenium	Control vs	1st study	0.049	0.008	.000	0.027	0.072
			2nd study	0.062	0.008	.000	0.039	0.084
			3rd study	0.070	0.008	.000	0.047	0.092
MD x 10-3 mm2/s	Midbody	Contrai vs·	2nd study	-0.063	0.019	.013	.:...111	-0.009
			3rd study	-0.088	0.019	.000	-.142	-0.034
	Splenium	Contrai vs	1st study	-0.081	0.0189	.. 000	-0.132	-0.029
		1st study vs	3rd study	0.084	0.021	.001	0.025	0.143
RD x10- 3 mm 2/s	Genu	Control vs	1ststudy	-0.074	0.016	.000	-0.117	-0.031
	Mîdbody	Contrai vs	1st study	-0.059	0.020	.021	-0.112	-0.006
			2nd study	-0.058	0.020	.025	-.0111	-0.005
			3rd study	-0.085	0.020	.000	-.0138	-0.032
	Splenium	Controlvs	1ststudy	-0.099	0.018	.000	-.0147	-0.051
			2ndstudy	-0.052	0.018	.027	-.0101	-0.004
		1st study vs	3rd study	0.060	0.021	.0029	0.004	0.115

Abbreviations: CC, corpus callosum; Cl, confidence interval; DTI. diffusion tensor imaging: FA. fractions! anisotropy; LB, lower bound; MD, mean dîffusivity; RD, radial diffusivity; TBI, traumatic brain injury; UB. upper bound.
"First study = within 2 waeks, second study = 6 months, third study = 24 months.

with TBI studied ·at 3 time points are summarized in Tables 1 and 2 and shown in Figures 2 to 5.

A significant decrease in FA values in the genu was observed at ail 3 time points in patients compared with contrais. In patients, FA values significantly increased in the genu at time points 2 and. 3 compared with time point 1. The FA values showed a significant decrease at time points 2 and 3 in the midbody in patients compared with conttols. FA values in patients declined significantly from time point 2 to 3 in this region. The FA values in the splenium decreased significantly at all 3 time points in patients compared with controls.

ln the genu, an increase in MD values was observed at ail 3 time points in patients compared with controls but did not reach the level of statistical significance. Al· though in patients, MD values decreased in the genu at time points 2 and 3 compared with time point 1, but no statistical significance was observed. A significant increase in MD values was observed in the midbody at time points 2 and 3 and in the splenium at rime point 1, respectively. in patients compared with controls. In patients, significantly decreased MD value was observed in the splenium at time point 3, compared with time point 1.

The AD values in the regions of CC did not show any significant change with time eitherin patients compared with controls or within patients, respectively.

Asignificant increase in RDvalueswas observed in the genu at time point 1 in patients compared with controls. In patients, a decrease in RDvalues was found over time in the genu but did not reach the level of statistical significance. In midbody, RD values significantly increased at ail 3 time points in patients compared with controJs. The splenium showed significantly increased RD values at time points 1 and 2 in patients compared with

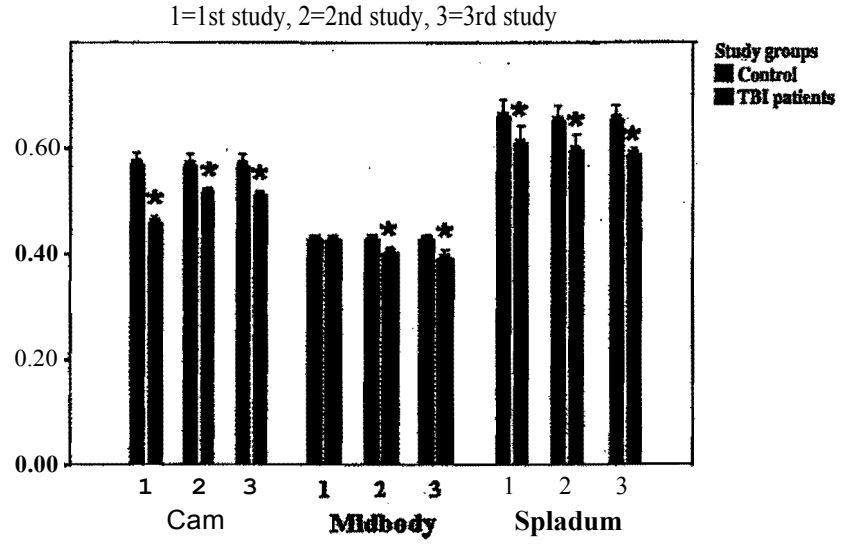


Figure Z. Bar plot of FA values from different regi.ons of corpus calloswn (gcnu. midbody, and spleniutn) studied at different rime points (first study = within 2 weeks, second study = 6 montbs, and third study = 24 montbs) in controls **as well** as in patients wîth TBL The asterisk (*) indicates significant difference observed in patients compared with controls. The bars represent standard deviation. FA indicates fiactional anisotropy; TBI, traumatic brain injury.

controls. In patients, a significant decrease in RD values was observed in the splenium at time point 3 compared with time point 1.

Changes in **CC volume**

No significant regional differences in CC volume over time were found in patients compared with controls or within patients, respectively (Tables 3 and 4).

Neuropsyehologicaltesù.

NCT A, NCT B, FCT A, and FCT B scores were significantly higber (ie, worse) while J>Cf, BDT and DST scores were significantly Jower in patients with TBI at time points 2 and 3, cornpared with controls (fables 5 and 6; Fig 6). In patients, FCT A {P = .002) and FCT B (*P* = .029) scores were significantly lower while the PCT (*P* = .001) score was significantly higber at time point 3 compared with time point 2 (Tables *5* and 6).

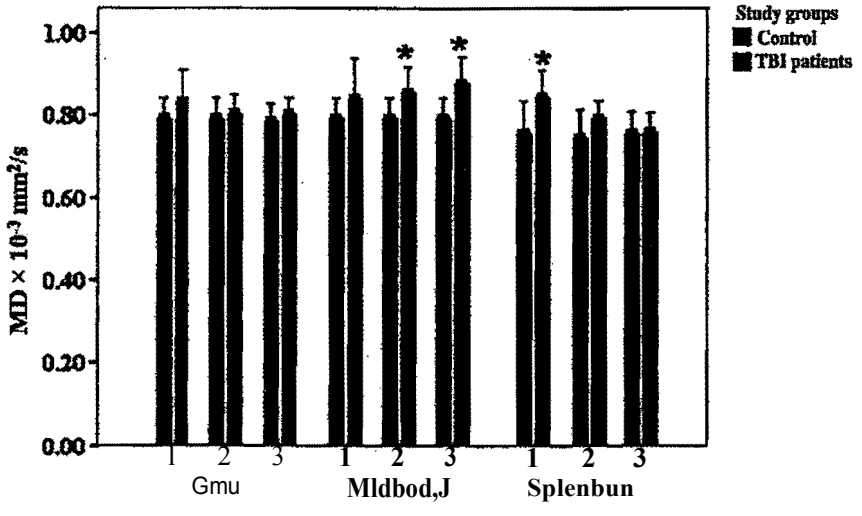
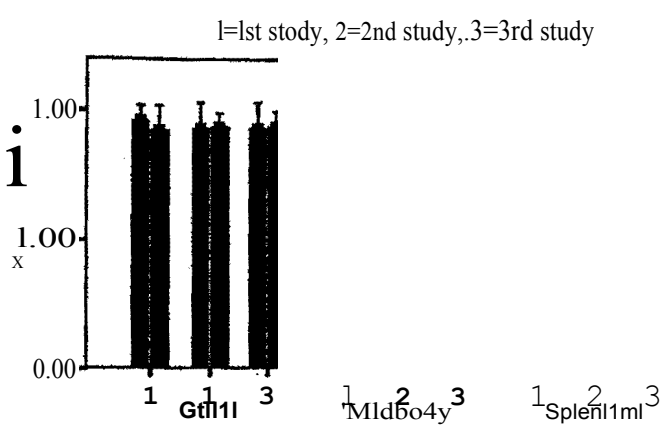


Figure 3, Bar plot of MD values fi:om different regi.ons of corpus callosum (genu, midbody, and splenium) studied at different rime points (first study = within 2 weeks, second study = 6 montbs, and third study = 24 months) in controls as well as in patients with TBI. The asterisk (*) indicates significant difference observed in patients compared with controis. The bars represent standard deviation. MD indicates mean diffusivity; TBI, traumatic brain injury.



P.lgme 4. Bar plot of AD values &om different regions of corpus callosum (genu, mîdbody, and splenium) studied at differcnt time points (first study·=within 2 weeks, second study == 6 months, and third study = 24 months) in controls as well as in patients with TBL No signifiant difference was observed in patients compared with controls. The ban represent standard deviation. AD indicates axial diffiisivity; TBI, traumatic brain injmy.

Correlation between On Metrics and NPT scores obtained at 6 montbs and 24 montbs follow-up

At 6 months follow-up, FA values in the midbody showeda positive correlation with PCTscores(*r*= 0.604, *P* = .022) in patients wîth TBI.

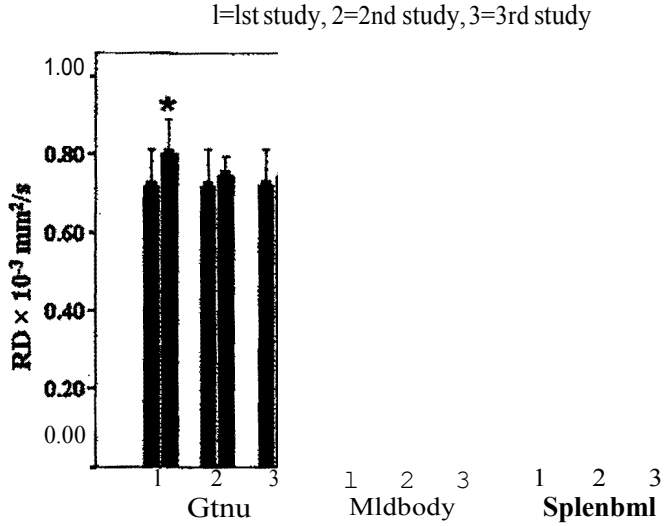
At 6 months follow-up, MD values in the midbody inversely correlated with BOT scores *(r* = -0.616, *P*= .019). A positive correlatlon was found between MD values in the genu and NCT A scores (r = 0.549, *P* = .042) after 24 months of injury.

At 6 months follow-up. AD values in the·midbody inversely correlated with BDT scores *(r* = -0.638, *P* = .014). AD values in the splenium inversely correlated with PCT scores *(r* = -0.590, *P* = .026) and BOT scores (r = -0.620, *P* = .024) after 24 months of injury, respectively.

At 24 months follow-up, RD values in the genu positively correlated with NCT A scores (r = 0.538, *P*= .047).

DISCUSSION

Using DTI, wc studicd Iongitudinally the white mat ter microstructure changes in patients with moderate TBI and investigated its correlation with NPT scores àt 6 months and 24 months following injury. In this study, a significant decrease in·FA values in the genu,



' Figme *5*. Bar plot of RD values ûom different regions of corpus callosum (genu, midbody, and splenium) studied at d t ti.me points (first study = within 2 weeks, second study = 6 months, and third study :::;: 24 months) in controls as well asm patients with TBL Theasterisk (•) indicates significant difference observed in patients compared with controls:The bars represent standard deviation. RD indicates radial diffusivity; TBI, traumatic brain injury.

im=fl#J *Change in volume values (mean ± SD) in units of cubic millimeter from the different regûms of CC in contro/,s and patients with TB/ at different time points (first study = within 2 weeks second study = 6 months, and third study = 24 months)*

Region	Control (mean ± SDJ			Patients (mean ± SDJ		
	FIrst study	Second study	Thirct study	ffrst study	Second study	Thirdstudy
Volume						
Genu	550.12±108.82	551.12±108.82	650.12±108.82	4n.18±168.87	516.75±94.99	443.06±77.04
Midbody	100.oo±s1.1a	798.00±91.78	799.00±91.10	851.62±326.99	101.31 ± 121.12	714.93±83.84
Splenium	796.12±115.37	796.13±115.37	796.12±115.37	744.93:1.:283.08	676.68±120.74	695.81±136.04

Abbreviations: CC, corpus callosum: TBI, traumatic brain injury.

splenium. and midbody along with significantly increased MD and RD values in the midbody and splenium over rime wa.s observed in patients compared with contrais. It has been suggested that the initial tearing. shearing, and misalignment of axons initiate a series of events that lead to further white matter damage, myelin loss, and gliosis.[33] Myelin degeneration is thought to continue for 1 to 2 years postin jury.[3] While we do not know the exact pathologie substrate responsible for the observed significant changes in the DTI-derived metrlcs at all 3 time points in different regions of the CC in patients compared with controls, this can be explained on the basis of axonopathy occurring simultaneously with degradation of myelin/gliosis within 2 weeks and persistence of these abnormalities after 6 months and 24 months following TBI. The myelin breakdown within 2 weeks of TBI reflects progressive structural degeneration changes, which correspond well to the findings from

lfiMl=II *Multiple comparisons using Bonferroni test for volume values from different regions of CC in controls and patients with TB/ at different time points (first study = within 2 weeks, second study = 6 months, and third study = 24 months)*

Region	Group	Group	Mean difference	Standard error	p	95%CI	
						LB	US
Genu	Control versus	Firststudy	72.937	41.579	.507	-40.514	186.389
		Second study	33.375	41.579	1.000	-80.076	146.826
		Third study	107.062	41.579	.075	-6.389	220.514
	First study, versus	Second study	-39.562	41.579	1.000	-153.014	73.889
		Third study	34.125	41.579	1.000	-79.326	147.576
	Second study versus	Third study	73.687	41.579	.489	-39.764	187.139
Midbody	Control versus	First study	--53.625	65.477	1.000	--232.284	125.034
		Seco_nd Stl!QY	16.687	65.477	1.000	-161.972	195.347
		Third study	83.062	65.477	1.000	-95.597	261.722
	First study versus	Second study	70.312	65.477	1.000	-108.347	248.972
		Third study	136.687	65.477	.247	--41.972	315.347
	Second study versus	Third study	66.375	65.477	1.000	-112.284	245.034
Splenium	Control vèrsus	First study	51.187	62.882	1.000	--120.391	222.766
		Second study	119.437	62.882	.374	-52.141	291.016
		Thirdstudy	100.312	62.882	.695	-71.266	271.891
	First study versus	Second·study	68.250	62.882	1.000	-103.329	239.829
		Third study	49.125	62.882	1.000	-122.454	220.704
	Second study versus	Third study	-19.125	62.882	1.000	-1®.704	152.454

Abbreviations: CI, confidence interval; CC, corpus callosum; LB. lower bound; TSI. traumatic brain injury; UB, upper bound.

iM=HI:1 *The scores of different components of NPT in controls and patients witk TB/ at different time points (second study = 6 montks and tkird study = 24 montks)*

	Scores (mean ± SD)		
		Patients	
NPT	Control	Second study	Thini study
NCT A	44.58 ± 6.74	84.99 ::1: 10.09	82.64 :¼.: 22.95
NCTB	74.42 ± 19.20	117.37 ±32.31	109.71 ±20.20
FCT A	n.58:1:: 11.81	188.64 ± 27,22	148.21 ± 44.17
FCT B	83.63 ± 11.44	198.43 ±20.30	175.00 ± 34.27
PCT	12.53 ± 1.87	5.89± 1.18	8.71 ±2.43
BDT	11.84± 1.89	5.29± 1.94	7.36±3.13
DST	10.05 ±: 1.87	3.43± 1.60	4.43±2.53

Abbreviations: BDT. block design test DST. digit symbol test; FCT. figure coimection test; NCT. number connection test; NPT, neuropsychologicartests; PCT. picrure completioo test; TBI. traumatic bn\in injury.

histopathological and DTI studies of wallerian degeneration in acute ischemic stroke.[39,40]

Serial **MRI** scans performed in patients with mild and moderate TBI over an average time of 1 year from the traumatic event have demonstrated progressive hrain atrophy even after mild brain injury.[41] This suggests that neuronal damage and loss occurring within hours of the 1nitial trauma might continue over an extended period as shown in experimental models.[42] Previous reports have suggested that AD and RD indices serve as biomatlcers of axonal and myelin damage, respectively[1,4,43] A longitudinal DTI study of mice demonstrated significantly reduced AD and FA values during the early acute phase after TBI (4-6 hours and 24 hours), corresponding to relatively isolated axonal injury. One to 4 weeks after trauma. AD "pseudonormalized," FA values decreased and RD values increased. These changes corresponded to demyelination, edema, and persistent axonal injury.[44] Sidaros et al[45] described longitudinal changes in 011 measures following severe TBI. They found decreased FA and AD values along with increased RD values in corpus callosum, posterior limb of internai capsule, centrum semiovale, and cerebral peduncles in patients compared with controk Regarding longitudinal changes, Sidaros etal[45] observed an increase in FA and AD values in patients with TBI in centrum semiovale and posterior limb of internai capsule suggestive of regeneration asopposed to degeneration.

In the current study, we observed a significant increase in FA values in genu and decrease in RD values in gcnu and splenium at rime points 2 and 3 compared with rime point 1, respectively, in patients. Although RD values showed a decreasing trend in genu over time, it did not reach statistical significance. However, FA and RD values continued to be abnormal in patients compared with

lfii=U=D *Multiple comparisons using Bonferroni test for NPT scores in controls and patients witk TBI at different time points (second study = 6 montks and third study = 24 montks)*

NPT	Group	Group	Mean dlfference	Standard error	p	95%CI LB	95%CI UB
NCTA	Contrai versus	Second study	-40.41	5.03	.000	-52.94	-27.88
		Third study	-38.06	5.03	.000	-50.59	-25.53
NCTB	Control versus	Second study	-42.95	8.48	.000	-64.06	-21.84
		Third study	-35.29	8.48	.000	-56.40	-14.18
FCTA	Control versus	Second study	-111.06	10.28	.000	-136.66	-85.47
		Third study	-70.64	10.28	.000	-96.23	-45.04
	Second study versus	Third study	40.43	11.04	.002	12.96	67.90
FCTB	Contrai versus	Second study	-114.80	8.05	.000	-134.83	-94.76
		Third study	-91.37	8.05	.000	-111.40	-71.33
	Second study versus	Thirdstudy	23.43	8.64	.029	1.93	44.93
PCT	Control versus	Second study	6.63	0.67	.000	4.97	8.29
		Third study	3.81	0.67	.000	2.15	5.47
	Second study versus	Third study	,--2.82	0.72	.001	-4.60	-1.04
BDT	Control versus	Second study	6.56	0.82	.000	4.51	8.61
		Third study	4.48	0.82	.000	2.43	6.53
DST	Control versus	Second study	6.62	0.71	.000	4.85	8.40
		Thirdstudy	5.62	0.71	.000	3.85	7.40

Abbreviations: BOT, block design test; DST, digit symbol test FCT, figure ccnnection test: NCT, number connection test: NPT. neuropsychological tests; PCT. picture completion test: TBI, traumatic brain injury.

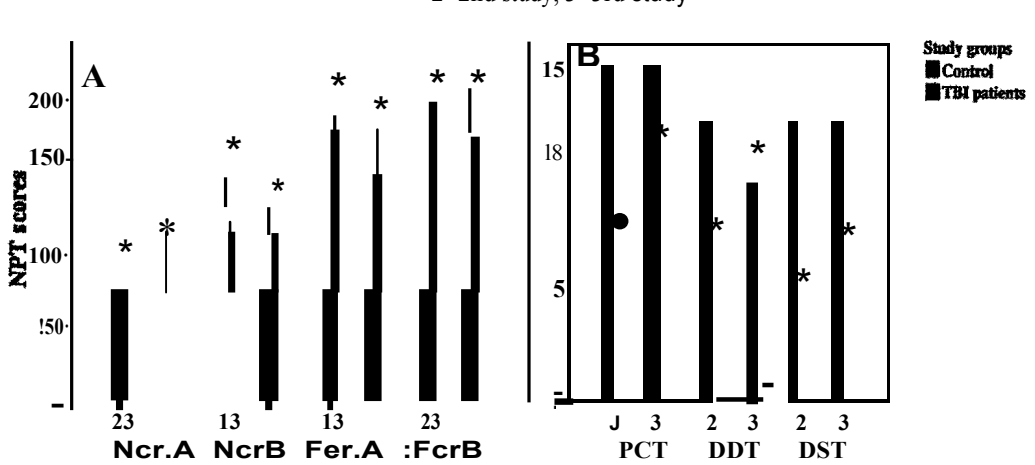


Figure 6. Bar plots sho the scores of various NPf in controls and in patients after 6 months (second study) and 24 months (third study) ofTBI. The connection tests (A) show significarit inc:reasc while the Wechsl.er Adult Intelligence Scale tests (B) show significant decreasc in patients group compared withcontrols. Asterisk (*) indicates significant difference in NPf scores relative to controls. The bars represent standard deviation. BDr indicates bloclc design test; DST, digit symbol test; FCT. figure connection test; NCT. number connection test; NPT, neuropsychological tests; PCT. picture completion test; TBI. txaumatic brain injury.

controls. This might be explained because of the incomplete a:xonal recovery or even axonal regrowth withoùt concomitant remyelination at 6 months and 24 months . postinjury. This indicates that some reorganization of· tissue microstructure might have ta.ken place ovcr time. However, patients' MD values decreased in the genu over rime but were still higher than controls' MD values, suggesting incomplete reversibility of the interstitlal edema.

Previous reports based on pathology, MRI, and DTI havedemonstrated cortico-callosal relations. Thesestudiesshow that changes in a particular lobe ofbràin are associated with degenerative changes in that region ofCC to which that lobe is connected through a:xons.46-48 In patients, more abnormal FA, MD, and RD values were observed over rime in midbody of CC than in genu and splenium, indicating that midbody worsened .over rime. These regional differences may beexplained on the basis of cortico-callosal relations. It is also evident from the cortico-callosal relations that the fibers originating from the frontal regions contribute to the anterior and mid part of the CC {rostrum, genu, and midbody) white the callosal fibers from the temporo-parieto-occipital junctional region course through the splenium and caudal portion of body of the CC.[49] The majority of the patients involved in our study had frontal injury and part of anterior parietal injury, which affected the midbody of the CC; this may be responsible for the regional dif.. ferences in *the* parts of *the* CC over time. Alth?ugh volume was quantified in the. different regions of CC, no regional difference in CC volume over time was found.

However, changes in DTI indices were observed, confinning that DTI appears to be a more sensitive measure than volume of injury in these patients.

In the current study, although the AD values showed an insignificant decrease in thegenu, midbody, and splenium of C:C within 2 weeks in patients compared with controls, this change did not persist at the 2 follow-up intervals. The insigni6cant decrease in ADvalues within 2 weeks of TBI can be due to some axonopathy occurringin patients, which recovered over rime, resulting in pseudonormalizatio of AD. This is also supported by the previous DTI finding in mice model, which showed that AD appeared to undergo a pseudonormalization, despite the continued presence of axonal injury 1 week to 1 month after injury.[44]

Cognitive deficits are more pronounced immediately following the injury and improve over cime.[50] In a previousstudy, patients with mild tomoderate TBI were compared with age-. gender-, and education-matched healthy controls on performance of NPT and informant-rated functional abilities at 1 and 2 years following injury.[51] No persisting cognitive or functional deficits were observed in these patients.[51] By contrast. although someof the NPT scores improved over time in our patients, these were still significantly impaired compared with controls, suggesting that these·patients may experience residual neurocognitive impairments at 24 months postinjury·.

Neuropsychological measures have been used to assess cognitive functions found to be impaired in patients with TBI, most conunonly in the areas of attention, visuospatial functions, psychomotor speed, and processing. Impairment in cognitive and multitask execution sequelae have been attributed to DAI or neural network disruption in the brain.[52] ln the current study, NPT scores were impaired in these patients at 6 months and 24 months, compared with controls. The DAI result· ing from the·shearing injuries associated with the head

trauma are believed to be responsible for persistent clinical symptoms and cognitive sequèlae. The observed significant correlation between D11 metrics in various CC regions and NPT scores at 6 months and *i4* months in patients with TBI indicates that CC axonal damage probably reflects axonal injury throughout the brain, and these neuropsychological functions are susceptible to impairment in a variety of differen:t sites and overlapping networks underlying these functions. Although this study shows some interesting observations in moderate TBI over time, it also has some limitations. Small sainple

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size and lack of histology for definitive intetpretation of the observed changes in the D11 metrics is a limitation of our study.

In conclusion, our study suggests that FA and RD in- dices aresurrogate markers of microstructural alterations in patients with TBI over time and correlate significantly with some NPT scores. The recovery in these indices in some regions of the CC is associated with recovery in neurocognitive deficits, suggesting that these indices may be used asan objective marker for the residual injury in these patients.

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Global White Matter Analysis of Diffusion Tensor Images Is Predictive of Injury Severity in Traumatic Brain Injury

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ABSTRACT

Conventional clinical nearobnaging is insensitive to axonal injury in traumatic brain injury (TBI). Immunocytocbemical staining reveals cbaages to axonal rnorpbology within houl"St suggating po. tential for diffusion-weigbted map.etic resonance (MR) in early diagnosis and manag.mient ofTBL Diffusion tensor imaging (DTI) characteriies the three-dimensional (3D) distribution or water diffusion, wbich is bigbly anisotropie in matter libers owing to axonal length. Recentlyt DTI bas been used to investigate traumatic axonal injury (TAI), emphaslzing regional analysis in more severe TBI. In the current study, we hypotbesized that a global white :matter (WM) analysis of DTI data woold be sensitive to TAI aeross a spectrum or TBl severity and injury to scan intervaL To investlgate this, we c:ompared WM-oaly histograms of a scalar, fradional anisotropy (FA), between 20 beterogeneous TBI patients recrulted from Detroit Medical Center, induding six mild TBI (GCS 13-15), and 14 healthy age-matcbed. controls. FA bistognun parameters were con:elated witb admission GCS and posttraumatîc amnesia (PTA). In an cases, induding mild TBI, patients' FA histograms were globally decreased compared with control bistograms. The shape of the TBI histograms aJ.so dift'ered from controls, being more peaked and skewed. The mean li'A, kurtosis and skewness were bighly correlated su.ggesting a eommon mechanism. FA histogram properties also c:orrelated wltb llPJury severity indexed by GCS and P'l'A, witb mean FA being the best predictor and duration of PIA (r = 0.64) bemg superior to GCS (r =0.47), Therefore, in this beterogeneous sample, the FA mean accounted for 40% of the variance in P'l'A. Increased dlffusion in the short axisdimension, Hkely reflecting dysmyeUnation and swelling of axons, ac:counted for most of the FA decnase. FA is globally deceased in WM, including mild TBit possibly refleding widespread in• volvement. FA changes appear to be correlated witb injury severity suggesting a role in earJy di,. agnosis **and prognosis of** TBI.

Key words: DAI; diffusion tensor imaging; DTI; fractional.anisotropy; TBI

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INTRODUCTION

r(1RAUMA11C BItAIN JN'JORY ('l'Bl) is a leading cause of .1. morbidity and monaüty in the United States that dis,. proport.ionately affeçts younger people. tberefore impacting individuals in the prime of life (Langlois et al., 2004), Head trauma is .most commonly associated with traospoltation-related accidents in addition 10 assaults, faUs m the elder1y and sport$ related injury (Man and Coronado, 2001; Meythaler et al., 2001). In fact. despite relaûvely fewer bodily .injuries tbaa in prior wars, neatly S01fl ofU.S. sokliffl .injured in the most recent Iraq war sustained TB!, bigher titan any previous war (7.oroya. 2005). The a>Sts are greai, botb to the .injured and family, but aJsotosociel.y due tolostor pmjecred loss of productivity, direct medical costs, disability disbmsements and frequent litigation {CDC, 2006). Medical costs inthe immediate post-injury perlod are exttemely high because of the need for critl cal care, while rehabilitation is o.ften intense and pIOtnlCled. The average direct hospital charges weœ esdmated to be $117,000 per admission in 1993 witbin the TBI Mode! Systems (Lehmkuhl et al.. 1993). These issues are further complicated by uncertainty in eslimat1ng injury severity and neurological outcome, pardcularly Jn the early post-iojucy perlod.

The ability to estimate the severity of in.jury and predict new:ological ouacome in the early pœt-iltjury periodielies onclinieal measures such asduration of coma and post-traumatic amnesia (PTA), wbich are prospective measures, white electroencephalography and neuroimagJng are most be)pful to rule out seizures (Vespa et al., 1999) and surgical complications (Smits et al., 2005), respectively. On the other hand, routine cranial computerlzed tomography (CT) and magnetic te$0nance imaging (MR.I) in TBI can be deœptively normal. be·lying significant diffuse injury (Rugg-Ounn et al.• 2001)•. Larger, focal lesi.on& such as contusion, extraaxial and parenchymal be.morrhages are visualized with clinical imaging, white diffuse injury is seen only the more severe cases.

The more clinically important pathology in TBI bas been shown to be diffuse rallier tbaa focal injury, resulting from hypoxic-ischemic injuty, brain swelling, and rraumatic axonal ,injucy (TAI}, the latter resulling from the stretcbing and shearing of white matter libers due to principally rollUional forces on the bmin within the eranial cavity (Gennnrem et al., 1982a). Patients may bave prolonged coma without focal lesions on imaging. TAI is DOt observed typically in conventional imagine but is evident on postmortem examination (Adams, 1988) witb eady, thickened axons and retracûon balls (Povlisboek, 1986), whicb represent afonn ofWallerian dcgeneration (F'ig. 1). Retraction balls can be visnalized using silver sœining and with immunocytochemical staining of amyloid precursor protein (APP) within 3 h (Sberriff et al., 1994). The development of *In vivo* imaging techniques sensitive to TAI in the acute post-injury period would be a major advance inthediagnœis and management ofTBl, possibly aiding in evaluaûon of new experimental treat·ments.

Recently, diffusion tensor magnetic-resonance imaging (DTI} of TAI basdemonstrated potential in TBI (Arfanakis et al., 2002; Huisman et al., 2004; Inglese et al., 2005; MacDonald et al., 2006; Meda et al.. 2006; Newcombe et al.,·2006; Ptak et al., 2003; Salmond et al., 2006). D'ITcharacterizes thethree-dhnensional(3D)spatial disnibutioa of water diffusion in each MR imaging vox.el (Bassel' and Pierpaoli, 1996; Conturo et al., 1996), This water diffusion is found to be anisotropie in indlvidual nerve fibers, being preferentiaJly oriented aloog the direction of the nerve fibers. Thus. in voxels witb nerve tracts naving fi.bers oriented in parallel, the principal direction of water diffusion reflects the direction of the nerve tnletl, In the presence of anisotropy, diffusion analysiscan bedescribed by atensor matrlx whlch issubject to a linear algebraic procedure known as diagonal·ization. The result is a set of three orthogonal eigenvalues, derived Crom thetbreeeigenvectors, representlng the major, intennediate, and minor axes chara.cterizing an ellipsoid. At least six diffusion gradients in non-eollinear

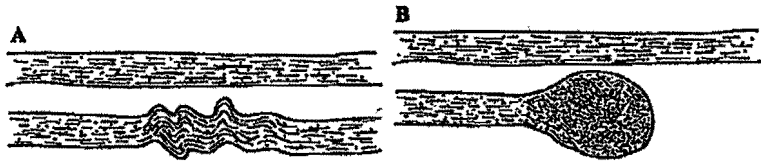


FIG. l, Dlastratlon of the changes Illat axons undefgo owing to cytoslœlettl pcrtUfbation Crom mikl traurnatic brnin btjury. (A) The top neuron is bealthy. In the bottom neuron, neurofilamemous and, generally, cytoskeletlll misalignmem is visible a short time aftet injury. This impairs axonal transpM. **(B)** Organelles accumulate in the injw:ed region. causing lhe uon 10 swell locelly ond subsequently disconneŒ fmm the *mt.* In Ibis figure. the dimeusinns of the axons relative to the interu.olllll spaœ do not neœssarily correspond to re4füy. (Reprinted ftom Arfanakis et al., 2002).

directions are applied to cak:ulate. for each pixel, a tensor (i.e.. 3 x 3 matrix) that. descrfües thls diffusion anisotropy. The overall magnitude and directionality of water diffusion in eaeh voxel also reflects the structural lntegrity of white matter fibers. DTI pl'O"lides us two sc:olatS called apparent diffusion *coefficient* (AOC} and fœctional anisotropy (FA)(Conturoet aJ., 1996; Sbimony et al.. 1999), which cJwactcrize the magnitude of water diffusion and the degree of anisotropy, œspectively, for each voxel. In addition., axiol (patallel to long axis of ftber) and radial (perpendicular) diffusivity are given by com:sponding eigenvector values.

The patbology of diffuse TAI in bumans *is* characterized histologically by widespread damage to axons in the brainstem. parasagittaJ white rnaner of the cerebtal cortoit and. corpus callosum and ls a consistent feature of TBI (Adams et al., 19'n; Adams et al., 1989; Blumbergs et al., 1994, 1995; McLcllan. 1990; Meythaler et al., 2001). The most frequent sites of TAI are in corpus caJ.. losum (CC), particulary. spleniwn, and fomix. which are found to beaffected even .inmild TBI (Blurnbergs et al., 1995). Hemispberic white mauer. brainsrem, and cerebellum are affected less fn:,quently but more often in seveie TBI (Blumbergs et al., 1995). Early investigmors reported diffusion changes in white malter reg.ions fre.. quently found to be involved in TBI (Arfanakis et al., 2002; Huisman et al., 2004; IngJese et al., 200S; Ptak et al., 2003). Reasoning that TAI i$ multifocal <*ir* diffuse. Inglese (2005) used a whole-brain DTI approach to mild TBI(MIBI). butdidnot findа difference between MTBI and controJs (lnglese et al.• 2005). One reuon for the lack of a differenœ between MTBI and eontrols using a wholebrain metbod may bave been the inclusion of gray matter and cerebrospinal tluid (CSF), neither of which would be expected to show a change in diffusivity following TBI. Therefore. in the current report we assess the sensitivity and clinical relevance of a whole--brain white matter-only metbod of analyzing diffusion tensor Images ûom a heterogeneous group of non-missile type TBl patients and age-rnatched healthy controls. Improvements in our ability to reliably segment gray and white malter in DTI images allowed us to test the bypothesis that this approach mittbt be more sensitive in MTBI.

METBODS

Palients

Twenty patients werewith injuries, including 17 trans·ponation reiated accidents and th.œe falls, were scanned. The mean delay-to-scan interval was 35.3 montbs. Inclusion criteria included (1) nonpenetrating TBI; (2) observer documented loss of consciousness (LOC) or posttcaumatic amnesia (PIA); (3) age> 11 yeors; (4) MR sof'e by routine clinical checldist. Exclusion criteria included (1) previously diaposed bnun disorder; (2) penetrnting TBI; and (3) parenchymal œid extraaxial hernorrhages witlt sutTtcient mass effect to cause midline shift or brain hemiation. Agemnge was I I-57 years (mean = *35.5;* SD = 14.6).As isconsistentwith moub.mininjuty studies and clinical cbamcteristics associated with traunultic brain lnjury, thete were a greater number of male participants (13)ascompared to females(7). lnjuryseverity as measured by depth of coma on the Glasgow Coma Scale (Teasdale, 1974) at time of admission nmged from mîld to severe TBI (Table 1). AU patients bad LOC or PTA (Table l) based on seriaI orientation testing using either the Galvtwton Orlelltation and Amnesia Test (00AT)(Levinetal..1979)ortheOrientationLog(Jacltson et al.• 1998). Patients were recnùted via physician-to-physician referral from within Detroit Medical Conter hospitaJs or outpatient clinics. Thirteen of the patients were participants in the Southeastem Michigan Traumatic Brain Injury System. which is part ofthe Traumatic Brain lnjury Mode!System Program {WWW.sem.tbis.org).

Controls

Fomteen bealthy volunteers without bistory of neurological·or psychiatrie disease or significant head trawna were smdied using the same DTI imaging parameterS as the patients. Age. range was 23-4.S (mean = 27.5; SD = *57)* for controls. whicb did not differ signifü:antly ûom patients *([J* =0.063. two-tailed t-test). The DTI scans were repeated tbree dines for each subject, to assess test-retest reliability. An patients or legal guardians and healthy contt0ls signed infonned consents and HIPAA (Heakh Insurance Portabnity and Accountability Act) forms approved by the Wayne State University Hwnan Investigational Committee.

Clinical Measures

Clinical measures sucb as initial and admission GCS were obtained from chart review. As noted above. duralion of PTA was assessed via serial testing using either the GOAT or Orientation log during the inpatieot rebabilitation stay.

MRI Protocol

Imaging wasperforrned ona l.5-TeslaSiemens sonata scanner using a standard binkage coil. Single shot T2-weighted, spin-echo echo-planar DTI was acquired insix non-colinea. directions on allsubjeçts asapanof amultiimaging protocol on bead trauma patients with the following parameters: 'FOY= *256* X 256 mm, 128 X 128

TAOI.& 1, PATU!NT DIIMOGRAI'llIC, CuffiCAL, AND UIAGINO CIIARAC'I'IWSTICS

Patienl no.	*Age <, ·ean)*	*Sex*	*Mechanistn*	*Delaysoscan*	*FAmean*	*GCS*	*PTA*	*Initial CT*
1	11.42	**M**	**MVA**	**2** months	0.376	3	135	L parletal hemorrhage
2	46.99	F	MVA	**8** days	0.394	*S*	*S*	**R** frontal contusion
3	24.76	**M**	**MVA**	4 years	0.411	6	24	Pontine, tbalamlc.. frontal bemot:rhages
4	**48.00**	F	Assallllffall	9 months	0.408	8	21	L frontal and temporal contusions, L parietal fx. R ott>ital fx
5	*42.SS*	**M**	**MVA**	lS years	0.386	6	27	**Negatlve**
6	26.79	**M**	**MVA**	*5* months	0.316	3	400	**TAI**
7	21.25	M	MVA	*S* months	0.357	3	9	Basllar skull fx, SAH, IVH. temporal contusions
8	S7.71	**M**	Fall *IS* ft	20 m0!1lhs	0.392	14	0	BJL temporal contusions
9	17.33	M	**MVA-bike**	4 months	0.328	*5*	73	L fronto-temporal contusion, skull fx
10	48.S5	F	**MVA**	3days	0.393	13	*9*	R. SAH, L hem. contusions, TAI
11	40.44	F	MVA	*45* days	0.387	8	**NA**	Contusions, hemO!Thages
12·	56.81	M	Pedestrlan vs. MVA	10 months	0.381	1S	1	L patietal contusion
13	20.90	F	MVA thrown 100 ft	7 weeks	0.389	13	37	L frontal ond R fronuil comusion. L frontal SDH
14	35.91	M	**MVA**	3 years	0.396	3	*S3*	Mldbrain hemorthage, occipital contusion
1S	25,89	M	Motàrcycle•tree, tbrown 15 ft	7 weeks	0.378	7	42	B/L frontal contUSiollll
16	18.81	M	Motorllycle-car	Il weeks	0.370	3	44	TAI
17	46.68	F	MVA	12 years	0.410	15	0	Negative
18	23.42	M	MVA	*S* years	0.409	6	*9*	LSAH
19	41.39	p	MVA	*9* yeara	0.403	13	3	Negative
20	*SS.16*	M	Pail 15 ft	22 days	0.391	7	*51*	L SDH, 1PG contuSion

matrlx size. in-plane resolntion of 2 X2 X4 mm. 3S slices. TR/1'B = *S800Jln* msee,. b values of O (corresponc:Ung toT2-weighted ima,es) and 1000sedmm2. and IOaveragea. Tbesequence wassimilarto previouslypnblished sequences (Huisman et al.• 2004; Sorensen et aJ., 1999). The tDtal acquisition tbne for tfûs sequeoçe was .41) sec (6.min S3 sec). In addition to DTI. the imaging protOCO! consisted of a conventional high-resohttion 3D FLASH Tl W for image co-regîstratlon and segmentation, T2W, Fluid Attenuation Inversion Recovery (FLAJR.). Arteria.l Spin Labeling (ASL). Snsc:eptibiUty Welghted 1maging (SWI). and MR specm,scopy seqoencea.

lmagq Procemng and Erutogram Generation

Ont approach W8$ motivated by Fillppi et al. (2001), who used a whole-bmin (GM, WM. and CSF) FA bistogram approach to multiple sclerosis. We soggest performing the analysis over WM followîng segmentation of the wholebrain intoathree-compartment model: **WM,** GM,andCSP.

All analyses were performed on a Windows plad'orm usingSPM2 (www.fil.ion.ucl.ac.uk) and other supportlngsoftware. FAmaps were genemted usingDTIStlldio v.2.02(cmnn.med,jhmi.edu) with 8Doptimalbackground noise suppœssion thresbold of SO uuits. Booh sobject's PA map (35 sllces) was segmented using SPM2 to give gray Dllltter, white matter and CSF companments. To achieve opthnal tissue segmentation, FA m.aps were initially spatial1y nonnalized to an FA templale image in standrud spaœ. The procedure included the following steps:

1. A single control $1Jbject's FA map was spatially normalized to the Tl templ.ate in SPM2 (affme only) and rhen used as a template for nonnallzing 13 c:ontrol FA maps (template 1).
2. A oew FA tenlplate was cieated by averaging 12 of the 14 spatia)ly normalized FA images. Two were omitted because of incomplete sainpling of the infe.. riot aspect of the brain.
3. Bach patient's original FA map was spaûally normalized(affine only) tothis new FA template; Bigenvalue images weœ spatlally normalized using the transfor. mation matrix computed from FA map.
4. Segmentation of each patient's spatialJy normalized FA image. using SPM2 to create a WM-only FA Image.

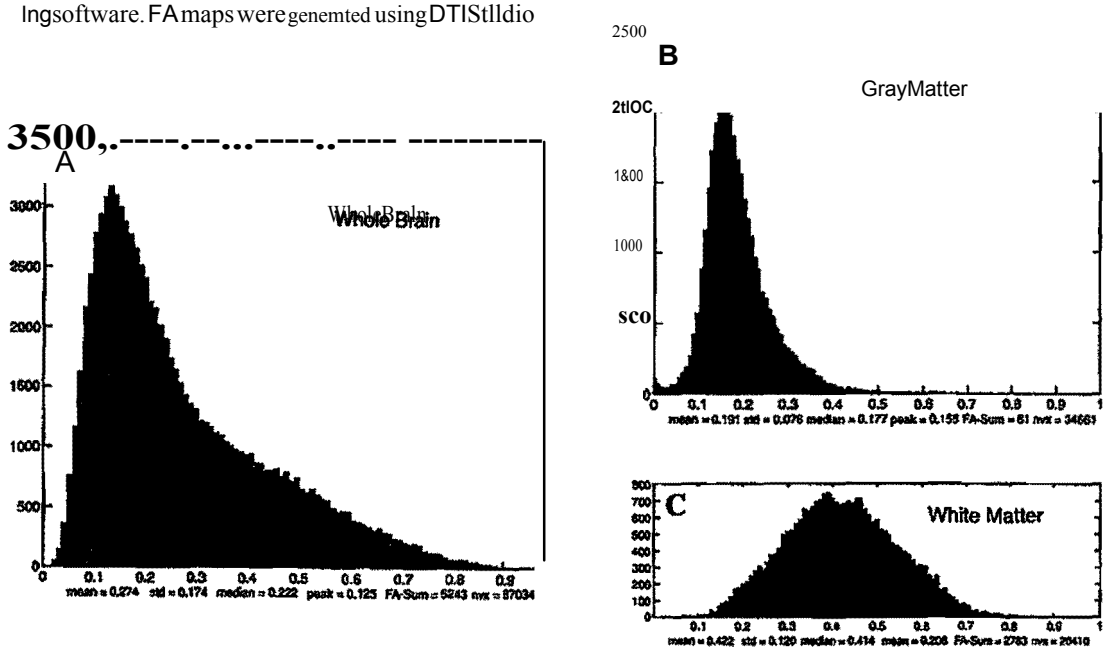


FIG.2. PA Hislograms. {A) Whole-brain histogtam aftef removal of FAof œtebrospinal fluid. (B) Gtaymatter-only.(C) White mauer-onJy. Not. the "shoulder" presenr ro therigbt of the peat of the whole-bmin bJstosnun. wbicb results front the superpo,-aition cf the WM and 0M bistogmms apparent aftef separation of WM and GM tissue classes. x-axis = FA (0-1}; y-axis = voxel frequeocy.

5. WM-only mask applied to Eigenvalue images to create WM-only Eigenvalue images.

The output *ot* eacli of the above steps wos inspected by anexperienced neurologist (R.R.B.) bef'ore moving to the nextstep.

MATLAB *v.* 6.5 (www.mathworb.com/) was used to create histograms after nonno.tizîng the total WM voxel number across subjects. The range of FA values (0-1) was divided into 100 equally spaeed bins. Figure 2 shows FA hist<>grams f'or one eontrol subject. com-.paring whole brain with gray matteM>nly and white matter-only histograms. For thecontrols. each of whicb were scanned tluee limes with DTI. an averaged histogram W. generated from the three indMduaJ PA histogtams.

Statistical Analysis

The mean FA (FAM) value for ail white matter voxels was computed from the white mauer mask. **An ANCOVA** was used to compare the FAM and Bigeilvalues between patients and controls aller conlrolling for age. Age effects bave been reported for PA (Char.Iton et aL, 2006; Ota et al.. 2006; Persson et aL, 2006; Pfetferbawn et al,, 2006; Salat et aL, 2005; Sullivan et al..2006) with :regional analyses typically reveallng dec.reased PA from early adulthood tbrough old age. A Speannan raak.-sum cœrel.ation was employed to œlate the FAM to clinical measures with dernonstrated prognostic value (i.e., ad-*mission* GCS and PTA). Slatisrieal analysis used **SPSS** v.14 (SPSS Inc. Chicago, IL). An obtained probability value of <0.05 was considered sign:ific:ant.

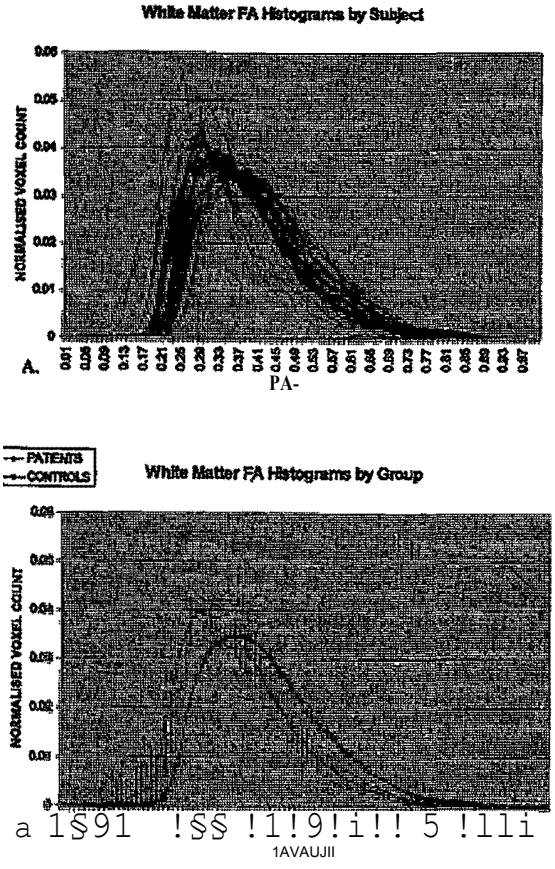


FIG.3. White matter FA histog'raml for ailsubjeds. Healthy volunteers in red, TBI patients in blue. (B)Twohl,mp.ms are group-averaged llistogtams. respecdvely, Whecœ taeh dota point is the meaa voxcl number for the FA bin range. FA tollll range \ffidmded into 100 eqœlly spaced bins with marker (elosed circle) at the cellfef of the bin range. Emir baB show stllndmddcviations.

TABLE 2. CoMPAIUSON OF FA IIISTomw(SuAPs PAIWU'I'IRS

PQI'GltlelU	Conm,l.s Meon	SD	T8l M	SD	Dlffermce	SN#knts t	P-vahte	F-t#t	p.w,t,u,
Slœw	0.944	0.062	1.19'2	0.174	0.248	*S.86*	<0.0001	*S.49*	<0.000S
Kurtosis	-0.692	0.137	-0.068	0.542	0.624	4.93	<0.0001	9.43	<0.0001
PA mean	0.431	0.013	0.38	*0.025*	-0.051	*1.1s*	<0.0001	3.01	<0.05
Peak	0..()36	0.001	0.042	0.00S	0.006	*S.23*	<0.0001	*1.26*	<0.0001

RESULTS

White Militer Freu.1ional Anisotropy Histograms

WM-only FA bistograms reveal.ed a sbift to the left. ie., decreased FA. of the entite distribution of FA valuesfor theTBI patientsoompared with controls, with vir• tually IIO overlap between groups (Fig. 3). 1n addition. thehistogramswere more peaked as they "shil'led" to the le.ft. The peak. c:hange was associated with other sbape changes sucb as (positive) kunosis and {positive) slœw for the TBI patients compaœd to the controls (îable 2). Thelle distribution eatures were highly cmtelated as migbt be e.x.pected (Table 3). Purtber examinatlon œ,- Yealed lhat the FA histogl:ams for the TBI patients wexe significantly l'llOre variable oompared witb controls witb k.urtœis de.monstr.atingthe greatest dilference in variance (Table 2. F-test). Histogram. panuneters (skew, kurtosis, FA mean. peak FA) were regœssed agaînst patient clinical scores (GCS and PTA) u.sing the group mean data for the controls once. FA mean was a beuer pœdi.ctor of clinical scores thon the otber parameters,. while PTA showed a greoœr correlation with histogram parameters than did admission GCS (fable 4).

Wlwle White Matter Fractional Ani.sotropy Mean

Test-rctest onthecontrols, eacbof whom were tluee tilnes in a single scanning session, revealed excellenttest--retest with a coefficient of variation CV = 0.006 (0.0025/0.424). As noted above, of the four bistogram sbape parametei:s, the wbole white matter FA mean (FAM) had the highest coxrelation with both OCS (r = 0.47, *p* = 0.04) and PTA (r = -0.64. *p* = 0,0CIT} (Ftg. 4) and was somewhat Jess corrdated with the other pamm.eters. whicb were hlgbly auto-conelated. Wbile irlter-subjeet varlability for FAM was twi<» for TBl patients thatof controls (wbich was J.ower than for the otber parameterS) the ANCOVA œvealed highly distinct distributions, as did a scauerplot of FAM (Fig. S).The six mild TBI cases were *oldot* than lbe controls (*p* = 0.02, t-test) but adjusling for ageinan ANCOVA stlllrevealed highly significant gmup differences (*F* = 20.24, *p* = 0.0001). The lime inrerval from injury to bnagjng, however, was nota predictor of FAM (*r* = 0.12. *p* = 0.1l).

Single Subject Compamon

Consistent with differences observed in histogram analysis. comparison of single subject images revealed differences ln FA rnaps, wbereconventional imaging was often unrevealing. FA differences could be apprec:iated after thresholding the images. Figure *6* compares a healthy control subject with a TBI patient (OCS = *5,* PTA .., S) eight days post motor vehk:le collision, demonstrating a 1eftward shift of the white matter FA histogram for the TBI patient compared with the comrol. FAM was 0.394 for the patient compared witb 0.457 for lbe oontrol snbject. with the coipus callosum clearly showing adecrease in FAfor theTBI patientafterthresholding.

Directional Di/fusivity

Fractional anisotropy was decreased in TBI patients compared with c:ontrol subjects as I10led above. A de-

TABLE J. CoRUL.\.TION IJE1'W8f:N FA IIJsToGaAM PARAME'I'ERS (h,\asON r)

Parameter	*Slœlv*	*K.1Ulœis*	*FAmean*	*Peok*
Skew		G.991	-0.886	0.989
Kurtosis	0.991		-o.ssa	0.990
PAme:m	-0.886	-0.8S3		-0.858
Peak	0.989	().99()	-0.858	

T.ut.E. 4. Coui:r.A'nON ICŒTWI'JI:N FA h'"IOORAM PAfWoŒTEIIS .\NI> Ct.INIC'AL SEvarn SI'EAJIM,\N *r*

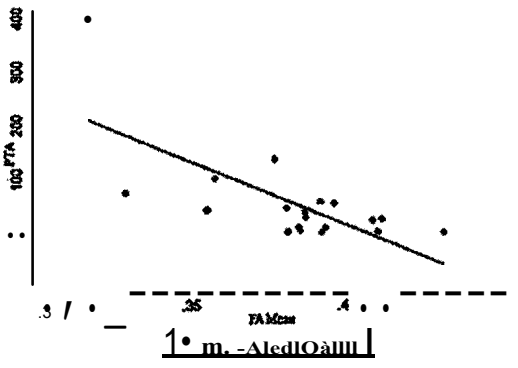
Para,nelf!r	*GCS*	*PTA*
SkeW	-0.163	O.S34
Kurtoais	-0.19	0.574
FAmenn	0.47	-0.64
Peak	-0.197	0.531

crease in FA can be due to a decrease in water diffusivity in the principal axis of diffusion (i.e., parallel to axonal fiber tracts), or an i.nciœse in the intennediate or minor axes (perpendicular to axonal fiberorientation), or a combination of eigenvalue change$, where the net result i$ moreisotropie diffusion. **A** decrease in parallet diffusivity would be caused by impainnent in axonal tran&port while an increase in perpendicular diffusivity would be caused by myelin or axolemma disruption (Song et al.,2002). Table *S* shows thealteœd diffusion for the TBI patients compared with the cootrols. Only perpendlcular {radial) diffusion {.\2, ,\3) was altered and was signifl.• cantly increased after adjusting for age. Of the scalar in,. dices-FA me.an. trace, and AOC-the FA mean was by fac- the most discriminating.

DISCUSS10N

The pœsent study demonstrates the ability .of a white matter FA blstogram-based method of analyzing MR diffusion tensor images to discriminate between persons with traumatic brain injwy and healthy volunœers and to predict sholHonn clinicat outcome from TBI. Histogram analysis revealed that tBr was 8$SOCÎated witb a global deerease in FA in white matter as well as a change in the shape of the distribution ()eptokurtotic; Fig. 3). For the FA mean. there wail no overlap between the 14 healthy controls and the 20TBI patients, including thesix MTBI cases (GCS 13-IS). Analysis of covariance was performed in order to adjust for age ditferences between groups and revealed highJy significant group differenœs for FA mean after ageadjustment. Despite the significant ago.adjusted group differences, the absence of any over* 1ap between the groups could be an artifact of age diffeœnces between the groups, since FA has been fOWld in a number of studies to decline with age (Charlton et al., 2006; Ota et al., 2006; Persson et al.. 2006; Pfefferbaum et al, 2006; Salat et al., 2005; Sullivan et al., 2006). The cllnical relevance of the change in FA was suggested l>y significant correlations witb indices of Injury severity, i.e•• GCS and PTA (l'abJe 3). The FA mean alone accounted for *40%* of the variance in PTA. This was lùgher rban for the other bistogram pammeœrs.

Regarding the shnpo difference and ieftward shift in TBI histograms. the peak FA. kurtosis. skew and PA mean were highly eotrelated. su.ggesting that a common mechanism (axonal injwy) was responsib1e for between-- and within-group diff'erences inlbese meosurements. The higher peak for the TBI pntients may reflect regression to the mean (i.e.. increased entropy} ond/or greater vul· nerability offibets with relatively higher FA than lower FA. Since the calloswn, corona radiata and capsules typically have the bighest PA values and are reponed t<> be most often htjW'ed in TBI (Adams et al., 1989: Blumbergs et al•• 199S). this may be the basis for the b.istogram shapechanae, Fw:thennore, TAIwould not be expected to be associated witb bigher FA values (decreased entropy) under.any cireumstances. since TBI..,_.. lated axonal injury will lead to decreased axial diffusion and inc:reased radial diffusion, both of which would Jead to rnott; isotropie diffusion. More specifically, axonal in· jury from TBI can result in primary or secondary axotomy which cause impaired axoplasmic uansport (Orady et al., 1993)(Christman et al.. 1994} and consoquent decreased axiaJ diffusion. TBI-related changes also include myelin breakdown. axonal swellings, retnk:tioa balls (Povlishock, 1986), and increased membrane penneability (PettUS et al., 1994), an of which Jead to an increase in radial diffusion. In the *cunent* study, only radial diffusion differed between the groups. being higher for the TBl patients. This findlng suggestS that for out heterogeneous group of TBI patients. wbich varled on delay to scan and TBI severity, demyelination, axonal swelling, and inc:reased membrane permeability were more impor-



PIG. 4. Scanerplot of nmk for Pl' A nnd PA mean. Cotrelatlon (Spearman r) w:11-0.64 for Pl'A and FA mean. *X-axis* is FA mem1; f-uisi.s!>TA (In days).

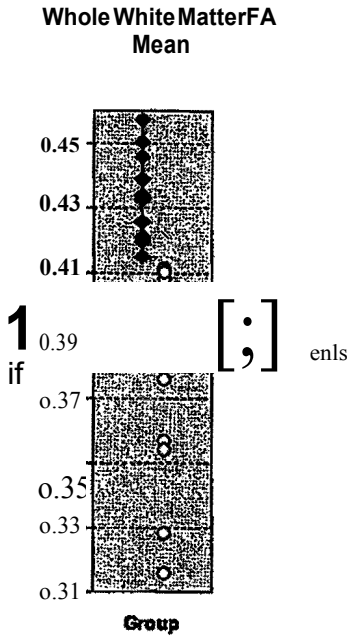


FIG. S. Scalter-plot of white malter PA means for an subjeds. Note theminimal overlap and gteater spread of FA.me® values for the TBI patients.

tant than changes in axonal transport and length. These findings are in agreement wltb Newwmbe et al. {2006) who scanned 42 acute (average of 2 daY$ post-injury), severe TBI patients and similarly foond only an increase in radial diffusivity using a whole-brain white mauer approach. Ontbe other band, these results should not be interpreted to imply that axial diffusivity is unaltered in TBL The current study utilized a whoJ.e..brain white matter analysis and therefoœ is not sensitive to regional variations in axial diffusion. whicb may average out over the entire wbile matter volume. Similarly. if axial diffusivity changes as a consequence of temporally discrete cellular and molecular changes following TB!, then a temporally beterogeneous group of TBI patients migbt not reveal a change, particularly if tbe crltical dme window is not sampled adequately. The latter is suggested by a longitudinal DTI study of miœ which demonstrated an early decrease in axial diffusivity in the füst 24 h in regi.ons or bistologically confirmed TAI (MacDonald et al, 2006). Wbile the timing of human and rodent axonal changes in response to TBl cannot be equated, these results highlight the imponance of D1 lscan timing in TBL As noted above, the FA mean was tbe best predictor orduration orposnraumatic amnesta, whicb is widely regarded as a good index or injury severity and cognitive outcome (Outhkelch, 1980; Kaœ and Alexander, 1994; Lewin et nt, 1979; McDonald et al.. 1994; Zofonte et al., 1997). Thestrength of tbe association wassomewbat surprising given therelatively smnll and heterogeneous sample ofTBI patients which varied widely intime from injury to imaging (3 da)'$ to 15 years), injury severity (GCS ""3-15) and presence of focal lesions and seoondary injury mecbanisms. The clinical correlation suggestS tbnt the histogmm chauges/FAM are reflective of a general effect on the brain of decœleration-accelemtion injury, Le.. diffuse axorud injury {Adams et al, 198S; Gennarelli, 1983; Oennarelli et at.. 1998; Gennarelli. 1993; Gurdjian and Webster, 1945; Holbum, 1943; Qm.. maya and Corrao, J969b). TAI patbok>gy bas been demonstraaed bistologically using sensitive immunocytochemistry {APP) from mild to severe head injmy (Blumbergs et al., 1994, 1995; Gentleman et al., Sbeniff et al,. 1994). Given that there was complete separation of patients fmmhealtby controls, including twomildTBI cases with nonnal conventional MRI from healthy controls, focal lesions could not account for tbese histogram differences.

To our knowledge, tlûs is the fll'St report demonstrating the relationship between the mean FA of the whole brain white matter and TBI severlty. Other groups bave investigated the useofDTIin TBIempbasizing acœgional approach, wbich is rooted in the observation tbat certain white matter structures. e.g., CC andsubcottical WM are commonly affected in T'.BI (Adams et al,, tm; Adams et al., 1989; Blumbergs et al., 1994, 1995; McLellan, 1990; Meytha]er et al, 2001). Arfanakis et al. (2002) looked at PA in flve regions includmg the CC and internai and exremal capsules in five MTBI patients and 10 contrOls scanned within 24 b of injury and foand asym--meuy in homologous WM regions in the patients and decreased FA compared with controls. Two of the panems were scanned again l month Iater with some nonnalization of FA values, suggesting a transient wîndow for PA decrease. Inglese et al. (2005) used early (avemge or 7 days from injury) and late (5 years from injury) imaged groups, wbich had cornparably decreased FA, suggesting. in contrast to Atfanakis et al. (2002), that_ tbe FA decrease may be permanent. It may be that the more severe cases studied by lnglese et al. (2003), compared with Arfanakis et al. (2002), explained lhe permanent FA decrease. Ptak et al. (2003) studied 15 patientS with a broad range of TB[severity and 30 controls, and developed a critical FA score from 12 ROis, which iroproved predic·tion of dichotomous outcomes using standard clinical predictors. Huisman et al. {2004) looked for a correlation between FA change and clinica.l measuresorseverlty and foundsignificanc:e formanuaJly derived ROlsin the sple-

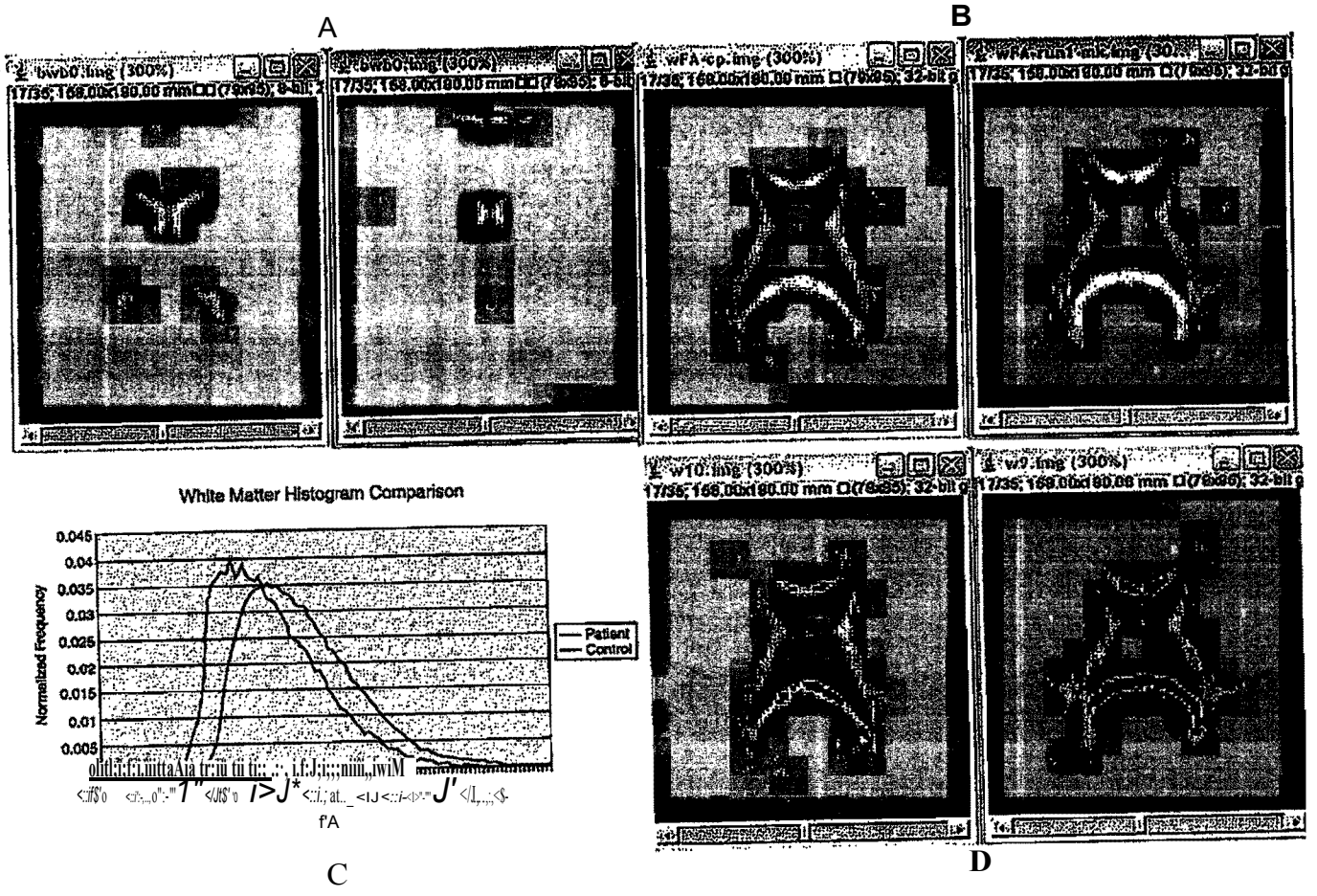


FIG. 6. Singlo-subject compllrillOll, Shows spatially normalized conventional and DTI FA MR images through corpus callosum {CC) and lnlernal capsule for single healthy '26-year-old contml and an acute 47-year-old TBl patient 8 days posi-injury (initial GCS = *S,* PJ'A'"*S* days), **(A)** Tl-weighted Images. **(B)** DTI FA map. (C) HblOgrams of FA valuea for healtby coatrol and TBI patient for ail white matœr vo,cels after gray•whito segmemation. (D) DTl FA map t.bresb-olded at FA> 0.7S wbere voxels excecding thi1thnlshokl are cololed red. Note the abselli:e or morphotoglcal featureS dlff'eren1Jating the TBI patient', imagea ln the top two po.nels. Conversely, the bottom clght two panels demonstrate the "leflward shlft" of the WM FA distribution and the relative paw:ity of very lùgh FA voxels for the TBJ patient cornpared witb the heallhy control. P, TBI patient; C. control aubject.

TABIE5. AND ScALAa ,oa Wum MAnD IN TBI PA.11EN'l'S ANI) CœrraoLS

		Ctmtrol:J		Patien4						
	Soitl'Clt	Metm	SD	MI1GI1	SD	Dlfference	Mean #JIII,IN	d/	F•ralio	P-wil1t1t
PA	Group	0.431	0.013	0.38	0.025	--0.0SJ	0.023	1	60.1S	0.0001
	Age						0.002	1	S.96	0.021
Àt	Group	1.188	0.016	1.194	0.038	0.00S	0.001	1	1.69	**NS**
	Age						0.006	!	7.6	0.01
Àl	Gtoup	0.711	0.02	0.776	0.216	0.065	0.042	1	27.76	0.0001
	Age						0.010	1	**6.8**	0.014
l)	Oroup	0.477	0.138	0.547	11.053	0.071	0.049	1	32.06	0.0001
	Age						0.010	1	6.5	0.016
Trace	Group	2376	0.0SS	2.517	0.141	0.141	0.214	1	20.01	0.0001
	Age						**0.078**	1	7.26	0.011
ADC	Oroup	0.792	0.019	0.839	0.047	0.047	0.024	1	19.88	0.0001
	Age						O.oo9	1	7.26	0.011

nium of CC and intemal capsule and clinicat measures (GCS and RaakJn scores) (R about 0.7). The cooelation waslow witbin thesubgroupofMTBI and controis.. however.

Inglese et al. (2005) sought to disdnguish 46 MTBI patients from 29 nomw controls us.ing both a whole-brain FA measure and an ROI approach. They found no diffeœnce between controls and patients for the whole-bœin analysis, but cc. internai capmle.. and centnnn semiovale had sign.ificantly Jower FA for the patients. This study differed in imponant ways from the cumnt study. First, Inglescet al.(2005) included only MTBI patients (GCS 13-lS), while the current study included six MTBI patients out of 20 TBI patients. Second, Ingleseet al. (2005} employed a whole-brain rather tban a whole white matter bistogram analysis. In our experience, inclusion of the gray matter, which is largely unaffected (at least FA) in non-missile type TBI, and whose FA distri• budon ovedaps with the left side of the WM FA histogram (Fig. 2}, reduces the differentiation by hîstogram analysis of TBI patients and bealthy controls. These IWO study design differences likely ex.plain the differing suit$. Thefact that theMTBIcasescould bedistinguished from the controls with histogram analysis suggests that the more important diffetenee between the two studies was not ln severity of TBI but in image analysis methodology.

Our approach differed importanlly from dlese prior studies by the use of a whole-brain, white matter-only, histogram-based method. Our hypothesis was that axonal hûury is suffJciently multi-focal tbat a regional approach may underestimate theextent of jnjury. Most regional approaches require some degree of manual interaction with thedata, whichcould addeuorand/or bias. An automated metbod of group analysis. voxel-based morphometry (VBM) (Salmond et al., 2006). is cummtly behtg investigated to identify sitesof common pathology across TBI patient$, but may not be cummtly optimized to bandle brains which may differ profoundly .in ventricular sizo and morphoJogy in subacute and cbronic cases. Mismgisttation of tissue classes forcven a small number of patients between groups will produce false positive er:rors.. caused by mistakenly c::omparingCSF(very low FA) with WM (high FA). The sensitivity of our whole whitemat• ter approach. however, depended on(1) the Invariance of the controls (i.e.., the baseline) and (2) the volume proportion of injured fibets with altered FA. We fowd that· the controls were hlgbly invariant in their FA dislribution. while the TBI FA histograms were ail shifted to the lefi relative to controls with the degree of the shift correlating with injury severity.

This preliminary srudy introduc:es a more specifü; global, histogram-based metbod tban pseviously reported methods by segmenting out and lncluding only white matter in the analysis. This method was able todiscriminate between controls and even MTBI patients. Further, there was a sttong correlation between our FA mean and PTA, despite the small number ofcases, variable time to scan (3days to15 years), variable lnjury mechanisms and presenceorabsence offocal Iesions. We believelllatclinicat relevance of our FA mean is rooted in its sensitivity to TAI, which is belîeved lO underlie LOC, PTA. and much of the neuropsychological impainnent in TBI. What caonot bedetermined from the current study is the specificity of the PA mean. since other disordets which affect w:M can show alteroo FA. Purthermore, the current report does not address the important Issue of diffu.. sivity or FA alteration over time. By necessity, a longi-

tudinal study in patients would best answer thisquestion. FmaJly, it is conceivable that a regional appiooch would discriminate controls and TBI better than the whole--bnùn white matter approach employed in theeutrent **paper and** might bea better predictor of cognitive outcome, butsuch an approach will require objective and sufficient sampling of WM regions. On the other band. optimal prediction of clinicnl outcome from TBI will likely entail determining both the proportionfvolume of white matter damaged by primary and secondary mechanisms **(e.g.,** hypoxia, hypoperfusion, and seizure} as well as focal injury. Therefore, multimodal MRI, capable of measuring metabolism, functional connec:tivity and perfusion will likely **be important** instruments in predicting global and domain-specific cognitive outcomes in the future. For now, the eurrent study and cited reports add to the literature supporting a prominent role for diffusion-based imaging in determining injury severity and outcome from TBI. These advances should Iead ro improvements in management ofTBI and to additional outcome measures with which to guide the development of new therapeutics.

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Original Research

Application of Vo:xelwise Analysis in the Detection of Regions of Reduced Fractional Anisotropy in Multiple Sclerosis Patients

Sunil A. Patel, MS,[1.2] Barbara A. Hum, MD,[3] Carlos F. Gonzalez, MD,[4] Robert J. Schwartzman, MD,[5] Scott H. Faro, MD,[1.2] and Feroze B. Mohamed, PhD[1 2]*

Pu.rpose: To lnvestigate the utility ofvoxelwise analysis in thedetection of lestons in the normal appearlngwhitematter (NAWM) of individual multiple sclerosis (MS) patients.

Materlala and Methods: Diffusion tensor imaging {DTI} was perfonned on 10 normal controls and sbc pàtlents with MS lestons. The fracttonal aniSOtropy (FA) inaps dertved from the diffusion-welghted bnages were then spatlallynormalized (via an affine transforniatlon) tnto Montreal Neurologtcal Institute (MNl) space. and the normalized FA map of each of the patients was compared voxelwisc with the narmaltzed FA maps of the group of normals in a one-sample t-test {P = 0.0001). Two lndependent board·certifted neuroradiologtstsreviewed the data.

Results ln the patient data for all six cases, the two reviewers determined detectton sensitivftles of 72% and 96% for the voxelwise technique based on known fiuid·attenuated tnversion-recovery (FLAIRJ lestons. In addl·tlon. between the two reviewers, nlne NAWM regtons ex·hlbtting FA reducttons were identifted in the six patients. However. numerous regions of abnormal FA were detected that were attributed to poor intersuqtect îmage registration.

Conclusion: Voxelwise analysis of spaUally normaltzed FA maps has the potential toidentify regtons of FAreduction in lesions and ln the NAWM of indMdual MS patients in a rapid and reproducible fashion.

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Key Wol'ds: fracttonal anisotropy: diffusion tensor lmag·mg; DTI: multiple sclerosts; voxelwtse analysts

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MULTIPLE SCLEROSIS **(MS}** 1s a demyelinatlng disorder of the central nervous system. Magnette resonance 1magtng **(MRI}** has been very useful in tenns of both quantitative and qualitative assessment of the disease and in tenns of providing insight into the pathological mechanisms underlying the disease (1). Conventlonal MRI lncludes T2-weighted, Tl-weighted, and flutd-attenuated inversion-recovery (FLAIR) 1magtng techniques that can identify and localize MS plaques. However, newer imaging techniques have recently emerged that can provide additional Infonnation from that which ts routinely available. One such technique is diffusion tensor imaging (DTI), which allows for assessment of tissue architecture based on the directional properties of the diffusion transport of tissue water molecules (2.3). These diffusion measurements conta.in useful in·formation about the tissue microstructure and architecture. Of the several indices used to charactertze the diffusion tensor. the most commonly used quantitles are mean ditfusivity and fractlonal anisotropy (FA}, which measures the degree of anisotropy of the dlffu.sion of water (4).

One of the uses of DTI ln studying MS lestons anses from the fact that changes in FA can be used to indtcate tissue damage. It is currently understood that anisotropy is attrtbuted to the presence ofbarrters todlffuston in certain directions (3). For example, in the white matter of the brain, water is moremobile along the direction parallel to axons and is obstructed by the axonal membrane in the directions orthogonal to thls direction. Also, the observed anisotropy increases in the brain postmyelination. suggesting that myelln is an important contributor to anisotropy (5). Thus, reductions ln antsotropy from normal values can be used as an indi·cator of dernyelination and axonal loss.

Several studies have recently shown changes in diffusion anisotropy in well-defined MS lesions as well as in normal appeartng white malter (NAWM) in MS pa-

tlents (6-8}. These tnclude changes not only in regions distant from the plaques but also in the periplaque regions, potentlally Ieading to a reevaluatlon of the true size of lestons (7.8}. This additional lnformatton on pathologtcal regtons is stgnificant considertng that there 1s not always a good correlation between lesion load measurements based on conventional T2-wetght-1ng imaging and clinical disability (9).

However. few. if any, ofthese studies have attempted to detect FA abnonnalities in the brains of indMdual subjects. Many, if not all, of the studies to date have been group comparisons of FAvalues between controls and patients, with the goal being to establish that there are differences in FA between the twogroupa. However. to be clinically useful, it ls necessary to ldenttfy regions of abnormality rapidly 1n a single subject. A voxelwise approach to detect vartous parameter changes in lndi-Vidual subjects has be.en investtgated by several research groups (10-13). In these studies, image data for both the control group and the patient group were spatially normalized into a common space to brtng homologous structures into allgnment across subjects. The data for each patient were then compared indMdually to the data for the entire group of control subjects at the Ievel of indMdual vox:els. For example, Eriksson et al (10} compared each of 22 patients afflicted with epilepsy and malformations of cortical development with a control group of 30 subjects and were able to detect differences in both mean diffusMty and FA 1n the brains of indMdual subjects.

Similarly, application of an automated technique for performtng voxel by voxel analysis to detect FA abnormalltles in a single subjectwould be extremely useful in the DTI analysis of MS patients· brains, especially in areas of NAWM, in whlch the lestons are not readily visible on conventtonal **MRI.** This could be useful to track the progression of the disease within a gtven subject or to monitor its response to treatment. To our knowledge. such a technique has not been applied in quantifying DTI changes in MS patients. Thus, in this study, we investtgated the feasibility of a vox:el-level approach in the detection of diffusion anisotropy changes (more specifically. reducttons in FA) in indMdual MS patients.

MATERIALS AND METHODS

Subject Demographics

DTI was perlormed on 10 control subjects and six patients that fulfilled the McDonald (14) crlterta for MS. The control group consisted of three females and seven males. The patients were all female, with disease duration rangtng from four to 19 years{mean disease duralion = 10.2 years; standard deViation [SD) 5.3 years). The MS phenotype was relapsing-remitting for five patients and secondary progressive for one pattent. The controls ranged ln age from 29 to 45 years (mean age = 33.5 years; SD = 5.3 years}. and the patients ranged in age from 44 to 56 years (mean age = 48.8 years: SD = 4.4 years). Thisstudy wasapproved by the Instltutional ReView Board (IRB) of our institution and informed consent was obtatned from all subjects.

Image Acquisition

DTI data were acquired using a 1.5TVision MR scanner (Siemens Medical Systems, Erlangen, Germany) that collected diffuston-wetghted images uslng a spin-echo echo planar imagtng (EPI) sequence. Diffuston-sensittzing gradients with ab valueof 1000 seconds / mm^2 were applied in six noncollinear directions to fully determine the diffusion tensor. An image (b_0 image) without diffusion weightlng (b = 0 seconds / mm^2) was also collected. A total of 20 ax:Ia1 sllces (with 6-mm thickness and an in-plane resolution of 1.8 x 1.8 mm) coverlng the enttre brain were tmaged for eachsubject. Astandard quadrature head coll was used for imaging, and the tmaging parameters included: TR = 6000 msec, TE = 100 msec, field ofview (FOV) = 240 mm. matrix siZe = 98 X 128 (98 zero-filled to 128), and four acquisitions. FLAIR imageswerealsoacqutred for the MSpatients. Atotal of 20 ax:Ia1 slices (with 5-mm thickness and an in-plane resolutlon of 0.86 X 0.86 mm) covering the entire brain were tmaged for each subject. Spacing between slices was 1.5 mm. The FLAIR imagtng parameters included: TR = 9000 msec, TE = 110 msec, TI = 2380 msec, FOV 220 mm, and a matrlx size = 256 x 256.

Spatial Nonnalization of Data into a Standard Space

After image acquisition, the data were transferred to an independent workstation for calculation of the diffusion tensors. FA images were then created for both the normals and the patients using an in-bouse modtfled version of the diffusion tensor toolbox (Russ Poldrack, Massachusetts General Hospital (MGH}-NMR Center, Boston, MA, USA) of Statistlcal Paramefric Mapping SPM99). A template in Montreal Neurological Institute (MNI) coordtnate space was then created (ustng a method stmilar to the one presented by Black et al (15)) by normalizing {Via a 12-parameter affine transformation) individual boimages of the normal subjects to the EPI template available in SPM99. Ali images, including the FA maps descrtbed below, were resampled to an isotropie voxel size of 2 x 2 x 2 mm and resliced to fit the bounding box of the template image in the spatial normalization process. The 10 normalized images were then averaged to create a mean bo image template. The ortginal bo images were then normalized to the new template and the restùttng transformation parameters were applied to the FA maps, whtch were then smoothed using a 4 x 4 x 12 mm Gausstan kemel The combined FA maps of the 10 normal subjects nowcomprised the FA atlas of the normal brain. Similarly, the FA maps of the indMdual MS patients were normalized into the same neuroanatomical space as the normal subjects and then smoothed with a 4 x 4 x 12 mm Gaussian kemel.

Comparison of Patient Data With the Contrai Subject Data

The nonnallzed and smoothed FA map of each pattent wasthen subtracted voxelwise from the normalized and smoothed FA map of each of the controls. resulting in 10 difference images for each patient. The difference

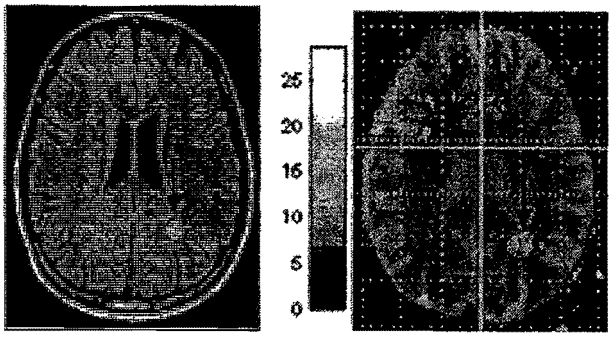

Figure 1. FLAIR Image Ueft] and statlsttcal map overlaid on top of the normallzed ho ùnage (right). Thecolor indicates the value of the t-stattstlc.The t-statlstic image was thresholded at $t = 6.01$ (P=0.0001 uncorrect.ed) so that only t-stattstic values greater than 6.01 are displayed.

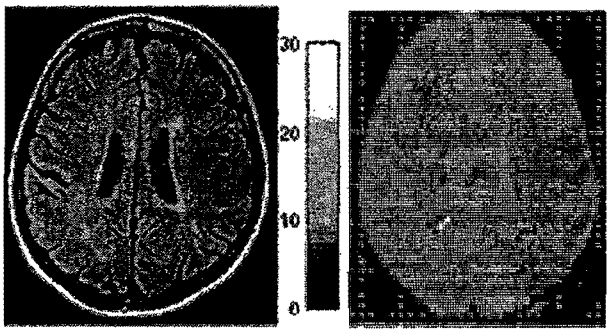

Figure 2. FLAIR image neft} and stattstlcal map overlaid on top of the nonnallzed ho image (right). [Color figure can be viewed in the online Issue, which is available at www.interscience.wiley.com.)

images were then analyzed at each voxel using a one-sample t-test in SPM99 to see if the difference in FA was stgruficantly greater than O (corresponding to a reductton of FA in the patient data). Maps of the t-statistlc were generated and thresholded at t 6.0 1 (P =0.0001 uncorrected) so that only t-values above the threshold were visualized.

Assessment of Per.form.ance

The thresholded t-statistic maps were then compared with FLAIRimages, which served as the "truth" or wgold standardfl datafor known lestons in thts study, to see if the t-statistic maps were able to detect FA reductlons in known MS lesions. To assess the performance of the method in detectlng FA changes in the NAWM. regions of interest (ROis) exhibiting low FA were identified by a board-certified neuroradiologtst based on the following crtteria to minimize the probability of false-positive values due to misregistratton and noise. Only regions that were larger than 10 contlguous voxels and that were substantially far from the ventricular system, subarachnoid space within the sulci, and calvarium were selected. For each region that was ldentified, an ROI was placed on the b_0 image of the patient and in the corresponding location on the bo image of one of the contrais whose image was deemed (by visual inspection) to be well-registered to that of the patient. Toese ROis were then used to measure the FA values on the FA maps, which were already in register with their corresponding hoimages. Foreach tdentified region, the FA values in the two ROls (one in the patient and onein the control) were compared usinga two-sample t-test. ROis were placed and the mean and SD of the FAvalues were measured using MRlcro (Chris Rorden, University of Nottingham, Great Britain). A second board-certified neuroradiologtst reviewed the images to confirm the findings of the first reader.

RESULTS

Figure 1 shows an example of the results observed in this study when comparing patient FA maps to those of the FAatlas of contrai subjects. (The color bar between the images represents the values of the ·t-statistic.) As seen on the t-statlstic map in the figure, there were numerous regions of statistically stgnificant FA reductions shown in red and orange. Note that the large lesion (arrow) on the statistlcal map in the left hemtsphere corresponds well in location with the known lesion (arrow) shown on the FLAIR image. lt can be seen that the center of the lesion (yellow) exhibits more stgnificant FA changes than the peripheral portions (orange}. Also, there are numerous reglons of FA changes in areas not containing lestons on the FLAIR image. Figure 2 shows the FLAIR and t-statistic data for another case. Notice that the locations of the two periventricular lestons on the statistlcal map are obscured by a substantial amount of FA change being detected along the border of the ventricles. Note also that the lesion posterior to the right ventricle was not detected. Figure 3 shows an exarnple of a potential **NAWM** lesion, whlch satisfied the crlteria for having a low llkelihood of representtng a false-positive lesion caused by misregtstration. Also shown in this figure is the location of the corresponding ROI used on the control subject for compartson.

Considertng the patient data for all six cases, 25 lesions were positively identified on FLAIR images by the first image reviewer (a board-certified neuroradiologist). Of these, 18 were detected by the statlstical analysis of the FA maps. **A** total of seven NAWM regions exhibiting

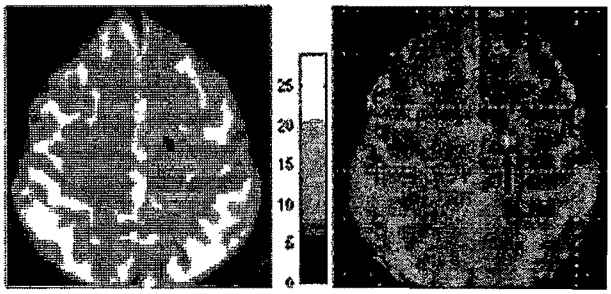

Figure 3. Example of a regton of FAreduction in NAWM (right) along with the ROI drawn on the control subject (left} for cornparison. (Color figure can be viewed in the online issue. which is available at www.intersctence.wiley.com.]

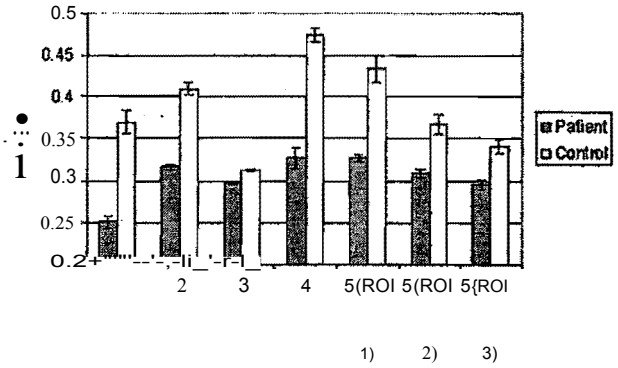

Figure 4. ROI data for regtons showing FA changes in the NAWM. {Error bars indicate standard error. No **NAWM** lestons were found by the first image reader in pattent #6.)

FA reductions were identified in five patients. These regions included one in the rightantertor temporal lobe, one in the right frontal lobe, two in the rtght postertor frontal lobe, one ln the left partetal lobe, one in the anterior limb of the right internai capsule, and one in the left posterior frontal lobe. ln all seven regtons, the FA values were lower ($P < 0.0002$) in the patients than in the corresponding reglons of the well-reglstered controls. The results for each of the seven ROJs are shown in Fig. 4. A second board-certified neuroradiologlst also reviewed the images and ldentified 26 lesions across all six subjects on the Fr.AIR images. Of these, 25 were considered by this second reader to have been detected by the statlstlcal analysis. The second radiologist agreed with the NAWM findings of the first neuroradlologtst but also identified two addit.ional regtons, one in the left frontal lobe of one patient and one in the right 'frontal lobe of another patient, which satisfied the crl· terta for: havlng a low likellhood of being caused by misregistration.

DISCUSSION

As can be seen from Figs. 1-4, the voxelwise analysls of the FA maps was capable of detecting known MS lestons and also ofidentifying potential lesions in regtons of **NAWM.** However, as can also be seen from the figures, numerous false positives appear in the t-statlstlc maps. Thus, care must be taken in interpretlng the regtons of FA differences detected using the voxelwise technique as some of these may bedue to mtsregistratton of images, whlch results in a comparison of different tissue types across subjects. These misregistratlonlnduced false-posttives should generally be more pr:evalent in reglons where gray matter or cerebrospinal fluld (CSF) is being compared to tissue **with**a higher FA. Thus, FA reductions shown in the CSFand gray matter should generally be disregarded. However, FA reductions shown in the white matter can be safely assumed to be valid FA r:eductions since there ls no other tissue type with higher.FA than the white matter. Theinability to reliably detect FA reductlons in the gray matter should be kept in mind when utllizing this technique, as it is now apparent that MScauses gray matter lesions as well as white malter lestons (16).

The major contrtbutor to the presence of these false positives 1s the use of the 12-parameter affine transformation (rotation, translation, scale, and shear) to bring homologous structures of different brains into alignment. The normalization algorithm has successfully matched the images globally but has not matched the variations in local structure, such as gyral and sulcal variations, differences in ealvartal shape, and changes in ventricular size. Thus, when performing the voxelwlse analysis, it iS possible for FA differences to occur as a result of poor local image regl.stration due to normal human structural varlability.

One obvious solution that mayaddress this problem is the use of a nonlinear reglstratlon algortthm that is capable of performing local deformations of brmn structure to match the local variation in brain structure across subjects (17.18). However, the use of nonrigtd regtstratton is complicated by the presence of leslons ln the images since the presence of these lestons would cause the algortthm to b:yto ll1inimize regtons of abnormality and introduce distor:tions in the surrounding tissue (19). A minimization of the leston itself is not a crttical issue since its presence ls already known (i.e.• it was seen on the routine clinical images). However, the distor:tion introduced ln the surrounding tissue maybe more problematic. One potentlal solution to thls problem oflesions interfering with the nonlinear registratlon algorithm is to use Iesion masking (19) to mask the cost function used by the registratlon algortthm ln the regtons where a lesion exists. However, this would substantlally reduce the degree of automation of the technique and would llmlt lts use in cllnical setttngs. Thus, it appears that a nonlinear normalization algorithm that ls insensttve to the presence oflesions ls requtred.

Another potential confoundtng factor in this study 1s age. There was a statistically significant ($P < 0.00004$) difference ln age between the control and patient groups. Severa! studies have shown an age-related decline in FA ln varlous regions of the brain, including the frontal white matter, the posterior Umb of the intemal capsule, and the genu of the corpus callosum (20,21). Thus, there ls the possibility that some of the FA reductions that were detected in the analysis may have been due, either in whole or in part, to the age difference between the patients and the contrais. However, it should be pointed out that these age-related changes appear to be localized to ccrtain regtons. For example, Salat et al (20) found that FA in the temporal and posterior areas was less affected by age. Thus, since many areas of the brmn do not show an age-related effect. the findings of this study are stlll valid in these regtons. Needless to say. future work should avoid this confound through more careful matching of age between patients and controls.

In this study. 18 out of 25 known FI.AIR lestons were detected by the voxelwise method. This corresponds to a detection sensltMty of 72%. A second neuroradiologtst identified 26 FI.AIR lestons, 25 of which were detected by the statlstical analysls. This corresponds to a detection sensitivity of 960/4. lt is possible that the mtssed lestons did not exhibit the samedegree of pathological changes (axonal loss and demyelinatlon) that would produce a reductlon in FA. FLAIR and T2-

wel.ghted MRI. although very sensitive to pathology. are not veryspeclfic in tennsof type of pathologtcal process detected. For example, inflammation, edema, demyelinatlon, and axonal loss will all causesignal hyperintensities (22,23). Regarding the regtons of reduced FA in the NAWM, unfortunately, a definitive conclusion regarding their pathology cannot be made without taldng tissue samples and performing histological analysis or without the collection of longitudinal data to see 1f the NAWM regions showing FA reductions eventually show signal changes consistent with MS plaques on conventional MRI.

One area in which the technique described in this study could have tremendous impact is the longitudinal studyof patients to monitor the progression and/or treatment of MS. Studies have shown a lack of correlation between T2 lesion load and measures of clinlcal disabillty such as the Expanded Disabillty StatusScale (EDSS) score (9.24}. Greater correlation using diffusion measures have already been shown (25) and it thus seems reasonable to monitor patients' dises.se progression and response to treatment with a technique thatis more complete and that more accurately reflects their disabillty.

In conclusion, the voxelwise analysis of FA maps as perfonned in this study is capable of detecting known MS lestons and also of identlfy:lng potential lesions in the NAWM of individual MS patients in a rapid and reproducible fashion. However, several issues (such as misregistration of the images} must be gtven careful consideration when using a technique such as the one utilized in this study. Future work will address these issues and attempt to interpret more deflnitively the pathological signilicance of regtons of FA change in the NAWM. These preliminary results, however, are very encouragtng and warrant further investigation.

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EXHIBIT 6

IN **THE UNITED STATES DISTRICT COURT**
FOR THE DISTRICT OF SOUTH CAROLINA

FLORENCE DIVISION

HUANNJ YANO-WEISSMAN,	)	**C.A. NO. 4:07..CV-3643**
	)	
PLAINTIFF.	)	
	)	
v.	)	
SOUTH CAROLNA PRESTRESS CORPORATION,	)	
	)	
DEFENDANT.	)	

AFFIDAVIT OFF. REED MURTAGH, M.D.

STATEOF FLORIDA)
)
COUNTY OF HILLSBOROUGH)

F. Reed Murtagb. M.D. being duly swomt deposes and states as follows:

l am over twenty-one years of age and am otherwise competent to mak.e this affidavit.

1. That I am carrently employed by lmaging Consultants of Florida at 3301 USF Alumni Drive. Tampa, Florida 33612. 1 attended the College of William and Mary and obtained a B.A. degree in 1966 and 1he Temple University School of Medicine where I obtained an M.D. degree in 1971. I did a Surgery Intemship at the University of North Carolina and Resîdency in Diagnostic Radiology at the University of Miami, Jack.'iOn Memorial Medical Center. I also did a fellowship in Neuroradiology at the University of Miami and I am certified by the Amerlcan Board of Radiology in which I have an added Qualification in Neuroradiology. My Curriculum Vitae is attached hcreto as lix.hibit A. l am a member of the American College of R.adiology as weH as the American Society of Pediatrlc Neuroradiologists, American Society of Functional

Neuroradiology, Amerlcan Society of Spine Radiology and Association of University Radiologists.

2. I servcd as the Direcior of the Division of Neuroradiology at the University of South Florida College of Medicine in Tampa Florida and was a Professor of Radiology at the University of South Florid.a CoUege of Medicine Department ofRadiology.

3. I am currently a membcr of the Diagnostic Imaging Department of the Moffltt Cancer Center and Research Institute and Professor, Department of Oncological Sciences at the University of South Florîda College of Medicine at the Moffitt Cancer Center.

4. I am a Journal Reviewer for the A.r.nerican Journal ofNeuroradiology. the Journal ofMagnetic Resonance Jmaging and Neuroradiology. r have published numerous papers a list of which is included in myCurriculum Vitae.

5. I have had signiticant training in the diagnosîs of cognitive disorders as well as resea.rch and development in applications of MRI. I am very familiar with Diffusion Tensor lmaging and Ùle fact that is well reviewed and peer-reviewed joumals. The technique is generally accepted by the medical comm.unity and is clinically reimbursable by most insurance companies.

6. DTI improves the diagnosis and management of patients suffering from traumatic brain injury. Thave been actively involved in MR Imaging since 1984.

7. I have bcen actively involved in MR imaging since 1984 and in Diffusion Tensor Imaging since 2004. The first DTI paper was publishcd in 1994. There are currently 3,472 papers on DTI which have been pub1ished in peer-revicw journals to date of whlch 83 are on DTI and TBI. A eontrol group was used for statistical analysîs of rcsults for 35 of the 83 papers.

1

8. I have reviewed the DTI studies dated 7/15/2009 performed on Heidi Yang, Weissman by Michael Lîpton, M.D. of Albert Einstein Medical Center and Montefiore Hospital in New York. Dr. Lipton is a well respected neuroradiologist who is published in this field.

9. The DTI studies performed by Dr. Lipton are state of the art and done properly in everyway.

10, DTI technology is currently being used to diagnose braîn injury ln individual patients using the methodology employed by Dr. Lipton. This methodo]ogy is set forth as the subject ofpeer reviewed literature ofwhich I am aware.

11. 1 agree with Dr. Lipton that the MRl/DTI studies performed by him on Heidi Yang-Weissman dated 7/15/2009 may reflect Diffuse Axonal Inju:ry and that this clinical diaanosis can be assisted by the· DTI imaging, technique and mmhodologies employed by Dr. Lîpton.

12. DTI studies are not experimental and may be used to diagnose bt'.ain iajury in individual subjeets.

FURTHER AFFIANT SAYETII NOT.

F. Reed Murtagh, M.D.

This 22nd day of April, 2010.

Patricia F. McGuigan

Notary Public for

PATRICIA F. MCGUIGAN
MY COMMISSION # DD 607708
EXPIRES: January 20, 2011
Bonded Thru Budget Notary Services

My Commission Expires:. -----

EXHIBIT 7

STA"rE OF MICHIGAN
IN THE WAYNE COUNTY CIRCUIT COURT

JOSEPH G. RYE and ANNE V. RYE,

Plaintiffs,

v.

KIA MOTORS AMERICA, INC., a foreign corporation, and DICK SCOTT KIA CANTON, INC., A Michigan corporation,

Oefendants.

Hon. Robert Ziolkowski

Case No. 07-701204- NP

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AFFIDAVIT OF RANDALL R. BENSON, M.D.

STATE OF MICHIGAN)

)SS

COUNTY OF OAKLAND)

RANDALL M. BENSON, being duly sworn, deposes and states and as foltows:

1 am over twenty-one years of age and am otherwise competent to make this affidavit.

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1. That I am currently employed by the Detroit Medical Canter and Wayne State University as a neurologist. fattended Hahnemann University in Philadelphia and did a residency at Boston University fn neurology. I completed a fellowship In behavioral neurology and cognitive neuroimaging at Massachusetts Genaral Hospital. This fellowship included clinicat training in cognitive disorders as well as research and development of clinical neuroscience applications of functional MRI . This technique has become generally accepted by the medical community and is now clinically reimbursable by most·1nsurance companies. J am also board certified in neurology and psychiatry. My curriculum vitae is attached to this Affidavit. That I have published extensively on brain injury and Diffusion Tensor Imaging [DTIJ in peer-reviewed joumals.

2. As part of my work, my group at Wayne State has been using advanced MRI imaging to study braln injuries in former National Football League football players. This work was funded by the NFL to study 120 former players, t recently was asked to testify before the United States House Judiciary Committee (January 4, 2010) at a field hearing on the subject of brain injuries In football players. 1 suggested that advanced imaging methods (including DTI} would improve the diagnosis and management of concussions in sports. 1 showed the committee and attendees imaging data from sports and non sports related brain injuries. Additionally, J am an investigator on a 15-year, continuously funded National Institute on Disability and Rehabilitation Research (NIDRR) grant (project entitled, "Utility of MRI Techniques in Prediction of TBI Outcome"). The current grant award includes both DT! and SWI imaging components and was subjected to peer reviaw by NIDRR which is a division of the U.S. Department of Education.

3. 1 have been actively invotved in MR imaging sincœ 1992 and in Diffusion Tensor lmaglng (DTI) sincœ 2004. The first DTI paper was published in 1994. There are currently 3,472 papers on DTI which have been published in peer review journals to date of which 83 are on DTI and TBI. A contrai group was used for stat!stical analysis of results for 35 of the 83 papers. Attached to this Affidavit is a bibllography related to Diffusion Tensor lmaging.

4. 1 have reviewed the defendant's motion in this case to exclude my testimony as well as the report of defanse expert Victor Haughton, M.D. The motion of defendant and report of defense expert Haughton utiHze flawed assertions.

5. The contrai group I utilized ftts within the generally accepted definition of "contrai group" in empirical science. The contrai group has been the subject of peer-reviewed literature. 1 have presented my methodology in the past for peer-review at The American Academy of Neurology and The International Society of Magnetic

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Resonance in Medicine. The methodology was used in a conference proceeding published in the Journal of Magnetic Resonance in Medicine.

6. Sorne of my criteria for selecting what has been referred to as the "Raz" control group1 included: 1) no subject with a known history of TBI; 2) wide age range so in order that any TBI patient would be included within that range and to allow us to regress out any' age affect on FA should one be present; 3) 1 wanted to exclude othar potential causes of diffusion abnormality such as known neurologie disorders; 4) 1 wanted ta allow for common co-morbldities that occur in the population from whence TBI patients arise, since to *not* do so would increase the probability that these co-morbidities (e.g, silent strokes) might be responsible for any difference in FA between a TBI patient and the controls. In my depositfon on page 26 1 characterized the 50 control subjects as a "normal healthy control group". What I meant by "normal healthy control group» is a group representative of the general population which includes TBI patients as described in this paragraph.

7. The presence of hypertension in the control group makes the control group a *more apprcipriate* group with which to contrast people from the general population including traumatic brain injury patients with hypertension. This contrai group was chosen to control for vascular and other morbidities that TBI patients are likely to have. In so doing, 1 was attempting to account for other potential causes of diffusion abnormalitîes. Inclusion of hypertension, which has been shown to lower FA slightly, has the desirable effect of reducing "false positive" rate or increasing the confidence that any differences are due to the presence of traumatic axonal injury. Wrth the foregoing being the rationale for using these 50 controls, in Mr. Rye's case, 1 have reviewad office records from his primary care physician, Dr. John Slaim, from 8/28/02, 9/18/02, 1/20/03, 12/1/03, and 12/29/03 and he was normotensive for each of these visits and was not on antihypertensive medication. Therefore, the control group was an appropriate control group for Mr. Rye•s DTI analysis.

8. With respect to Dr. Haughton's report, while there are some "voxels[1]" in the controls that have Jow FA values, they typically occur singly or In small clusters but not in large clusters. The presence of large clusters occurring in the canters of these white matter tracts indicates more than spurious or random low FA voxels which are seen in the contrais. What is accepted practice in the medical imaging community is to correct for the multlple statistical comparisons by submitting the results to a *post hoc* correction such as cluster analysis which takes into account the likeUhood of obtaining contiguous *clusters* of reduced FA. This is because the probability of obtaining large clusters of reduced FA in a population of individuals without white matter disease is

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1 "Voxels" are volume pixels.

exceedlngly low. A cluster analysis was performed on Mr. Rye's image and found that the clusters were greater than what is observed in the controt group.

9. In formulating opinions regarding Joe Rye I utilized the same intellectual rigor that I have brought ta bear in the evaluation of other TBI patients whom I see clinically, most of whom are not In litigation. It is my opinion that the contrai group that 1 am using is far superior than the 10-person control group utilized by Dr. Haughton in a paper in which he is coauthor entitled, *Diffusion Tensor MR /maging in Diffuse Axonal Injury,* {AJNR, 2002). This is because Haughton used only tan (10} volunteers with the only crlteria being that the volunteers have no known neurological disorders. The investigators did not indicate the methodology by which they recruited or excluded volunteers with neurological disorders and did not exclude subjects with hypertension, psychiatrie dlsorders or "silent strokes". In addition, his TBI and control group were not age-matched. In spite of the foregoing deficiencies in his own control group, Haughton claims to be to able to distinguish reduced FA caused by TBI. The methodology utilized by me is more rigorous because the reference group specffically accounts for potential other causes of low FA basides TBI such as vascular disease and aga affects. Furthermore, the larger number of contrai subjects (50 vs, 10) provides a superior estimate of normal variation in FA, thus increasing the validity of the statistical results.

1O. Based on my experience in detecting mild ta moderate traumatic brain injury with imaging I disagree with Haughton's assertion that the internai capsule is seldom involved. In *my* experiance it is frequently involved, partlcular!y in mater vehicle accidents. Aise, Haughton refers to the symmetry in the images when in fact most of the ftndings are vary *asymmetric* with the exception of the corpus cal!osum which is usually found in autopsy studies ta have lesions in the center of the splenium and genu.

11. ! agree with Haughton that the lesions in Joe Rye's images do reflect diffuse axonal injury, and that acceleration/deceleraton was operative in Mr. Rye's case. It is my opinion based on my education, experience and training as well as the wealth of peer-reviewed literature that blows to the head are the most common cause of diffuse axonal injury. In Mr. Rye's case both impact and non-impact forces could have reasonably cauaed his brain injury.

12. My clinical examination of Joe Rye, together with his neuropsychological deficits validated the detection of diffuse axonal injury with DTI. 1 utilized the results of medlcally accepted neurological and mental status examlnation techniques to formulate my clinical assessment. Wlth respect to my overall opinions I relied on my education, experience and training and generally accepted scientific methodologies.

FURTHER AFFIANT SAYETH NOT

RANDALL R. BENSON. M.D.

Subscribed and sworn to before me

thls S+ day of t./,J.btl.J.Q.Jlj , 2010.

Notary Public
My commission expires: 9/25/14

CURRICULUM VITAE

RANDALL R. BENSON, M.D.

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Bloomfield Hills, MI
48201

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&-Mail: rbenson@med.wayne.edu

PERSONAL DATA:

Date of Birth	December 13, 1959
Place of Birth	st Louis, MO. U.S.

EDUCATION:

1978-82	B.A. in Biology	Washington University, St Louis, MO
1983-87	M.D.	Hahnemann University, Philadelphia, PA

RESIDENCY TRAINING:

1987-88 Intern, Internal Medicine, Crozer-Chester Medical Center, Chester, PA
1988-91 Resident, Neurology, Boston University School of Medicine, Boston, MA

FELLOWSHIP TRAINING:

1991-1993 Functional Neuroimaging, Massachusetts General Hospital, Boston, MA

FACULTY APPOINTMENTS:

1996-2001	University of Connecticut Health Center, Farmington, CT
12/01-present	Wayne State School of Medicine, Detroit, MI

HOSPITAL OR OTHER PROFESSIONAL APPOINTMENTS:

12/01-prasent Detroit Medical Center and Hospitals, Detroit, MI

PROFESSIONAL SOCIETIES MEMBERSHIP:

American Academy of Neurology
The Society for Neuroscience
Society of Behavioral Neurology
Society of Magnetic Resonance In Medicine
Linguistics Society of America
National Neurotrauma Society
International Neurotrauma Society
North American Brain Injury Society

LICENSURE AND BOARD CERTIFICATION:

Medical Licensure: State of Pennsylvania (inactive)
State of Massachusetts (inactive)
State of Connecticut {Inactive)
State of Michigan {active)

Board Certification:

1887	National Board of Medical Examiners 33486036
1996	Diplomate, American Board of Psych!atry and Neurology

HONORSIAWARDS:

1982	University Honors, Washington University
1986	Senior Honors Program, Hahnemann University
1986	Letter of Commendatlon in Psychlatry, Hahnemann University
2004	Detroit's Best Doctors-Hour Magazine
2005	Member Metropolltan Professlonal Honor Society
2008	Top Scorlng Abstract and Presentatlon Award (first place), 6th North Amerloan Brain lnjury Society (NABIS) Annual Conference, Oet 2-4, New Orleans, LA.

SERVICE:

Patient Care

*Staff attending at Harper Hospital, Detroit Reœivlng Hospital
*General Neurology ambulatory cRnic
*Behavioral Neurology consultation ln- and outpatlent
*Preoperatlve funetlonal mapping of eloquent cortex uslng fMRI

Editorial

Journal of Cognitive Neuroscience	Ad-hoc revlewer
Annals of Neuro/ogy	Ad-hoc re er
Epflepsla,	Ad-hoc reviewer
Human Brain Msppfng,	Ad-hoc reviewer
Journal of Neurologica/ Sciences	Ad*hoc revlewer
Brain and Language	Ad-hoc reviewer

MedIcal Advisory Board Membershlp

Michigan Dementla Coalition	2004-present

Intramural Commi

Magnetic Resonance Research Revlew	2004-present
Departmental 5-year Internai Revlew-CHnlcal Subcommittee Chair	2007-2008

Grant Reviewer

National Science Foundatlon	2007 (Ad-hoc) **2004-2007**
Henry Ford Hospital Intramural Grant Program	

TEACHING:

2002-present	4-6 weeks per year Cllnical teachlng rounds for residents, students, rotators, observers on Neurology inpatient service, Harper and DRH Hospîtals (4-8 resldents and rotators)
2002-present	4-8 weeks per year Clinlcal teaohlng rounds for residents, students in Neurology outpatlent service (4-B residents and students)

2002-present	3-5 lectures on behavioral neurology at noon-tlme lecture sertes to residents, students {5-20 resldents and students}
2002..present	Yearly core lectures to Medicine, Physlcal Therapy, Physlcian Assistant programs on dlsorders of cognition
2008-present	Lecture on braln lmaglng to Neuropsychology interns.
SUmmer2006	Graduate course PYC 7150-Fundamentals of Neuropsychiatrie Disorders {slng!e lecture" Dlsorder of Hlgher Cortical Functlon")
Winter2008	Graduate course PYC 7320-MR lmaglng of Neurovascular Oisease {course Instructor)

ONGOING RESEARCH PROJECTS

1. Neuromodulation of cortical functlon using electrical and magnetlc stlmulatlon
2. Mapplng of "eloquent" cortex using flVIRI In neurosurglcal patients
3. Use of nonconventlonal MR imaging methods to detect brain injury
4. Use of diffusion, perfusion and BOLD lmaging to improve stroke management and outcome

INVITED LECTURES OR PRESENTATIONS

1994-5 Lectured in Semi-annuel Workshop on "Funct!onal Magnetlc Resonance lmagingu, IVIGH-NMR Center, Charlestown, MA
5/95 Symposium speaker at French Society of Cerebrovascular and Metabollsm, Lyon, France
6/95 Guest Lecturer Department of Psychiatry, The Psychiatrie Instltute, London, UK
11/95 Grand Rounds, Department of Neurosurgery, Mass. General Hospital, Boston, MA
6/96 Grand Rounds, Departrnents of Neurosurgery and Neurology, University of Florida, Gainesvllle, FL
8/96 Grand Rounds, Departments of Neurosurgery and Radlology, Michigan State University, East Lansing, Ml
10/98 uclln!cal fMRI" course sponsored by Mass. General Hospital, Boston, MA
6/99 "Functlonal MRI and Cognition" symposium at Amerloan Psychological Association annual meeting, Boston, MA
1997-01 Neurology Grand Rounds at Hartford Hospital, Hartford, CT
3/02 Lecture ent1tled "Aging and Cognition" to Women's Health Initiative Memory Study
4/02 Grand Rounds lecture, "Functional IVIRIu, Rehabllitation Instltute of Michigan, Detroit, Ml
8/02 Grand Rounds, Department of Internai IVIedlclne, WSU, "Alzhelmer's Dlsease Update"
9/02 Grand Rounds, Department of Neurology, WSU, "Alzhelmer's Disease Update"
10/02 Krieger symposium, lecture, "Dementla and Alzhelmer's dlsease"
5/03 "Vou heard It here first Experts dlscuss the latest advances In their fleldsn lecture to WSU Alumnl Association on recent advances in Alzhelmer's disease
9/03 Lecture entltled, "Gerlatrlc Neurology", to Gerlabic Psychtatry Fellows and staff
7/03 Lecture to prlmary care physlclans, housestaff, "Dementla and Alzheîmer's disease; sponsored by Pfizer Pharmaceuticals, Inc.
7/04 Grand Rounds, Department of Neurology, WSU, "Aoute Confuslonal State and Delirium"
9/04 Lecture on the topic of memory, aglng and hormonal affects at thlrd annual "Speaking of Wornen's Health", conference hosted by Hutzel Hospital
10/05 Grand Rounds, Department of Psychiatry , WSU, "The Neuropsychiatry of Epilepsy"
8//05 WSU Trauma Symposium, "Diffusion Tensor lmaglng of Brain Trauma"
10/05 flVIRI Workshop, Harper Hosp. MR Research, "MR lmaglng of Trauma"
1/106 Grand Rounds, Department of Neurology, Henry Ford Hospital, "Cortical Stimulation for the Treatment of Hemlparesls from Stroke•
9/28/07 Lecture to Brain Injury Association of Michigan (SIAM) Annual Meeting, Lansing, Ml 2007. "MR Vieuallzation of TBI Pathology: A Multi-Dlmensional Approach-Diffuslon Tensor Imagingp

1

10/27/07 Invlted lecture at 7th Annual Neurology for the Non-Neurologlst Conference, CME course, "Current Approaches to the Treatment of Dementla and Alzheimer's Disease.•
10/14/07 Invlted lecture at Annuel Meeting of the Michigan Academy of Physlclan Assistants, "Dementta and Alzhelmer's dlsease."

PUBLICATIONS
Peer Reviewed Papers

BENSON, R. R. (2009). Book revlew: The Orbltofrontal Cortex. JNeurol Sol. In **press,**

BENSON, R. R. (2007). Book revlew: Funottonal MRI: Applications In Clinlcal Neurology and Psychiatry. J Neural Sol. **258,** 103.

BENSON, R. R., MEDA, S. A, VASUDEVAN, S., KOU Z., GOVINDARAJAN, K. A, HANKS, R. A., MILLJS, S. R., MAKKI, M., LATIF, **Z.,** COPLIN, W., MEYTHALER, J. and HMCKE, E. M. (2007). Global White Matter Analysls of Diffusion Tensor Images ls Predlctlve of Injury Severity in TBI Journal of Neurotrauma. **24,** 446-459.

BENSON, R. R., RICHARDSON, M., WHALEN, D. H. and LAI, S. (2006}. Phonetlc processing areas revealed by sinewave speech and acoustic:aUy slmilar non-speech. Neurolmage. **31,** 342-353.

WHALEN, D., BENSON, R., RICHARDSON, M., SWAINSON, B., CLARK. V., LAI, S., MENCL, W., FULBRIGHT, R., CONSTABLE, R. and UBERMAN, A. (2006). Differentiation of speech and nonspeech processlng within primary audltory cortex. Journal of the Acoustical Society of America. **119,** 575-581.

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WOL.FSON, L., WEI, **X.,** HALL, C., PANZER, V., WAKEFIELD, O., BENSON, R. R., SCHMIDT, J. A., WARFIELD, S. K. and GUTTMANN, C. R. (2005). Accrual of MRI White Malter Abnormalities In Elderly with Normal and Impaired Mobllity. Jaumal of the Neurologlcal Sciences. **232,** 23-27.

CRAMER, S., BENSON, R., BURRA, V., HIMES, O., CRAFTON, K, JANOWSKY, J., BROWN, J. and LUTSEP, H. (2003). Mapplng individual brains to guide restoratlve therapy after stroke: rationale and pilot studies. Neurologlcal Research. **25,** 811-814.

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WEI, **X.,** WARFIELD, S. K, ZOU, K H., WU, Y., LI, X., GUIMOND, A., MUGLER, J. P., 3RD, BENSON, R. R., WOLFSON, L., WEINER, H. L. and GUTTMANN, C. R. (2002). Quantitative analysis of MRI signal abnormalltles of braln white matter wlth high reproducibllity and accuracy. Journal of Magnetic Resonance Imaglng. **15,** 203-209.

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BENSON, R. R., GATTU, R., RAZ, N., KENNEDY, K., KOU, Z. and HAACKE, E. M. (2009b). Variation in DTI-FA as a Function of Age and Brain Reglon: setting the Stage for Mild TB. JMRI.

GATTU, R., LATIF, Z., KOU, K., HAACKE, E. M. and BENSON, R. R. (2009). Effect of Voxel Size on DTI Fractlonal Anisotropy. IMRI.

KOU, Z., BENSON, R. R., GATTU, R. and HAACKE, E. M. (2009). Susceptlbillty Weighted Imaglng Complements Diffusion Tensor Imaglng In Traumatic Brain Injury. JMRI.

GATTU, R., BENSON, R. R., MYRTHEUNJAYAN, B., KENNEDY, K, RAZ, N., KOU, Z. and HAACKE, E. M. (2008). Ageing and Fractlonal Anisotropy: Global and Reglonal Results. JMRI.

KOU, Z., BENSON, R. R., GATTU, R. and HAÀCKE, E. M. (2008a). Region--of-Interest Analysis of DTI: FA Histograms Differentiate Mlld Traumatic Brain tnJury from Contrais. Brain Injury. **22,** 44-45, 94·95.

KOU, Z., BENSON, R. R., GATTU, R. and HAACKE, E. M. (200Bb). Improvlng the detect!on of diffuse axonal Injury by complementary use of advanoed MRI. Journal of Head Trauma and Rehabilltatlon. **23,** 57-58.

ELFAKHANI, M,, KANG, A., GREENWALD, M., FUERST, D. and BENSON, R. (2007). Case Report of Aphasie Respondlng to a 6-Week 1O Hz rTMS Protoool. Electrophysiology and Cllnical Neuroscience **38,** 190.

GOVINDARAJAN, K., MEOA, S., LATIF, Z., HAACKE, E. M. and BENSON, R. (2006). Reliabillty of Language paradigms In fMRI for Pre-operative Mapplng. JMRI.

KOU, K., SHEN, Y., KALLAKURI, S., ZAKARIA. N., YU, Y., HU, J., CAVAVAUGH, J., BENSON, R. and HAACKE, E. M. (2006). Ex Vivo diffusion tensor Imaglng detects Impairments of white matter Tract of. Rat Brain after Trauma Uslng Marmarou Modal. Journal of Neurotrauma. **23,** 1020.

MEDA, ••BENSON, R. R., VASUDEVAN, S., GOVINDARAJAN, K., HANKS, R., MILLIS, S., KOU, Z., MAKKI, M., COPLIN, W., MEYTHALER, J. and HAACKE, E. M. {2006a). Diffusion Tensor MRI of Whole Brain White Malter is Predlctive of Severlty of TBI. Journal of Neurotrauma. **23,** 1001.

MEDA, S., GOVINDARAJAN, K., HANKS, R., MEYTHALER, J., MILL1S, S., LATIF, Z., MAKKI, M., COPLIN, W., HAACKE, E. M. and BENSON, R. R. {2006b). Whole Brain FA Hlstogram analysis for improved detectlon of DAI. JMRI.

MEDA, S., KOU, Z., GOVINDARAJAN, K:, HANKS, R., MEYTHALER, J., MILLIS, S., LATIF, Z., MAKKI, M., COPLIN, W., HAACKE, E. M. and BENSON, R. R. (2006c). Diffusion Tensor MRI of White Matter Correlates with Traumatlc Brain Injury Severlty. Journal of Neurotrauma. **23,** 754.

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EXHIBIT 8

STATE OF MICHIGAN

IN THE **WAYNE COUNTY CIRCUIT COURT**

JOSEPH G. RYE and ANNE V. RYE.

RYE JOSEPH G v KIA MOTORS AMERICA
Hon. Robert L Zielkowski 01/12/2007

Plaintiffs,

v.

KIA MOTORS AMERICA, INC., a foreign corporation, and DICK SCOTT KIA CANTON, INC., A Michigan corporation,

Defendants.

Craig E. Hilborn (P43661)
David M. Kramer (P63740)
Hilborn & Hilbom. P.C
Attorneys for Plaintiffs
999 Haynes, Suite 205
Birmingham, MI 48009
{248) 642-8350

Peter M. Kellet (P34345)
' Andrew J. Kolozsvary {P68885)
Dykema Gossett P LC
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400 Renaissance Center
Detroit, MI 48243
(313) 568-6668

Christopher C. Spencer (VSB # 21878)
Elizabeth Kinland Shoenfeld (VSB # 65635)
O'Hagan Spencer LLP
Co-counsel for Kia Motors America, Inc.
6806 Paragon Place, Ste. 200
Richmond, VA23230
(804) 285-5220

ORDER ON DEFENDANTS' MOTION IN LIMINE TO PRECLUDE TESTIMONY OF DR. RANDALL BENSON

At a session of said Court held in the City of Detroit,
County of Wayne, State of Michigan

on FEB 16 2010

PRESENT: HONORABLE ROBERT L Z
Circuit Court Judge

This matter having coma before the Court upon Defendants' Motion in Lirnine to

Preclude Testimony of Dr. Randall Banson; the Court having heard oral argument; and being otherwise fully advised in the premises;

IT IS HEREBY ORDERED that Defendants' Motion is DENIED.

SO ORDERED.

ROBERT L. ZIOLKOWSKI
CIRCUIT COURT JUDGE

Approved as to form:

Counsel for Plaintiff

Counsel for Defendants

A TRUE COPY
CATHY M. GARRETT
WAYNE COUNTY CLERK
BY DEPUTY CLERK

1

EXHIBIT9

Written Testimony

Randall R. Banson, M.D.

Assistant Professor of Neurology

Wayne State University School of Medicine

Co-Director. Memory Disorders Cllnic for Detroit Medical Center

Co-Director, Traumatic Brain Injury Imaging Program, MR Research Program, Harper Hospital,

Detroit Medical Center

Hearing before the House Judiciary Committee

Legal Issues Relating to Football Head Injuries

January 4, 2010

Mr. Cha!rman and Members of the Committee:

Thank you for the invitation to testify today on *Jegal* issues *relating to football head injuries.* My name Is Dr. Randall Banson. 1 am an assistant professor of Neurology at Wayne state University School of Medicine where I have a neurology clinic, teach students and residents and do research. 1 am also an attending neurologist at Detroit Recelvlng and Harper Hospitals ten weeks per year where I admit patients and consult on others. 1 am the sole fellowshlp trained behavloral neurologist in the practice so that my clinicat, teaching and reseerch are strongly focused on brain function and disorders of braln functlon.

1 received my medlcal degree In 1987 and am board certified by the American Board of Neurology and Psychlatry. 1 did my neurotogy training at Boston University and then at the NMR-Center of Massachusetts General Hospital where I trained in functlonal neurolmaging and then pioneerad the use of a new MRI technique, functional MRI, for mapping !anguage areas In the brain. This technique, 1 am pleased to report, is now clinically relmbursed by health Insurance companies. Followlng thls work, my goal was to combine functlonal lmaging with electromagnetlc stimulation of braln to enhance neuroplasticlty (neural reorganization underlying functional recovery) in Injured brains. 1 applled this experimental treatment psradlgm to stroke patients wfth language impaJrment and hand weakness, the latter study a Phase Ill multi-slte, pivotai trial sponsored by Northstar Neurosciences (Seattle, WA).

Since my arrivai at Wayne State in 2001 my research emphasis has gradually shifted to the application of "functiona1" MRI methods to traumatic brain injury. This was in large part driven by cross-campus strengths in TBI at Wayne. Wayne State University has a long and Jllustrious hlstory of biomechanics head trauma research beginni,ng in the 194D's with Gurdjlan and

Lissner's studies utilizlng cadaver bra!ns which led to the Wayne State Concussion Tolerance Curve, which continues to be the foundation for most currently accepted head injury indices. Under Dr. Albert King's leadership for three decades, three dimensfonal mathematical models of the brain's response to impact and blast forces have resulted in improvements in automobile cabin safety and in football helmet design used in the NFL. On the medical sida, hospltals at the Detroit Medical Center are world leaders in the acute and rehabllitation stages of TBI, respectively, and have had continued NIH research support. My clinic is comprised largely of patients with braln dlsorders, the majorlty of which are dementia evaluations and traumatic brain injury cases. In a given week I will see as many as 3-4 new patients wlth TBI and an equal number of memory disorder cases.

1 would like share with you some observations from eight years of evaluating traumatic brain injury cases, the vast majority of which I obtain neuropsychological testing and advanced MR imaging: 1) people with TBI are frequently misdlagnosed, often by multiple physicians; 2) the most frequent diagnostic category given is psychiatric-anxiety, depression, conversion disorder; 3) two neuropsychologists studylng the same patient may dlffer considerably regarding existence of TBI; 4) TBI symptoms overlap considerably wlth those of "primary" psychiatrie disorders; 5) without the ability to "see" the brain Jnjury with imaging, there Is no completely objective way ta determine what is TBI and what is something else, e.g., po.sttraumatic stress, conversion, malingering; 6) people with brain injury seem ta vary considerably in severity of symptoms and recovery in the face of similar falls, crashes, etc. This may speak ta population differences In resistance to injury or effectiveness of neural recovery mechanlsms and is in agreement with Collins, et al. who found large differences in recovery from single concussion (North American Brain Injury Society Annual Meeting, 2009); 7) advanced MR imaging techniques, includlng susceptibility-welghted {SWI), diffusion tensor (DT!} and MR spectroscopy (MRSI} are able to reveal brain injuries where CT scans and conventional MRI appear normal.

Sports-related TBI or concussion ls not different from non sports-related TBI except that severity is usually mild, but repetitive concussions are the rule in sports which have an increasingly poorer prognosis.

1 am involved in several ongoing research studies involving traumatlc brain injury, which have in common the application of newer lmaglng methods but which differ by severity, time frame to imaglng, fundlng status, specifics of scanning sequencœs and mechanism of injury. Each of these imaglng studies ls done at the MR Research Canter at Wayne State University under the directorship of Mark Haacke, Ph.D., an MR physicist internationally recognized for his achievements in vascular and susœptibility mapping. For example, one study looks at acute mlld TBI or concussion while in the ER, a second looks at more severe TBI when medically stabllized, another study has been ongoing for 15 years supported by NIH but has a new imaging component. We have, more recently, studied former NFL players in two capacities. The flrst, sponsored by the NFL, is an imaging study using imaging methods proscribed by our group wlth imaging performed at a clinical imaging facllity (ProHealth) in New York. Images are then sent by CD-ROM to us for analysls. Ta date we have received and analyzed 41 scans, sending reports back to Ors. Casson and Viano in New York. My role is as a consultant on bath image quality and data analysis and reporting. This study projected toscan more than twlce this number and thus ls incomplete at this Juncture. The second study is a pilot imaging study of former NFL players with scanning and analysis performed in Detroit. Ta date, we have enrolled eight subjects.

1 would like to now review some of the lmaging methods we have developed and applied ta TBI. The unabashed emphasls of our work is to image traumatic axonal injury (TAI) also known as diffuse axonal injury (DAI} which is responslble for the bulk of the chronic cognitive deficit following TBI. In addition, the most devastating consequence of repetitive TBI, chronic

traumatic encephalopatny (CTE) (McKee, et al. 2008) ls thought to be the result of diffuse axonal lnjury, posslbly caused by a serles of concussions before full recovery oecurs from the prior concussion (Dr. Ann McKee, persona! communication). This hypothesis ls supported by the existence of phosphorylated Tau proteln within damaged axons which is known to be toxic to neurons. Electrophysiologie data from avent related potentiels (ERP) (Brogllo, et al. 2009) indicate that even after symptoms have abated from sports concussion, the brain has not normalized. This suggests that clinical symptoms are not a rellable lndlcator of recovery and that to rety on symptoms exclusively to guide retum to sport is to put the athlete at risk for permanent neurologie lmpalrment. In summary, head lnjury including mUd TBI causes varylng amounts of axonal injury whlch a) recovers slower than clinlcal symptoms; b) underiies the more important and longstanding functional impairments; c) gives rise to phosphorylated Tau in damaged axons and d} Hkely leads to CTE wlth repetitive concussions (posslbly in genetically predisposed individuels (Teasdale, Lancet, 1997}.

Most of our work has used vlctims of transportation related Injuries and falls, however our principle research focus has always been closed head injury, under which concussion falls and is otherwlse known as mlld head injury. 1 wlll also include soma examples of former players scans. The focus of my testimony will be susceptiblilty-welghted imaging (SWI) and diffusion tensor îmaging (DTI}. An equally important imaging method for addresslng concussion is MR Spectroscopie lmaglng (MRS!) a technique whlch is measures metabol!c and biochemical processes. We (WSU) have been collaborating on TBI research witn Loma Linda University School of Medicine (Ors. B. Holshouser and K. Tong) who have demonstrated the sensitivity and predlctlve al)illty of MRSI ln TBI. Space and time prevent me from saying more on MRSI but an lmaging study of concussion on current and former NFL players should contain SWI, DTI and MRSI at minimum.

Susceptlbllity-Welghted Imaglng **(SWI)**

Imaging research of TBI began at WSU in 2004 when an eleven year old boy (C.G.) survived after his family's ATV skidded off a mountwn road in Colorado plunging 200 ft. He was Still in coma two months later when we scanned hlm at WSU. His CT and standard MRI revealed a skull fracture and atrophy but not much more. **Figure 1** compares a standard, clinically available T1...weighted image with a *susœptibillty-we/ghtad image* (SWI) through the temporal lobes and brainstem for C.G. sixty days after lnjury. Note the many "black holes" present tnthe SWI image which are small ("micro") hemorrhages indlcating severe diffuse axonal lnjury (DAI) from TBI.

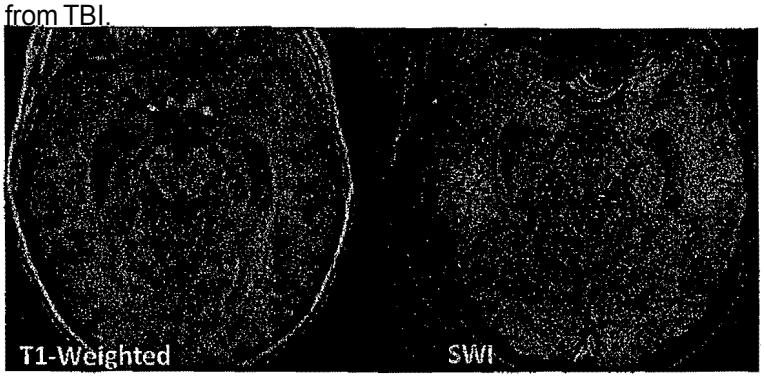


Figure 1. Comparison of T1 and SWI Images for C.G. Note the many dari< "holes" In the SWI Image that are not present on the T1 welghted image. Thes& "black holes" are caused by signal loss lnducecl by paramagnetic hemoglobin or other lron containing blood preo,uets,

Developed by Mark Haacke, SWI ls extremely sensitive to iron and blood products and detects microhemorrhages where conventional MRI falls. SWI detects hemorrhage at ail stages, sinœ iron remains even after the fluid from blood is reabsorbed. Prlor work by Dr. Haacke wlth Loma Linda University (Karen Tong, M.D.) had demonstrated the value of SWI for detecting DAI In children wlth "shaken baby syndrome" where lt was flve times more sensitive than gradient echo imaging. In a sertes of 20 TB! patients (transportation related and falls) varying in severlty and alapsed time slnce injury, we found an excellent correlation (P=0.54) between total hemorrhage volume and the number of days in posMraumatic amnesla which is known to be a good

predlctor of one-year neurological outoome *{JMRI,* 2009). We have, slnce 2004, scanned over 100 TBI patients wlth SWI at WSU alone and a slmilar number at Loma Linda. In addition to TBI, it is being used In stroke, cerebral amylold anglopathy (CAA) (Figure 2), Alzheimer's dlsease and disorders of Iron metabolism. SWI is now clinically available on GE and Siemens MRI scanners.

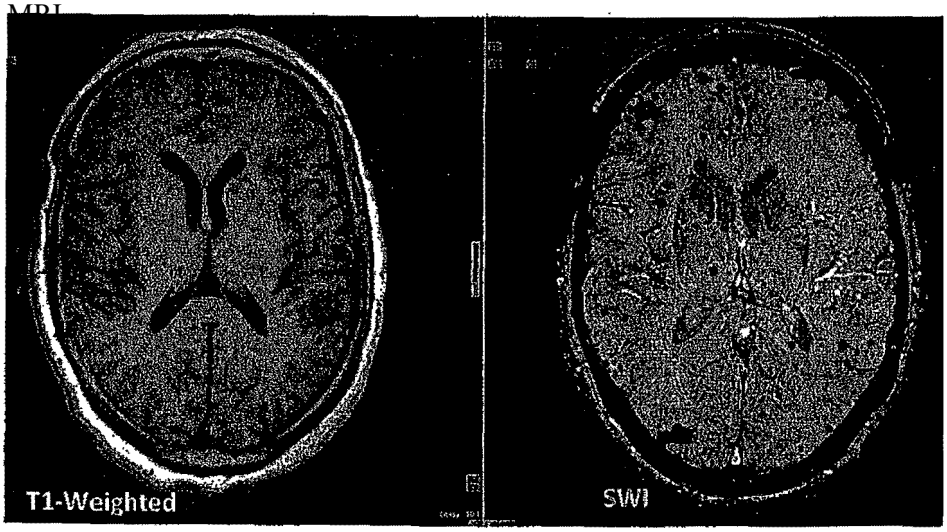


Figure 2. Oomparlson of T1 welghted and SWI Images for cerebral amyloid angiopathy, another dlsorder involvlng multiple smaff braln hemorrhages In the elderly.

In our experience with mlld TBI/concusslon, hemorrhaging withln the brain substance is more often caused by the direct blow {contusion) than diffuse axonal injury. More severe blows *will* cause microhemorrhages from diffuse axonal lnjury, which is the result of nonelastlc deformation of brain white matter and vessais (shear in]ury} {see Figure 3).

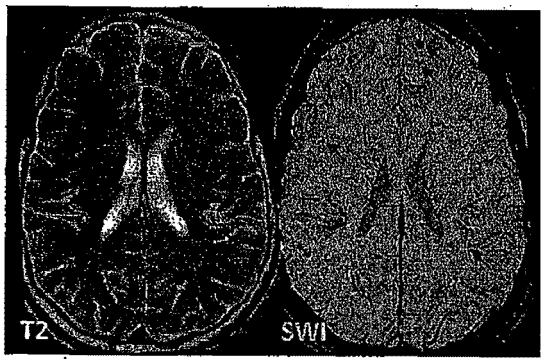


Figure 3. 41 year old female (N.D.) scanned elght days after motor vehlole accident with LOC and 3 days of post-traumatlc amnesla (GCS=13). Red arrows Indicate microhemorrhages revealed In the SWI Image but not the conventlonal T2 Image or the other standard cllnlcal Images.

Figure 4 Is an exemple of a cortical contusion In a 63 year-old woman with persistent mild cognitive Impairment following a fall.

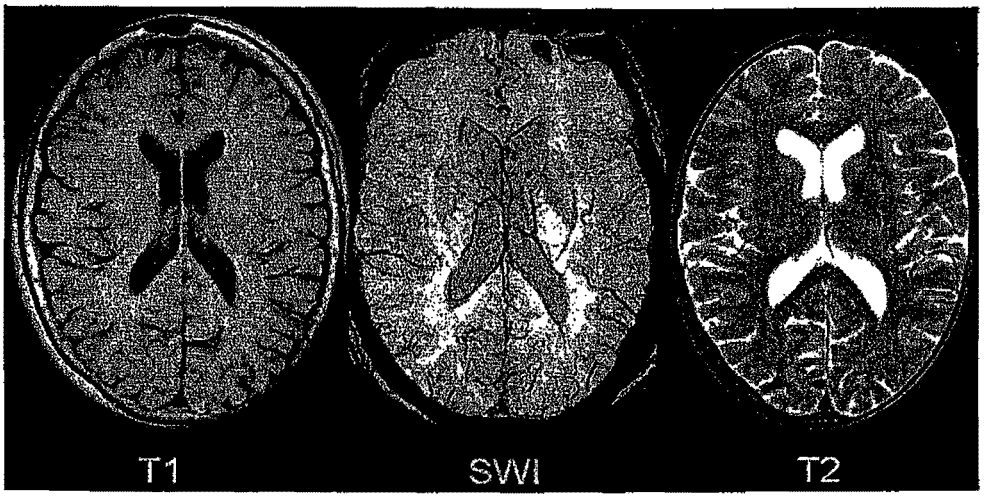


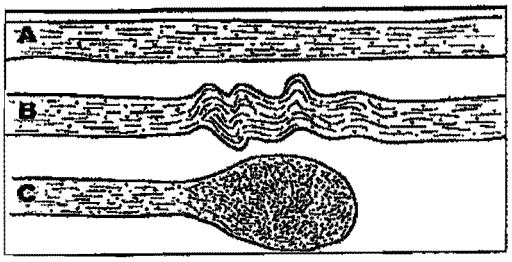
Figure 4. on1y SWI claarly reveals a superflcial hemorrhage in the left frontal lobe In a 63 year-old woman who tripped and hlt her head on an iron bar. No loss of consclousness but mlld confusion and persistent mlld cognl!lve deficit.

In summary, SWI reveals large and smalt hemorrhages occurring as a consequence of trauma and detects aoute as wetl as chronlc hemorrhage, although systematic study of the evolution of hemorrhage In SWI has not been performed to date. In addition, measurement of total brain hemorrhage on SWI Images using automated methods is predlctlve of neurologlcal outcome at one year post injury. The hemorrhages, it should be noted, probably do not, In and of themselves, cause neurologlcal impalrment but are a marker of significant diffuse axonal înjury.

Diffusion Tensor lmaglng

Developed ln the mld-1990's, diffusion tansor lmaglng {DTI) ls sensitive to the 3D flow of **water** lnslde and outslde of white matter ffbers {the. long extensions from nerve cell bodies which connect nearby or distant cella). Cfosed head injuries (non-penetrating} lncluding concussion are caused by sudden acceleration or deceleratlon of the head which causes local deformations of the brain within the crenium. The anatomical and biomechanlcal propertles of the brain are such that white matter fibers are stretched and damaged, resulting ln diffuse axonar injury (DAI) whlch is the hallmark pathology and accounts for most of the neurologlcal disablllty ln TBL The typical cognitive deffclts in TBI, i.e., slowed information processing, decreased attention and memory, and psychiatrie symptoms are caused by damage to the "cables" which allow for efficient transmission of information between neurons. TBI reduces brain network effìciency resutting in decreesed capaclty and global functîonal impalrment. Concussive lnjury such as occurs in football wlth hlgh speed collisions also causes deformatlon of braln substance and is fait to account for many of the lmmediate and delayed symptoms lncludlng 1he post concussive syndrome. ERP studles of sports related concussion suggest that symptomatic recovery may occur while neurologie and braln metabolic functloning continues to be impalred from weeks to months after injury. lncurrlng a second concussion before neurologie recovery has been shown to worsen outcome and may begin a downward spiral culmlnating in chronlc traumatic encephalopathy {CTE) but thls is not known. Diffusion tensor imaglng {DTI} is able to detect damaged white matter flbers (axons) which have altered flow of water molecules compared wlth healthy axons **(see Figure 5).** DTI, like SWI can be performed on a standard cllnical scanner {1.5-3 Tesla} and ls available on vlrtually all clinlcal scanners.

Figure *S.* Schematlc of healthy and Injured axons. A. deplots an unlnjured axon which is long and thln; B. Early lifter Injury flber becomes shows unduletlons C. Late stage of degeneration •retractlon bulbs" are seen scattered throughout the white matter. Water flow is alte.red as flber geometry Is changes and 1s deteotable wlth DTI.



Our initial investigation of DTI in 20 TBI cases found that (similar to SWI and hemorrhage) an Index of DTI, fractional anisotropy (FA), is decreased uniformty in TBI compared with 14 contrais **(see Figure 6),** and that the magnitude of the decrease In average FA for global white matter Is highty correlated with TB! severity (Figure 7). Even the 6 mHd TBI cases (GCS 13-15) had decreased FA compared with the contrais. The separation of the milds from the oontrols is especially relevant to sports concussions where the great majorlty of injuries are mlld. Figure **Sa** shows the non-overlapping FA distributions between the TBI and control subjects.

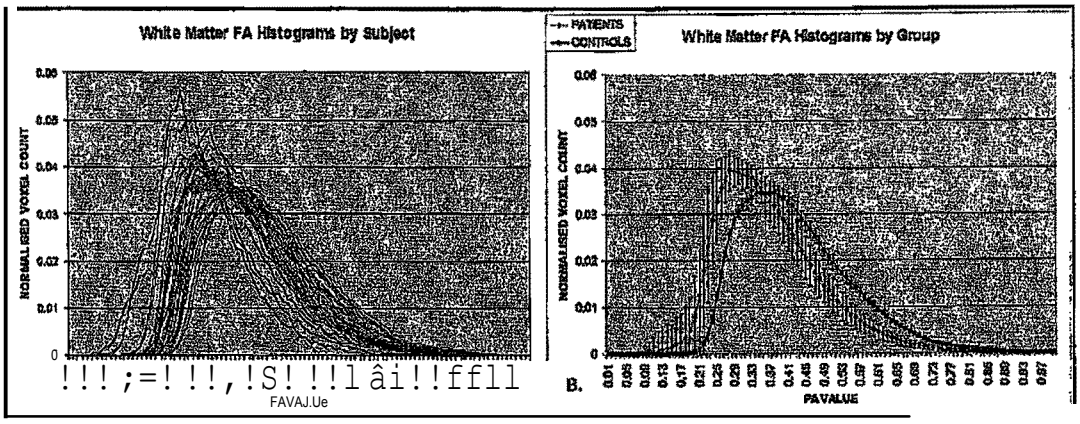


Figure &. Comparison between 20 TBI œses (blue) and 14 healthy controle (rad) on distribution of FA (0-1}. **A.** Ali subjects' FA dlstributlons given; **B.** Group average distributions shown with standard error of the mean plotted for error bars. Note the leftward shlft, hlgher peak and greater variance for the TBI cases oompared with the control group.

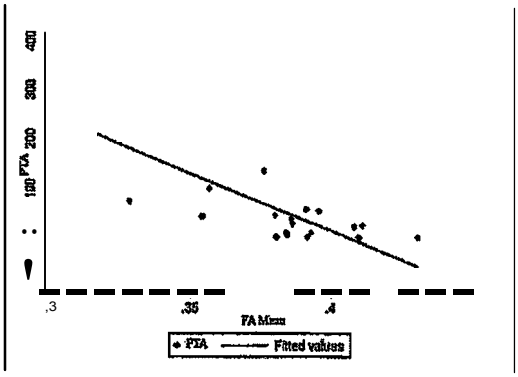


Figure 7. Plot of mean FA and length of post-traumatlc· amnesla for 20 TBI cases. Each dot represents a single case. Note that lower FA values are assoclated wtth longer period of post-traumatlc amnesla durlng whlch patients cannot learn new Information. Correlation is (-) 0.64 (Spearrnan}.

To lncrease the sensitivlty of DTI to axonal injury in mlld TBI we have employed two regional analysls methods. Beth of these methods require "normalizing" the images into a standard brain space and then cor:nparing regional FA values of a single TBI patient *statistica/Jy* with those of 50 healthy contrai subjects taking into account normal variation. The first of these methods, ("regional" analysis}, divides the total white matter into atlas--clefined white matter regions **(see Figure 8),** while the second method ("voxel-based" analysis) compares the FA value of each voxel location (i.e., three-dirnensional pixel) with the corresponding voxel from the 50 controls and displays abnormally low FA voxels in color **{see Figure 9).**

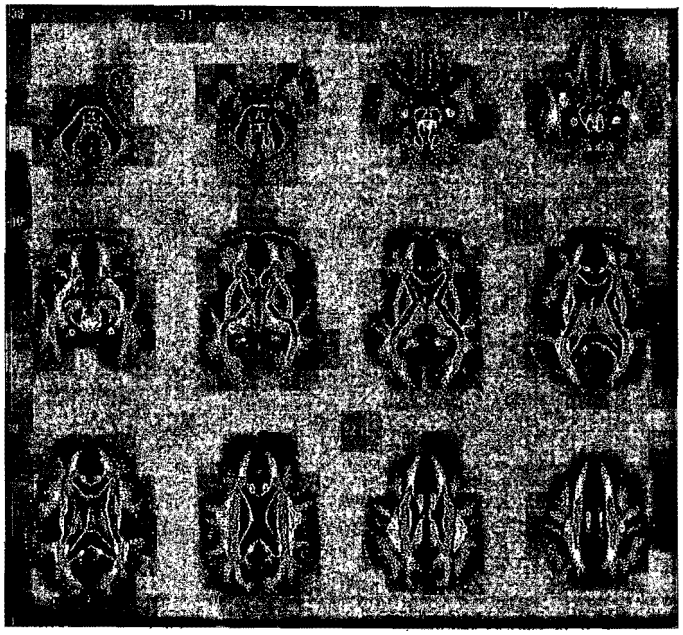


Figure 8. Atlas used for reglonal analysls. Reglons are iru:llcatad uslng color masl<s. Subject's FA map ls spatlaHy normalized to fit referance anatomy. After transformat!ori Into standard space, reglon masks are appl!ed automatlcally to obtaln reglonal FA means. Key advantages over the global approach ls to increase sensitivlty (In mild TBI} and to locaHze axonal lnjury to speclflc reglons whk:h may correlate wlth neurocegnltlve lmpalrments.

Computer programs such as Statistical Parametric Mapplng (University College, London) and DTI Studio (Johns Hopkins University) allow for near automation of these processing steps. These two methods have lmproved our abllity to detect axonal injury in the milder cases which have less extensive damage.

Figure 9 Is the voxel-based analysis for a 43 y/o prevlously healthy woman who was in a parked car when her car was struck hard by a van. She was dazed at the scene but did not lose consciousness. She was extremely fatigued for a month and found to hava cognitive slowing, speech difficulties, mood labillty and loss of motor coordination. SWI did not reveal hemorrhage but DTI showed abnormallties in motor pathways and deep temporal lobe.

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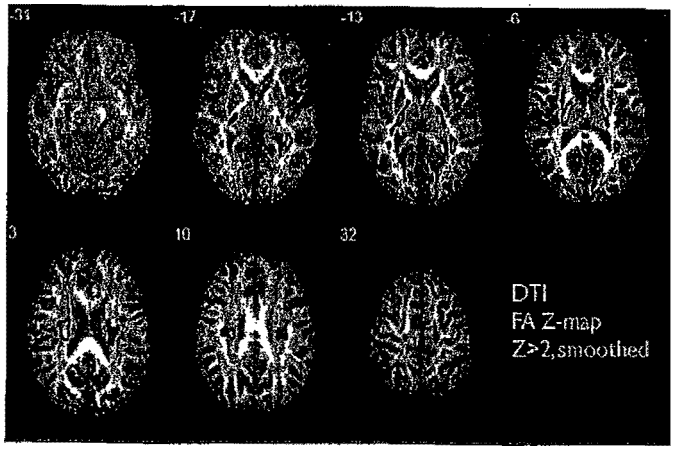
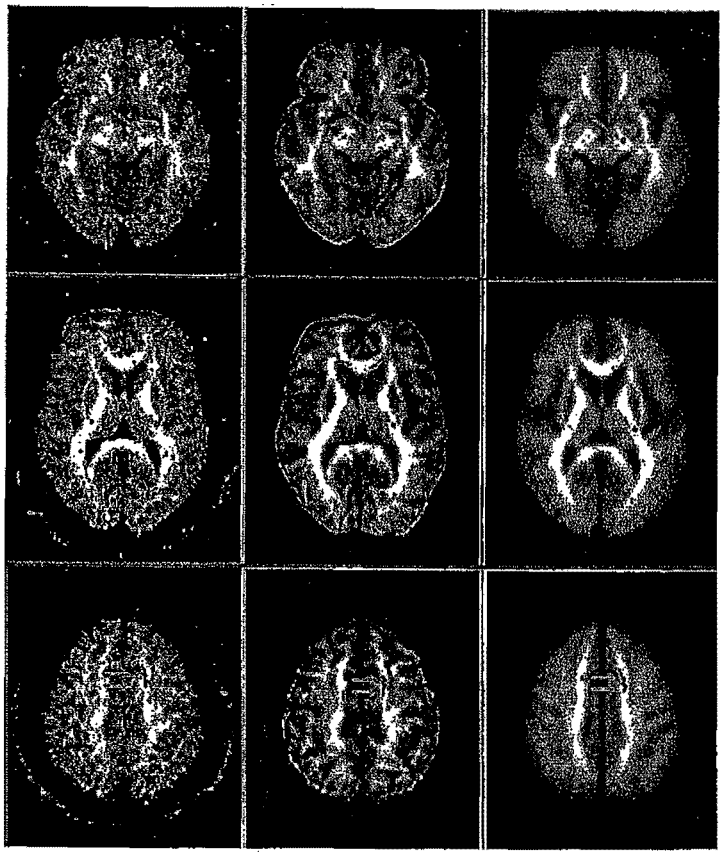


Figure 9. Voxel Based Statistical Map
- **43 year old woman, scan 21 months post**
- **Unrestrained and parked when struck hard by a semi-truck to rear of car.**
- **No LOC but was dazed and speaking slowly.**
- **She suffered whiplash, herniated disk at C3-4, cognitive slowing, stuttering, irritability, loss of fine motor dexterity.**
- **Dx'd with depression and/or anxiety.**
- **Colorized voxels had significantly decreased FA compared with controls**

In an effort to optimlze the Image quallty at ProHealth in New York with our own image quallty we scanned the same subject at bath ProHealth and at WSU wlthln a 4 month period. He was a 37 y/o former nnebacker who played seven years in the NFL and reported multiple concussions throughout his colleglate and pro career. He reported mild forgetfulness. **Figure 10** shows the striklngty similar flndlngs in the left hemisphere (right of Image) with results indicatlng axonal lnjury ln hls corticosplnal tract and corona radiata. No other reglons obtalned significance. The average of the two scans revealed the same flndlngs, desplte the scans being acquired on two different scanners months apart. The reproducibllity, although ln a single subject, is encouraglng and suggests that a multi-site study may be feaslble wlth proper image quatlty.



WSU ProHealth Average

Figure 10. Retlred NFL player. Reprodudbllity across two lmaglng **sites.** Column on left contalns Images acqulred at WSU. Mlddle cotumn Images acqulred at ProHealth (N.Y.). Rlght column ls average of both WSU and ProHealth statistical maps overlald on an anatomical Image whlch ls ltself our average of 50 controls. Three sl!ces of 181 are dlsplayed. Actual native DTI dimensions are 2 x2x3 mm but resampled to 1mm isotropie. Left of image ls right hemlsphere and vice versa.

Another former NFL player was scanned at WSU in 2009. He was 36 y/o and was a fullback playing for 11 years as a starter for most (1995-2006}. Ha suffered "over 50" episodes of vision loss after hits lasting a minute or so and several episodes of belng "dazed" and needing help to get to the huddle. He did not report these symptoms which became more frequent as he "became aider". **Figure 11** shows. the most prominent abnormality which is located in the splenlum of the corpus callosum, a white matter bundle whlch cames visual information between the hemispheres. In fact, thls white matter tract has been shown in autopsy studies to be one of the most common locations of traumatlc axonal lnJury. Interestingly, he reports no ongolng visual lmpairment despite the multiple transient episodes and the imaging findings.

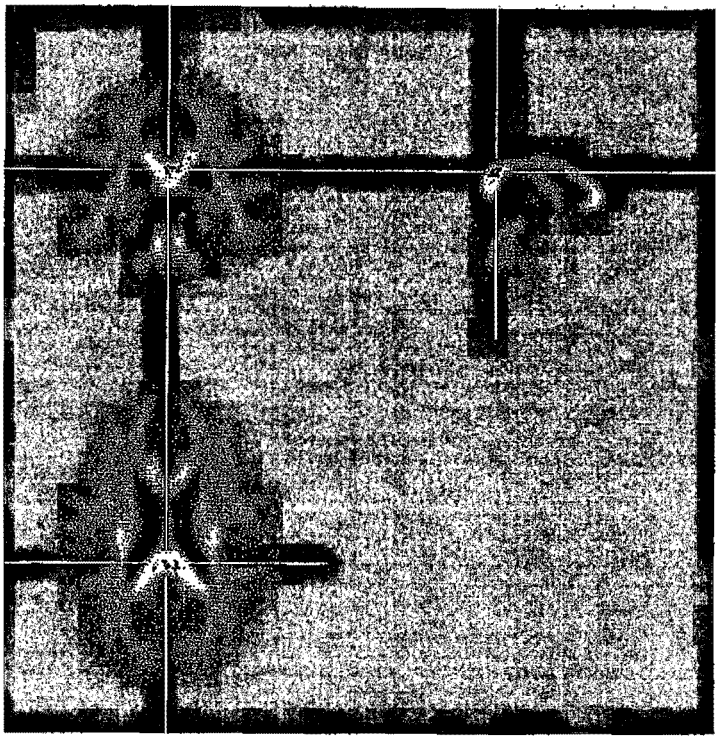


Figure 11, Voxet-based statlstlcal map for a 36 y/o eleven year veteran of the NFL who retired three years prlor to scannlng. Crosshairs are on a large reglon of low FA (Z<2) In the splenlum which contalns vlsual fibers.

In **summary,** DTI is able to "vlsuallze" diffuse axonal lnjury from TBI. In some cases location of lesions appears to correlate wlth speciflc symptoms but generally the severity of DAI as lndlcated by DTI ls strongly predictive of general neurooognitlve disabillty. Since concussion produces axonal injury, particularly repetitive concus5:ion, imaglng wlth DTI·would appear to be ideal to study NFL players. Certalnly, a large scale cross-sectlonat study wherein head lnjury history, position, age, genetlc risk (ApoE genotype), neuropsychological testlng (fooused) and posslbly electrophysiologlcal testlng wlth EEG (ERP, qEEG) and PET are factors. In addition, a prospective study with serial scans over a player's career, tracking concussions or hits and relatlng imaging to neurocognitive performance (IMPACT or s!milar) and other factors as in cross sectional study. lmaglng would also facilitate the evaluatîon of helmet and neck support designs inanimal modela and ln the field.

My strong recommandation Is that these studles ara lnltiated soon sine& TBI is epidemlc and is not solely an urban problem and occurs at all levels of footbaU and other sports such as hockey and soccer. The braln begins losing cells in the second decade of llfe and TBI does not enhance lntellectual functlonlng in the maturlng braln. The answer is to more thoroughly investigate the Issues and attempt to minlmize brain lnjury at any cost. Certainly improving recognition of TB! and identifying the !maging predictors of adverse outcomes would be an lmportant beginning.

1 thank this committee for allowing me to testify on thls important issue.

EXHIBIT **10**

Slip Copy, 8 Misc.3d lOOl(A), 2005 WL 1364515 (N.Y.Sup.), 2005 N.Y. Slip Op. 50882(U)
(Table, Text in **WESTLAW),** Unreported Disposition
(Cite as: **2005 WL** 1364515 (N,Y.Sup.))

H

NOTE: THIS OPINION WILL NOT APPEAR IN A PRINTED VOLUME. THE DISPOSITION WILL APPEAR IN A REPORTER TABLE.

Supreme Court, New York County, New York.
Salvatore LAMASA and Ana G. Lamasa, Plaintiffs,
v.
John K. BACHMAN, Defendant.
No. 129996/93,

April 13,2005.

MARTIN SHULMAN, J.

***1** Defendant, John K. Bacbman ("defendanf' or "Bachman"), moves for an order seeking the following relief in. relation to a jury verdict rendered on June 7, 2004 FNl:

> FNI. Normally, a motion to challenge a jury verdict pursuant to CPLR § 4404(a) is governed by the 15-day time Iimit of CPLR § 4405. This Court permitted the parties to stipulate to extend their time to present written arguments. *See,* "(CPLR 2004; see, 4 Weinstein-Korn-Miller, N.Y. Civ Prac para. 4405.05) ..." *Brown v. Two Exchange Plaza Partners,* 146 A.D.2d 129, 539 N.Y.S.2d 889 (1st Dept.,1989).

1) dismissing the complaint; 2) setting aside the jury verdict as against the weight of the evidence (CPLR § 4404[a]); 3) alternatively, seeking remittitur; 4) seeking defense costs and fees as against the plaintiffs, Salvatore LaMasa and Ana G. LaMasa (where appropriate: "plaintiff', "Salvatore" or "plaintiffs") in connection with plaintiffs' counsel's "withdrawal of his proffer of PET and QEEG evidence following the ruling of the Court precluding said evidence during the trial and for costs in connection with plaintiff's egregious discovery abuses." Plaintiffs oppose the motion and cross-move for additur.

The motion and cross-motion are consolidated for disposition.

Salvatore initiated what had become a protracted action against the defendant in November, 1993 for injuries be purportedly sustained as the driver of the stationary, front vehicle Bacbman rear-ended during the early morning hours ofNovember 25, 1992 at the intersection of Delancey and Clinton Streets just prior to entering the Williamsburg Bridge (the "Collision"). After being rnarked off the calendar at least three times, this matter was restored to the trial calendar and thereafter trans ferred to the New York County Civil Court on November 10, 1999 (see, CPLR § 325[d]). After languishing for four years, the parties appeared at several pre-trial conferences and the case was eventually referred to the Supervising Judge ofthat court.FN2

> FN2. Due to the confusing procedural posture of the case and an inordinate number of complex *in limine* motions/issues as well as the potential value of the case (based upon a prima facie showing), the parties' counsel concurred that the matter should be re-transferred to the Supreme Court and this Court agreed to preside over the jury trial.

Jury selection began on May 4, 2004 and the trial ended on June 7, 2004. As noted on the Jury Verdict Sheet (Exhibit A to Bacbman Motion), five out of the six members of the jury reached an agreement and preliminarily reported that defendant's negligence in causing the rear-end collision was a substantial factor in causing Salvatore's injuries. The same five members of the jury further reported that as a result of the Collision, plaintiff suffered a serious injury under the No-Fault Law, Insurance Law § 5I02(d) (see, Jury Question Nos.: lA-lC). Salvatore was then awarded the following damages:

a) Past pain and suffering	$240,000

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b) Future pain and suffering	$400,000 (over 20 years)
c) Past Lost Earnings	$460,713
d) Future lost earnings	$774,892 (over 13 years)
e) Past medical expenses	$40,768
f) Future Medical expenses	$ 95,040 (over 20 years)
g) Past loss of medical insurance	$38,985
h) Future loss of medical insurance	$ 95,840 (over 13 years)
i) Future loss of social security	$122,273 (over 7 years)

The jury also awarded Salvatore's spouse, Ana LaMasa, $250,000 for past loss of services (on her derivative claim for loss of consortium) and awarded an identical sum for future loss of services (the latter to cover a period of 20 years).

It should be readily apparent that both parties had a full and fair opportunity to argue and brief the court (where necessary) and make their record, *inter a/ia,* concerning their respective *in limine* motions, evidentiary issues and procedural and substantive trial issues (e.g., the proper jury charges, verdict interrogatories, etc.). While this Court granted Bachman's counsel leave to make this post-verdict motion, nonetheless, to avoid any redundancy, this Court expressed an unwillingness to entertain any application addressing the liability issues and/or the varied evidentiary rulings made prior to and during the jury trial. However, this Court stated it would consider whether the jury awards were excessive and unreasonable (CPLR § 5501[c]). Still, defendant took advantage of his right to move under CPLR § 4404(a) and "reargued" almost every one his overruled objections and denied motions duly made on the record during the course of the trial and duly preserved for a potential appeal.In its post-verdict motion, defendant's counsel argues that: Salvatore's proof of injuries never met the statutory threshold to constitute a serious injury (i.e., no loss of consciousness and no complaints of pain and/or other physical or cognitive disabilities at the time of the Collision made to the police or his Iate brother-in-law, no loss of ambulation, no emergency room or hospital admission at the time of the Collision, no initial cornplaints of headaches, depression and/or anxiety at or close in time to the Collision, a normal neurological examination seven weeks post-Collision, no evidence of either temporary or permanent traumatic brain injury ("TBI") at or close in time to the Collision and no objective findings of injuries to Salvatore's neck and back); plaintiff's proof was insufficient to show a causal connection between the Collision and Salvatore's alIeged injuries *(viz.,* all of plaintiffs experts failed to opine on causation and any and all purported positive findings of TBI, post-traumatic stress disorder ["PTSD "] and neck and back injuries were reported years after the collision by medical experts rctained by plaintiffs' counsel solely for trial); and plaintiffs' discovery abuses warranted the extreme sanction of dismissal of the plaintiffs' complaint.

***2** Defendant's post-verdict motion further took issue with various court rulings he deemed erroneous such as permitting plaintiff's expert neuroradiologist, Dr. Michael Lipton, to testify with respect to an innovative MRI modality utilizing Diffusion Tensor Imaging ("DTI") FN[3] as this modality is not generally accepted in the field of radiology or neuroradiology to diagnose TBI or diffuse axonal injury; precluding defendant's expert neurologist from testifying conceming Evoked Potent1al testmg FN[4] wh1eh plam1ff argu cd was not addressed in defendant's expert witness disclosure notice; granting plaintiff a directed verdict on the issue of negIigence; overruling certain objections to references about insurance made by various plaintiffs' witnesses; denying defendant's request for a missing witness charge with respect to various witnesses such as Dr. Wiseman (pain management specialist who treated Salvatore), Dr Leo J. Shea III (psychologist who treated Salvatore) and Mariusz Ziejewski, Ph.D. (accident reconstruction engineer); granting plaintiffs' counsel's application to modify certain no-fault interrogatories on

the verdict sheet to eliminate the phrase, "[a]s a result of the accident" but otherwise accurately reciting the text of these no-fault questions in accordance with Pn 2:88E, 2:88F and 2:880; and granting plaintiffs' counsel application to amend certain damages questions on the verdict sheet after completion of instructions to the jury to include a claim for loss of past and future medical insurance and future loss of social security benefits (or payments) and fumishing the jury with a supplementary charge with respect thereto.

FN3. DTI is an imaging technique used to study the random motion of hydrogen atoms within water molecules in biological tissue (e.g., brain white matter) and spatially map this diffusion of water molecules, *in vivo*. DTI provides anatomical information about tissue structure and composition. Changes in these tissue properties can often be correlated with processes that occur, among other causes, as a result of disease and trauma.

FN4. Evoked Potentials sometimes called evoked responses are tests that record the brain's responses to sound, touch and light. These tests help to evaluate a number of neurological conditions.

After the foregoing challenges, Bachman's motion then raises the issue of remittitur urging the court to either set aside or reduce the Jury awards for past lost camings ($460,713) and future lost earnings ($774,892) FN[5], reduce the jury award for past medical expenses from $40,780 to $25,000, set aside the jury award for past and future medical insurance as being duplicative, set aside the jury award for future loss of social security retirement benefits as being totally speculative or altematively reduce the $122,273 award to $80,700 and reduce the jury awards for Joss of past and future services to Ana LaMasa from $500,000 to $50,000.

FN5. Specifically, defendant contends that Salvatore's pre-accident employment history reflects a patchwork of short-term jobs, that plaintiff's most recent employment before the accident at Ogden Allied was only for two and a half years, that Salvatore intended to leave Ogden Allied to become a Con Edison meter reader rendering plaintiff's expert economist's projections and calculations uncertain and speculative, that the calculation of the past and future lost eamings on an annualized basis erroneously utilized an increase rate of 3.5% rather than the union contract increase rate, that the economist failed to consider plaintiffs pre-accident health condition (i.e., scoliosis and degenerative dise disease), that the jury ignored testimonial evidence proffered by Dr. Remling, Salvatore's treating chiropractor, to the effect that plaintiff could retum to work at a less demanding job or seek part time work, and that plaintiff's expert recogniz.ed that the rate of increase for future lost eamings could have been 3.5% rather than 4.5% justifying a reduction of this award by approximately $50,000 or $60,000.

Finally, due to plaintiffs purportedly frivolous efforts to seek the admission of QEEGFN [6] and PET scan FN? evidence, Bachman should be awarded attomey's fees pursuant to 22 NYCRR § 130-1. l as well as defense expert witness expenses totaling approximately $50,000.

FN6. EEG is the recording of electrical patterns at the scalp's surface showing cortical electrical activity or brain waves. This recording is called an electroencephalograph, commonly referred to as an EEG. As a diagnostic tool, Quantitative EEG or QEEG provides a digital recording of the EEG which is apparently utilized to perform a comparative analysis of many EEG tracings of a patient suffering from brain disease or trauma against a normative data base of EEG tracings.

FN7. Positron Emission Tomography ("PET") is a medical imaging technique which scans a body's chemistry and function to detect cancer, Alzheimer's and other medical conditions.

Plaintiff's cross-motion seeks additur and through the following argnments tells a different story:

Testimonial and documentary evidence presented before the jury preponderated in favor of Salvatore establishing that he suffered serious injury (Insurance Law § 5102) including, but not limited to, neck and back injury, TBI FN8, post-traumatic stress disorder ("PTSD" FN9) and a non-permanent, medically determined injury, *viz.,* non-performance of customary and daily activities for 90 of 180 days after the Collision. Each of these conditions standing alone, plaintiffs argue, would satisfy the statutory serious injury threshold;

FN8. Plaintiffs contend that treating specialists Dr. Lewis Weiner (Salvatore's treating neurologist), Dr. Steven Stein (neuropsychologist), Dr, Daniel Kuhn (Salvatore's treating psychiatrist) and Dr. Joshua Greenspan (pain management specialist), Dr. Rachel Yehuda (neuroendocrinologist/psychologist) and experts Dr. Nils Varney (neuropsychologist) and Dr. Lipton jointly and severally opined that LaMasa suffered TBI as a result of the Collision. Their findings, impressions and conclusions, counsel argues, were based on hundreds of clinical examinations performed and duly reported, treatment regimens (i.e, series of drug treatments administered for over 12 years, all proven unsuccessful), medically accepted batteries of neuropsychological tests, MRI and/or DTI studies (the latter imaging studies revealed anatomical damage such as frontal lobe, hippocampus and para hippocampal atrophy and hemocitarin residue [from internat bleeding] consistent with frontal lobe injury).

FN9. Plaintiffs similarly contend that the severity of Salvatore's PTSD defies text book analysis. Salvatore's counsel, drawing from Dr. Yehuda's testimony, starkly captures a singular feature of what this specialist diagnosed as one her worse cases of this disorder: "[A]s a result of the immense psychological barriers inflicted by bis PTSD, LaMasa remains psychologically frozen in time. He really has no present or future, since his PTSD holds him captive in a perpetual state of fear and terror, stuck in the moments surrounding the [Collision] ..." (Flomenhaft Aff. In support of Cross-Motion at ,r 37 paraphrasing from the Yehuda trial transcript at pp. 16 and 42-45).

*3 Unrefuted testimonial and documentary evidence presented before the jury established that as a result of the Collision, Salvatore suffered, and continues to suffer, from panic disorder, severe depression accompanied by suicidai ideation and bouts of violence, electrical dysfunction of the brain, epilepsy, chronic severe headacbes, sleep cycle disorder/insomnia FNlO.

FNlO. Studies done at Mt. Sinai Medical Center Sleep Laboratory revealed "abysmally abnormal qualities in Salvatore's sleep cycles and sleep oxygenation." (Flomenhaft Aff. in support of Cross-Motion at ,r 32).

Defendant unnecessarily reiterates his objections to the many discovery issues fully argued and briefed prior to and during the trial, which the court ruled upon on the record FN11 and requires no serious rebuttal. Moreover, defendant conveniently overlooked his counsel's own discovery "abuses" during the course of the trial;

FN11. To illustrate, plaintiff's counsel acknowledged defendant's understandable concern about the "eleventh hour" proffer of Grahme Fisher, an accident reconstruction specialist. Exercising its discretion to ameliorate any perceived prejudice and surprise, this Court afforded defendant's counsel ample opportunity to depose Mr. Fisher during the course of the trial and obtain all relevant data be relied upon to not only conduct effective cross-examination, but also to fumish an appropriate defense to the effect that the Collision was Iow-impact in nature and incapable of causing the mixed bag of injuries Salvatore claims to have suffered therefrom. In this context, plaintiffs' counsel retorted that the court ruling precluding defendant's neurologist from testifying about

> Evoked Potentials testing was proper because the relevant CPLR § 310I(d) notice made no mention ofthis subject for testimony.

References to the word, "insurance", during the testimony of some of plaintiffs' witnesses were benign in context and non-prejudicial as most of the references to insurance were made in the context of discussing the payment of plaintiffs medical bills and did not warrant a mistrial;

This Court correctly granted plaintiffs a directed verdict on the issue of negligence, correctly denied defendant's request for a missing witness charge, vis- a-vis, Drs. Weissman,, Shea and Ziejewski; correctly permitted the semantic changes to the no-fault interrogatories eliminating the introductory phrase, "[a]s a result of the accident", while rctaining the text of cach question in accordance with the Pll. After determining if plaintiff suffered a serious injury by responding affirmatively to the three no-fault questions, the jury properly determined the issue of causation by answering Question No.2, namely, "Was the collision involving the plaintiff and defendant a substantial factor in causing any of the injuries alleged by plaintiffl" (Exhibit A to Bachman Motion at p. 2)

Contrary to defendant's confusing assertions, the jury awards for past and future medical insurance costs were not duplicative of the awards for mcdical expenses, but rather awards for loss of income, that is to say, the replacement costs of hcath insurance Salvatore ostensibly would have to purchase in lieu of free union health care covcrage he would have otherwise received had hc continued working at Ogden Allied (Exhibit B-4 to Bachman Motion; Leiken trial transcript at pp. 24-30) FN[2];

> FN12. In explaining his calculation ofthis loss, the expert economist determined an annualized cost of health insurance for an individual to be $5000 from 1995 (after the Collision, Salvatore's union continued to provide him with health insurance coverage for a few years) through age 65 and factorcd in an annual 6% increase thereto for a total cost of $134, 796 (past medical insurance cost of $38,985 and future medical insuranee cost of $95,840).

Dr. Leiken similarly projected the loss of social security retirement benefits as an additional component of lost income to be $170,000 (see, Exhibit B-4 to Bachman motion at pp. 26-30) and the jury furthcr rcduced this sum to $122,273 over a seven year period. Defendant's counsel blurs this item of income loss with Bachman's right to pursue adjustments of the judgment at a post-verdict collateral source hearing;

Without proffering any economist to refute Dr. Leiken's assumptions, calculations and projections on behalf of plaintiffs, defendant's challenges to the past and future lost earnings awards rest on a selective and skewed analysis of the testimony, expert and other FNl[3], thus, the jury awards were fair and reasonable;

> FN13. Counsel contends it was reasonable for Dr. Leiken to assume that LaMasa would have remained at Ogdcn Allied, becausc the Con Edison position, if taken, would have becn in addition to his porter work at New York University. Counsel furthcr argues that LaMasa's work history reflected plaintiff's ongoing dcsire to work regularly, that no part time work was available after the Collision and that even assuming some incremental improvement of his neck and back through chiropractie treatment, LaMasa still suffered from TBI and its concomitant psychiatrie problems rendering him disabled from the time of the Collision.

*4 Plaintiffs agree that the past mcdical expense award should be reduced from $40,768 to $25,000 based upon the evidence of record; and

The aggregate award of $500,000 to Ana LaMasa for loss of services was fair and reasonable based upon her credible testimony (Mrs. LaMasa had to replace Salvatore as the head of the household raising their two sons and constantly had to care for her husband since the Collision and must continue to do so for the

rest ofhis life).

Counsel's cross-motion, further addressed the mean- to the potential proffer of testimony conceming spirited nature of defendant requesting costs referable QEEG and PET testing performed on Salvatore finding said request to be without merit as a matter of law.

Finally, plaintiffs seek additur to increase the total $640,000 to an appropriate seven-figure number. Counawards for past and future pain and suffering from sel finds support from appellate case law involving similarly situated plaintiffs who suffered from TBI and PTSD. (Flomenhaft Aff. in support of Cross-Motion at pp. 34-41).

In reply, defendant's counsel factually distinguishes the case law plaintiffs rely upon for additur, reiterates her objection to the trial testimony of Salvatore's treating specialists questioning the value of their testimony due to purported gaps in time and in treatment (i.e., Dr. Greenspan did not see Salvatore until eleven years after to the lack of record evidence of causation and serious the Collision, etc), and reiterates defendant's position as jaiury. For ease of reference, defendant's counsel pretherefore seeks an order vacating the jury award *in toto* pared a chart as part of his "wherefore" relief. Bachman and granting a new trial or, altematively, reducing plaintiff's total lost eamings award to $60,000, reducing plaintiff's past medical expenses award to $25,000, reducing plaintiff's total past and future loss of medical insurance costs award to $0, reducing plaintiff's future loss of social security benefits award to $80,700 and reducing Ana LaMasa's total loss of services award to $50,000.

Discussion

defendant's motion reducing the past medical expense Preliminarily, this Court grants the unopposed branch of award from $40,768 to $25,000.

Having otherwise carefully reviewed the relevant portions of the trial transcript fumished by the parties, this Court finds the jury verdict is supported by sufficient evidence as a matter of law. Stated differently, the verdict is not utterly irrational and there was sufficient evidence to mise issues of fact (i.e., causation and serious injury) for the jury to resolve. *Garricks v. City of New York*, 1 NY3d. 22, 769 N.Y.S.2d 152 (2003). Further, there were valid lines of reasoning and permissible inferences for the jury to draw upon that would lead these rational jurors to reach their conclusions based upon the testimonial and other admitted evidence presented at trial and decide the triable issue of whether Salvatore suffered serious injury causally related to the Collision. *Cohen v.. Hal/mark Cards, Inc.,* 45 N.Y.2d 493, 410 N.Y.S.2d 282 (1978). This ample trial record does not justify a judgment notwithstanding the verdict dismissing the complaint without re-submission of the action to another jury.

***5** Having found sufficient evidence in the trial record to support the verdict, this Court must then inquire as to whether the conflicting medical and other expert testimonial evidence presented by the parties and which resulted in "a verdict for the plaintiflts] ... so preponderate[d] in favor of the defendant that [the verdict] could not have been reached on any fair interpretation of the evidence ...." *Moffat y. Moffatt,* 86 A.D.2d 864, 447 N.Y.S.2d 313 (2nd Dept., 1982) and quoted with approval with bracketed matter added in *Lolik et al., v. Big y. Supermarkets, Inc.*, 86 N.Y.2d 744, 631 N.Y.S.2d 122 (1995). In conducting a factual inquiry of the trial record, this Court further finds no basis to set aside the verdict as against the weight of the evidence and direct a new trial.

The facts of the Collision are essentially undisputed, i.e., a rear-end collision of a stationary vehicle waiting for a light change which occurred on a wet roadway. And the issue of Bachman's negligence was rcsolved as a matter of law in favor of Salvatore when this Court granted plaintiffs' application for a directed verdict on the question of negligence.

This Court digresses to discuss the merits of that branch of Bachman's post-verdict motion rearguing his opposition to plaintiffs' application for a directed verdict on this issue. Bachman again makes reference to a pre-trial decision and order of the Hon. Joan A. Madden issued

Slip Copy, 8 Misc.3d lOOl(A), 2005 WL 1364515 (N.Y.Sup.), 2005 N.Y. Slip Op. 50882(([])
(Table, Text in WESTLAW), Unreported Disposition
(Cite as: 2005 WL 1364515 (N.Y.Sup.))

January 13, 1998 (Exhibit C to Bachman Motion) which denied plaintiffs' motion for summary judgment finding defendant's purported negligence to be a triable issue of fact. For reasons fully stated on the record at the close of the entire case and prior to summations, this Court made it clear that Justice Madden's decision and order did not mandate that the jury decide the issue of Bachman's negligence. lt must be emphasized that "[a] denial of a motion for summary judgment is not necessarily *res judicata* or the Iaw of the case that there is an issue of fact in the case that will be established at trial ..." *Sackrnan-Gilliland Cmporation v. Senator Holding Corp.,* 43 A.D.2d 948, 351 N.Y.S.2d 733 (2nd Dept., 1974). Further, the "proof offered to defeat a motion for summary judgment does not meet the standard of proof required to resolve an issue of fact at trial ..." *Cushman & Wakefield, Inc., v. 214 East 49th Street Corp.,* 218 A.D.2d 464,468, 639 N.Y.S.2d 1012,1015 (1st Dept., 1996). Bachman's testimony and other supporting evidence in his defense neither included any non-negligent explanation for the Collision nor rebutted the presumption of negligence under ail of the circumstances underlying the Collision. Defendant's excuse that the roadway was wet preventing him from stopping sufficiently in time to avoid the impact was wholly unavailing. *Mitchell v. Gonzalez,* 269 A.D.2d 250, 703 N.Y.S2d 124 (1st Dept., 2000). Thus, plaintiffs were not foreclosed from obtaining a directed verdict on the issue of negligence. See, *Gubala v. Gee,* 302 A.D.2d 911, 754 N.Y.S.2d *504* (4th Dept., 2003).

*6 As to the issues of causation and the precise physical injuries Salvatore suffered from as a result of the Collision, the parties had numerous expert witnesses testifying and "in considering the conflicting testimony fo the parties' respective expert witnesses, the jury was not required to accept one expert's testimony over that of another, but was entitled to accept or reject either expert's position in whole or in part ..." *Mejia v. JMM Audubon, Inc.,* 1 AD3d 261, 767 N.Y.S.2d 427 (1st Dept., 2003). To reiterate, the verdict as to the Collision being a substantial factor in causing Salvatore "serious injury" as defined under the Insurance Law § 5102(d) was not

FNI4. In answering Question# 2 on the verdict sheet (Exhibit A to Bachman Motion), the jury deliberated on the precise issue of causation and the wording of the question made it clear that it had to determine whether the Collision was a substantial factor in causing *any* of Salvatore's injuries. The Jury's answers to QuestionslA, 1B and lC determined the no-fault threshold issue of whether Salvatore's injuries constituted a "serious injury". This Court does not find that the deletion of the phrase, "[a]s a result of the accident", from these three threshold questions prejudiced defendant in any way or ran afoul of the applicable "serious injury" Pil charges underlying these jury questions. ln short, the jury squarely disposed of the separate and discrete issues of causation and serious injury under the no-fault statute.

Defendant's disguised reargument of certain *in limine* motions this Court denied and which defendant perceives, if granted, would have otherwise either resulted in a judgment of dismissal notwithstanding the verdict or its vacatur and a directive to conduct a new jury trial is witl:J.out merit.

As to defendant's charge of discovery abuses [15] it is

FN ,

against the weight of the evidence and will not be dis- turbed.FN14

FN ,

essentially admitted that raw EEG epochs contained in the treatment records of Dr. Kuhn were belatedly tumed over and similar records of Dr. Weiner were pur- portedly destroyed in the ordinary course of that physi- cian's business. Yet, this Court ruled that Dr. Weiner could not testify about any alleged objective findings of TBI noted on such EEG data. As noted in the trial tran- script, defendant was able to have an expert witness, Dr. Marc Nuwer, testify eoncerning Dr. Kuhn's data at trial, who offered a contrary interpretation of sueh data and, for that matter, a contrary opinion coneerning the colli- sion not being a competent producing cause of Sal- vatore's deteriorating physical condition. Defendant's motion stridently argues about the severe prejudice in belatedly receiving the respective CPLR § 3101(d) no- tices and reports/data of plaintiff's experts in the fields of neuropsyehology (Nils Varney, Ph.D.}, sleep medi-

cine (Dr. Stasia Wieber) and accident reconstruction/en-

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gineering (Grahme Fisher, P.E.).

> FN15. Defendant claims plaintiff failed to produce and/or timely produce raw EEG data from certain treating physicians and laboratories, failed to produce neuropsychological testing records from psychologists and untimely served expert witness notices reflecting changes in the theory of Salvatore's case (i.e. mild-TBI changed to "moderate to severe" TBI and a low speed collision changed to a moderate to high speed collision).

Nonetheless, this Court afforded defendant sufficient time and opportunity prior to, and during, the trial to review such notices, reports and data and consult with and produce their own expert witnesses in these respective fields for purposes of mounting an appropriate defense; all borne out by the extensive trial record. Moreover, this Court issued rulings which tailored certain of the plaintiffs' expert witnesses' testimony after considering certain defense arguments.[FN16]

> FN16. In written communications to this Court after the motion and cross-motion became *sub judice,* Plaintift's counsel urged this Court to resolve an issue concerning the unantieipated costs plaintiffs incurred in obtaining the printout of raw data EEG data of Salvatore taken at the New York University School of Medicine, Department of Psychiatry as well as Dr. Wieber's raw sleep study data collected at Mt. Sinai School of Medicine which were ordered to be produced and turned over to defendant prior to and during the course of the trial. Consistent with this Court's discussions with respective counsel on this matter, this Court directs that these costs incurred in this data production should be shared by the parties.

Counsel has also reargued certain adverse rulings concerning the merits of defendant's *in limine* motions to preclude due to plaintiffs' failure to timely tum over and/or not tum over records of Dr. Leo J. Shea (neuropsychologist-treatment records), Dr. Charles Wetli (pathologist), Dr. Kenneth Alper (neurologist-QEEG records),

Dr. Monte Buchsbaum (psychiatry-PET scan data). Neither the potential testimony of these witnesses nor their records, reports and data were proffered during the course of the trial based on this Court's rulings and/or other considerations. Revisiting these issues again appears to be pointless. Ali of defendant's remaining challenges to this Court's rulings on the admission of evidence and/or at the formai charge conference are without merit and require no additional discussion.[FN17]

> FNI 7. However, one example should suffice. The mere mention of the word, "insurance", during the course of testimony and the context of how insurance was discussed was not prejudicial to defendant. No testimony was elicited which publicly noted that Bachman had liability insurance and the resources to satisfy any potential judgment. In this vein, this well-educated jury evidently could not have lost sight of the fact that Bachman was represented by two prominent law firms from New York *and* Washington D.C. with no less than three attorneys at the defense table each day of trial. Since Bachman was a retired airline pilot, the jury had ample reason to speculate where the source of funds for the enormous defense costs of this lengthy trial was coming from even if no witness ever mentioned the word insurance.

*7 In continuing the requisite analysis as to the correctness of the verdict, CPLR § 550l(c) states, in relevant part:

> In reviewing a money judgment in an action in which an itemized verdict is required in whieh it is contended that the award is ... inadequate and that a new trial should have been granted unless a stipulation is entered to a different award, the appellate division shall determine that an award is ... inadequate if it deviates materially from what would be reasonable compensation.

Trial courts may also apply this material deviation standard in overtuming jury awards but should exercise

its discretion sparingly in doing so. *Shurgan v. Tedesco,* 179 A.D.2d 805, 578 N.Y.S.2d 658 (2nd Dept., 1992); *Prunty v. YMCA of Lockport,* 206 A.D.2d 911, 616 N.Y.S.2d 117 (4th Dept., 1994); see also, *Donlon v. City of New York,* 284 A.D.2d 13, 727 N.Y.S.2d 94 (1st Dept., 2001) (implicitly approving the application of this standard at the trial level). For guidance, a trial court will typically tum to prior verdicts approved in similar cases, but must undertake this review and analysis with caution not to rigidly adhere to precedents (because fact patterns and injuries in cases are never identical) and/or substitute the court's judgment for that of the jurors whose primary function is to assess damages. *Po Yee So v. Wing Tat Realty, Inc.,* 259 A.D.2d 373,374,687 N.Y.S.2d 99, 101 (1st Dept., 1999).

With the exception of the conceded reduction for past medical expenses, this Court finds that the jury were able to assess the severity of Salvatore's physical injuries, his physical and mental disorders, his historie and current treatment therefor and his poor prognosis. Accordingly, the pain and suffering and medical expcnses awards did not deviate materially from what would be reasonable compensation under the circumstances. *Barrowman v. Niagara Mohawk Power Corp.,* 252 A.D.2d 946, 675 N.Y.S.2d 734 (4th Dept., 1998). Thus, the branches ofBachman's post-verdict motion for remittitur and plaintiffs' cross-motion for additur as to these awards are respectively denied.

Plaintiffs' expert's *per se* calculations of Salvatore's past loss of earnings ($460,713) and future Joss of eamings ($774,892) were essentially unchallenged. Plaintiff had sufficient job continuity as a porter for Dr. Leiken to properly rely on Salvatore's 1992 annualized salary of $32,380 and it was perfectly reasonable for this economist to utilize a conservative rate of interest of 3.5% set by the U.S. Department of Labor to calculate annual salary increases (after 25 years, the U.S. Department of Labor set an increase rate of 4.5% which Dr. Leiken utilized for the year 2005 and going forward) to compute these tosses. Bachman submitted no evidence of negotiated union contracts covering Salvotore's job title which contained annual salary increases which were lower than the percentage increases Dr. Leiken relied upon for his calculations. Ali of defendant's challenges to the loss of eamings awards are meritless and unsupported by trial evidence (e.g ., Salvatore would have left bis job as a porter to become a full-time Con Edison meter reader, etc.). In short, the expert's reliance on certain facts as well as certain fair and reasonable assumptions and bis calculations based thereon are fully supported by the extensive trial record. *Diaz v. West 197th Street Realty Corp.,* 290 A.D.2d 310, 736 N.Y.S.2d 361 (1st Dept., 2002).

*8 Conceming the jury's awards to Ana LaMasa for loss of services, the trial record amply established that since the Collision in 1992 and during the ensuing years, Salvatore's physical and mental condition precipitously declined and Ms. LaMasa was forced to assume his familial duties in addition to her own and to provide for her family's financial welfare. The jury has had the opportunity to assess ber trial testimony and the corroborating testimony of her children as to the diminished quality of her life with Salvatore. And as borne out by expert testimony, Ana LaMasa must continue to spend the rest of her life providing "24/7" care to a spouse with, *inter alia,* severe psychiatric/psychological disorders, a role which renders ber a "captiv[e][to] her marital responsibilities ..." (Flomenhaft Aff. in support of Cross-Motion at 1 94). Therefore, the $500,000 total award to Ana LaMasa for Joss of services similarly does not deviate from what would be reasonable compensation under her circumstances. *Cf, Dooknah v. Thompson,* 249 A.D.2d 260, 670 N.Y.S.2d 919 (2nd Dept., 1998).

In addition, the cost of medical insurance is a component of lost income and in Salvatore's case constituted a "soft dollar" benefit he had been receiving under his union contract and potentially would have been receiving had he continued working as a porter until age 65. The costs for obtaining medical insurance coverage and unreimbursed medical expenses are clearly not one and the same (see, *Schlachet v. Schlachet,* 176 A.D.2d 198, 574 N.Y.S.2d 320 [1st Dept ., 1991]). Accordingly, the expert's calculation of medical insurance costs were fair and reasonable and the jury awards based thereon do not constitute a double recovery for past and future medical expenses.

As noted earlier, Bachman took issue with this Court's somewhat novel ruling to amend the verdict sheet to add two additional categories of damages for past and future loss of medical insurance and future loss of social security benefits as components of lost eamings/income. Plaintiffs' counsel's request for this change was made immediately after summations and completion of the jury charge and just prior to deliberations. While conceding this amendment was unorthodox, nonetheless, Bachman has failed to show how the amendment to the verdict sheet prejudiced defendant's substantive and due process rights. First, defendant did not proffer his own expert economist to take issue with any of Dr. Leiken's testimony and particularly the calculations of these components of lost income. Second, defendant's counsel's closing argument did not even address any deficiencies, vis-a-vis, Dr. Leiken's trial testimony including his calculation of the past,and future loss of earnings and their sub-categories. It cannot be said that Bachman's counsel relied on the pre-amendment version of the jury verdict sheet to structure his summation and therefore had been prejudiced by the inclusion of these new sub-categories of loss of earning damages on the verdict sheet ultimately introduced to, and considered by, the jury with additional jury instructions. Finally, defendant has neither shown that this verdict sheet amendment violated any trial rule or procedure nor constituted an abuse ofthis Court's discretion.FNl&

> FNI 8. Unlike the sub-category of loss of medical insurance, defendant's counsel apparently recognized some merit to the jury award for loss of social security benefits when, in the alternative, counsel requested the court to reduce this award from $122,273 to $80,700. (Murphy Aff. at ,i 98 annexed to Bachman Motion).

***9** To conclude this discussion, it is necessary to address defendant's requests for costs and attorneys' fees in mounting a vigorous defense opposing the potential admissibility of expert testimony about QEEG and PET scan studies plaintiff was relying upon to corroborate Salvatore's TBI caused by the Collision. While this Court ruled that the QEEG and PET scan studies did not meet the *Frye* standard to warrant their admission and granted Bachman's *in limine* motions to preclude such testimony with respect thereto, plaintiffs' counsel's trial strategy to proffer such data as evidence of TBI in low to moderate impact collisions was not beyond the pale and certainly not frivolous. Nor can QEEG and PET data be viewed as junk science. In addition, counsel's withdrawal of certain expert witnesses who would otherwise have testified utilizing QEEG and PET studies was directly due to this Court's bench colloquy and rulings on the record. Parenthetically, defendant's counsel overlooks the fact that this Court conducted a *Frye* inquiry relying on dueling expert affidavits and respective supporting scientific literature as well as dueling affirmations and memoranda of law; ail without the need for either party to incur the exorbitant cost of producing experts for a forma! *Frye* hearing. While this Court concluded expert testimony relying on these tests did not meet the *Frye* standard at this time; still, these tests and related research are "works in progress" as to their potential, broad-based applications in the diagnosis and treatment of disease. Thus, there is simply no legal/factual basis to invoke any 22 NYCRR § 130-1.l sanction against plaintiffs and their counsel for attempting to proffer evidence of Salvatore's TBI utilizing QEEG and PET studies to support their case.

For the foregoing reasons, this Court grants the unopposed branch of defendant's post-verdict motion reducing the award for past medical expenses from $40,768 to $25,000. In all other respects, the remaining branches of defendant's motion and plaintiffs' cross-motion are respectively denied. Plaintiffs shall submit a proposed money judgment, on notice, for signature consistent with this Court's Decision and Order. This constitutes the Decision and Ortler of this Court. Courtesy copies of same have been provided to counsel for the parties.

N.Y.Sup.,2005.
Lamasa v. Bachman
Slip Copy, 8 Misc.3d lOOl(A), 2005 WL 1364515 (N.Y.Sup.), 2005 **N.Y.** Slip Op. 50882(U)

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EXHIBIT 11

56 A.D.3d 340

(Cite as: 56 **A.D.3d 340,869 N.Y.S.2d 17)**

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NY,2008.

56 A.D.3d 340869 N.Y.S.2d 17, 2008 WL 4936507, 2008 N.Y. Slip Op. 09162

Salvatore LaMasa et al., Respondents
v
John K. Bachman, Appellant.
Supreme Court, Appellate Division, First Department, New York

November 20, 2008

CITE TITLE AS: LaMasa v Bachman

HEADNOTES

Motor Vehicles
Collision

Court correctly directed verdict in plaintiffs' favor; defendant saw plaintiff's car stopped at red light, braked bard and sbifted to low gear, but his truck skidded on wet roadway and bit rear of plaintiff's car; rear-end collision with stationary vehicle created prima facie case of negligence, and wet roadway did not suffice as nonnegligent explanation for defendant's failure to maintain safe distance.

Witnesses
Expert Witness

Conway, Farrell, Curtin & Kelly, P.C., New York (Jonathan T. Uejio of counsel), for appellant.
Flomenhaft & Cannata, LLP, New York (Benedene Cannata of counsel), for respondents.
Judgment, Supreme Court, New York County (Martin Shulman, J.), entered August 11, 2006, after a jury trial, in favor of plaintiffs and against defendant in the total amount of $2,774,460, unanimously affirmed, without costs.

On the issue of fault, the trial court correctly directed a verdict in plaintiffs' favor based on defendant's own testimony that he saw the injured plaintiff's car stopped at a red light, braked hard and sbifted to Iow gear, but bis pick-up truck skiddcd on the wet roadway and bit the rear of plaintiff's car. A rear-end collision with a stationary vehicle creates a prima facie case of negligence requiring a judgment in favor of the stationary vehicle unless defendant proffers a nonnegligent explanation for the failure to maintain a safe distance *(Mitchell v Gonzalez,* 269 AD2d 250, 251 [2000]). A wet roadway is not such an explanation. A driver is expected to drive at a sufficiently safe speed and to maintain enough distance between himself and cars ahead of him so as to avoid collisions with stopped vehicles, taking into account weather and road conditions *(id.).* On the issue of serious injury, plaintiffs' experts, relying on objective medical tests, testified to brain damage and other injuries that they attributed to trauma, and the conflicting medical evidence and opinions of defendant's experts conceming the permanence and significance of plaintiffs injuries simply ra.ised issues of fact for the jury *(see Noble v Ackerman,* 252 AD2d 392, 395 [1998]). Conceming defendant's motion to preclude expert testimony, with respect to the nonproduction of raw data produced in tests conducted by the experts, defendant fails to show either prejudice or willful and contumacious conduct. With respect to the experts wbose designations were made shortly before trial, CPLR 3101 (d) (1) ***341** (i) does not require a party to retain an expert at any particular time, and the court allowed defendant appropriate additional disclosure. With respect to the discrepancies between the trial testimony of some of plaintiffs' experts and their reports, defendant did not show a willful attempt to deceive or prejudice, and such discrepancies, which defendant was free to raise on cross-examination, go only to the weight, not the admissibility, of the testimony *(see Hageman v Jacobson,* 202 AD2d 160, 161 *[1994];Dollas v Grace & Co.,* 225 AD2d

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319,321 [1996]). On the issue offoundational support for expert opinion, while some ofplaintiffs' experts relied on new technology or methodologies, the same experts also opined based on well-established and recognized ****2** diagnostic tools, and we find that they provided reliable causation opinions *(see Parker v Mobil Oil Corp.,* 7 NY3d 434, 447 [2006]). We have considered defendant's other arguments and find them unavailing. Concur-Lippman, P.J., Mazzarelli, Buckley, McGuire and DeGrasse, JJ.

NY,2008.
LaMasa v Bachman

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