High-Definition Fiber Tractography: Unraveling the connections of the human brain

by Juan C. Fernandez-Miranda, MD; Sudhir Pathak, MS; Walter Schneider, Ph.D.

Early two decades ago, Sir Francis Crick, neuroscientist, discoverer of the DNA molecule and 1962 Nobel Prize for Medicine, wrote: “to interpret the activity of living human brains, their neuroanatomy must be known in detail. New techniques to do this are urgently needed, since most of the methods now used on monkeys cannot be used on humans.”

The introduction of Diffusion Tensor Imaging (DTI) a decade ago represented a major step toward this goal. DTI is a Magnetic Resonance Imaging (MRI) technique that measures the diffusion of water within the axons (“wires”) of the brain. The information obtained with DTI-MRI is then processed mathematically to obtain a graphic representation of the water channels or tracks within the brain, a method called fiber tractography. The ability to non-invasively map fiber tracts in the living human brain will facilitate numerous applications in the diagnosis and treatment of brain disorders, and for this reason, the National Institute of Health (NIH) stated that the Human Connectome Project (the complete description of the “wiring” of the human brain) is one of the great scientific challenges for the upcoming decade.

We initiated our studies of the brain fiber tracts using DTI almost a decade ago, and we demonstrated that DTI provides accurate reconstruction of the major stem of fiber tracts, in agreement with classical and contemporary neuroanatomical studies. DTI, however, has several limitations since it is unable to solve the crossing of fibers and determine with accuracy the origin and destination of fibers, producing multiple artifacts and false tracts. These limitations significantly decrease the accuracy of the technique in the clinical setting.

For the last four years, our group at University of Pittsburgh has focused on optimizing brain fiber mapping techniques to obtain what we refer to as High Definition Fiber Tracking (HDFT). HDFT is a novel combination of processing, reconstruction, and tractography methods that can track several hundred thousand fibers from cortex, through complex fiber crossings, to cortical and subcortical targets with at least millimeter resolution. This disruptive technique has been applied in dozens of normal subjects and more than a hundred neurosurgery patients.

In this newsletter, we aim to introduce to the community our results with the application of HDFT for the study of structural connectivity in normal subjects, and we present our experience with the clinical application of HDFT for neurosurgery patients. This remarkable innovation has been possible at University of Pittsburgh thanks to a unique collaboration between clinicians and researchers with expertise in diverse disciplines such as neurosurgery, neuroanatomy, psychology, computer science, mathematics, and physics.

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T he history of the Department of Neurological Sur- gery at the University of Pittsburgh has been high- lighted by the developer and implementors of important advances in neurosurgery that have altered the manner in which neurological care is delivered. Initially, these changes were viewed with caution and, at times, have taken decades to be widely accepted into neurosurgical practice. Implementation of these novel approaches has ultimately resulted in paradigm shifts for mainstream neurosurgery.

The most notable examples of such transformative technical advances include microvascular decompression for trigeminal neuralgia, hernial repair and other neurovascular compressive pathologies, skull base surgery for complex skull base pathology, neurosurgery for vascular malformations, tumors and functional disorders; and finally endoscopic endonasal surgery for anterior skull base lesions. These advances, in their own way, revolutionized the care of neurosurgical patients. These approaches provided options to patients who, either had no options, or significantly reduced the overall morbidity and mortality for the treatment of their specific diseases. We are extremely proud of the remarkable impact these advances have made in our field.

A new game-changer in the care and manage- ment of neurosurgical patients is the application of High Definition Fiber Tracking (HDFT). As described in this issue of our newsletter, the broad application of HDFT for surgi- cal planning, intraoperative management and for prognosticating head trauma is far from reaching. As neurosurgeons, having the ability to see what we have never been able to see (i.e. the actual connections within the brain), provides an opportunity that we previously could only have imagined. The potential of HDFT is boundless and is now changing the practice of neurosurgery. As we look forward to its broad implementation in the years to come.

Robert M. Friedlander, MD, MA Chairman, Department of Neurological Surgery UPM C Endowed Professor of Neurosurgery & Neurobiology University of Pittsburgh School of Medicine University of Pittsburgh Medical Center

Using high resolution white matter mapping to detect traumatic brain injury

Jo-Samuel Shin, David Okonkwo, MD, PhD; Walter Schneider, PhD, Timothy Westenbroek

FA map provided a low resolution represen- tation of the impact tract and did not show the projection field of the tract. To compare to DTI, HDFT was used to track corona radiata, cingulum, and superior longitudinal fasciculus.

Analysis of HDFT data identified 67% difference in tract volume between the right and left corona radiata (image below), whereas cingulum and superior longitudinal fasciculus had no major differences between the two sides. Further analysis of the data identified right corona radiata fiber tracts projecting to the central sulcus and precentral gyrus to have 58% more compared to the left. Right corona radiata fiber tracts projecting to premotor areas had 97% less compared to the left. Finally, corticospinal fiber tracts of the patient were analyzed and compared to the tracts of six age and gender matched control subjects to identify large loss of fibers at the level of medullae (figure below). Major losses were found predominantly in the tracts projecting from the ventrolateral area of the primary motor cortex, which is responsible for upper extremity control.

These test findings suggest that HDFT may one day provide a definitive imag- ing modality for TBI. This will also become important in the future as various therapeutic options for TBI will become available, and optimal management of TBI will be tailored to reflect patient-specific injury.

In addition to the above research, HDFT has achieved a number of significant milestones. The HDFT will be presented at the American Academy of Neurology in April and the Society of University of Pittsburgh Neurosurgery News is virtual and online. The newsletter can be accessed at our website or by email. The newsletter is available in print format upon request.

Some Key Department Phone Numbers

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Lateral view of the corona radiata of TBI subject (a) shows fiber tract loss on the right side (outlined in red). Oblique view (b) and magnified view of the tracts at the level of midbrain (c) reveals the details of fiber loss.
Deep brain tumors are often not considered for surgical removal because of concern for morbidity related to tumor access and visualization. However, it is known that surgical resection can improve both neurological and oncological outcomes for patients with brain tumors. The Neuroendoscopy™ is a minimally invasive access tool for deep tumor resection that has been implemented in the removal of deep brain tumors using a technique called endoscopic port surgery (EPS). It is a transparent cylindrical retractor, 11.5 mm in diameter and of varying length, which facilitates deep brain access with minimal brain trauma while still allowing for binomial microsurgery to remove the tumor. At UPMC, a significant experience has been developed using the Neuroendoscopy to remove deep tumors.

Prior experience with endoscopic port surgery has demonstrated that high-definition fiber tracking (HDFT), a MRI-based technique of white matter imaging, can be used to guide cannulation of a tumor using an endoscopic port, minimizing damage to functional surrounding nerve fascicles. This technique helps to ensure that critical fiber tracts, such as the corticospinal tract (CST), the optic radiations, or the acoustic fasciculus are not damaged by the port during deep brain surgery.

Illustrative Case

A 47-year-old, right-handed woman was referred for a surgical evaluation of a right thalamic glioblastoma. The patient initially presented with headaches, left-sided numbness and left hemianopia. Following diagnostic biopsy, she underwent concomitant temozolomide chemotherapy with radiation therapy followed by temozolomide monotherapy. MRI scans demonstrated a heterogeneously enhancing mass surrounded by substantial peri-tumoral T2 signal change. Given the presumptive diagnosis of a high-grade glioma, surgical resection was recommended. The key concern was the presence of the tumor abutting and possibly involving the corticospinal tract (AKA motor tract) at the anterior portion of the tumor. Injury to these fibers would result in a significant risk for motor deficit. In order to better visualize peri-tumoral motor fibers, the patient underwent HDFT prior to surgical resection. We found that the motor fibers appeared to be displaced anteriorly by the tumor, which infiltrated much of the parietal lobe.

We elected to resect the tumor via an awake craniotomy with cortical mapping, which would facilitate real-time monitoring for any neurologic deficit. The HDFT images were transferred into our image-guidance navigation software by an image uplink interface to allow them to be tracked during surgery. The fiber tract imaging was cross-referenced to the anatomical images of the T1 MRI. As expected, intra-operative cortical mapping identified that the motor cortex was anterior to the tumor. A corticectomy was made immediately posterior to the motor cortex, and tumor was identified and the resection started using an ultrasonic aspirator. The navigation workstations showed the motor fibers either projected to the skin surface of the patient or overlaid on the structural MRI of the patient as the tumor resection proceed. The anterior portion of the resection approached the motor fibers as visualized on HDFT on the image guidance system, but these fibers were all left intact. Post-operatively, the patient was neurologically stable and her motor symptoms improved to normal within weeks. Diagnosis was made of a glioblastoma multiforme, and the patient underwent adjuvant temozolomide with concurrent fractionated irradiation followed by temozolomide monotherapy. One year after surgical resection, her disease remained reasonably controlled, and her Karnofsky performance score was 90, with preserved motor function.

Uploading fiber-tracking data into image guidance is a difficult task, due to software compatibility issues. The use of an image uplink interface provides a solution to this problem, and we are now able to utilize image-guidance system with imaging of fiber tracts of interest with high fidelity and extreme accuracy. This ability to have in-depth analysis of peri-tumoral fiber tracts for tumors in and around the motor strip or speech areas imported into our navigational system allows for the ability to track and avoid these critical pathways. In the present case during the operation, we were able to correlate the findings of the awake cortical mapping with the localization of the motor fibers as identified by the HDFT-based image guidance. Of the patient's deep combined with the techniques of awake cranial mapping had a dramatic impact on the pre-operative planning and intra-operative tumor resection of this patient.

Cortical mapping allowed us to guide the surgical resection in a safe manner, allowing for the preservation of motor function. Postoperatively, the patient maintained motor function and her neurologic status remained stable.

Cortical mapping allowed us to guide the surgical resection in a safe manner, allowing for the preservation of motor function. Postoperatively, the patient maintained motor function and her neurologic status remained stable.
HDFT provides key edge in presurgical planning of brainstem cavernomas

By Robert M. Friedlander, MD; Juan C. Fernandez-Miranda, MD; Amir Faraji

Brainstem cavernomas are one of the most complex challenges a neurosurgeon can face. The natural history of such lesions must be weighed against the risk of surgical resection. Surgical access to the brainstem is extremely delicate given the intricacy and eloquence of the fiber tracts and nuclei that form its structure. Historically resection has been fraught with significant rates of complications. One of the complexities in accessing the brainstem is that it is not predictable in which direction has the cavernomas displaced functional fibers. Here we report the innovative application of HDFT to map the fiber tracts within the brainstem and around a cavernoma to safely access and remove the lesion. HDFT provides information on the remaining normal fibers in relation to the cavernomas.

Understanding this relationship provides the surgeon the ability to plan a trajectory through the brainstem which maximizes the safety of resection of such lesions. Tipping the balance towards increased safety and efficacy allows for the ability to offer a therapy that is overall safer than the natural history of the untreated malformation. We have used HDFT to resect a number of different types of lesions in eloquent areas of the brain and brainstem. Here we describe a case of the first cavernoma resection removed from the brainstem, using the information provided by HDFT to plan the trajectory and execute the resection.

A 24-year-old female patient experienced a hemorrhage from a previously undiagnosed left pontomesencephalic cavernous malformation, and was subsequently admitted to an outside center. She suffered from a dense right upper and lower hemiparesis, right gaze preference, and moderate dysarthria. Brain MRI demonstrated a left cavernous malformation removed from the brainstem. Here we describe a case of the first HDFT scan. Moreover, her neurological examination continued to progressively improve. She is able to perform her activities of daily living with minimal to no assistance. HDFT provided an edge in order to be able to offer a procedure in this specific young patient. Knowing the exact location of critical fibers within the brainstem provides us the ability to approach and remove these lesions with much higher degree of safety. The surgeon can not see these fibers when operating under the microscope. However knowing where they are located allowed us to provide the excellent result to our patient.

Upon arrival the patient was awake, alert and oriented to person, place, and time. She had a right facial droop and double vision. She developed significant weakness of the right arm and leg. She had slurred speech and her tongue deviated towards the right. Brain MRI demonstrated that the cavernous malformation had bled one more time, and had more swelling around it. Given the aggressive nature of this malformation we recommended that the lesion be resected. The challenges of such a procedure are as well as deciding the specific location in which to enter into the brainstem. Once inside the brainstem, understanding the location of the remaining normal structures provides the ability to remove the lesion with the greatest degree of safety.

To gather information as to the location of the normal fibers, the patient underwent on MRI study with HDFT imaging analysis. HDFT indicated severe deformation of the ipsilateral motor tract, with apparent disruption of some of its fibers with significant posterior displacement of a large number of motor fibers. Based on this tractography data and image guidance correlation, the surgical approach was carefully considered and a trajectory was selected to provide more immediate access to the intra-paraparenchymal hematoma and cavernous malformation, while preserving the intact motor fibers. This trajectory involved accessing the brainstem just in front of the motor fibers that were posteriorly displaced by the hematoma and cavernous malformation. In accordance with this pre-operative planning, the patient underwent a left-sided frontotemporal, subtemporal transtemporal approach to access the pontomesencephalic cavernous malformation under image guidance. The lateral surface of the midbrain was visualized with a surgical microscope and a subtle yellow stain was observed, suggesting that this may be the most superficial location of the malformation. A small opening was made into the brainstem where the cavernous malformation was readily encountered. The hematoma and cavernous malformation were completely resected.

Her immediate post-operative examination revealed improvement in her double vision, her facial droop, as well as her right sided weakness. Her sensation remained intact postoperatively. Post-operative HDFT study was completed to evaluate the impact of surgical resection on the motor fibers, demonstrating preservation of the posteriorly displaced motor fibers and transection of the previously disrupted fibers, as expected.

Over the course of the next six months, the physical displacement of white matter fibers continued to resolve, as revealed by a third HDFT scan. Moreover, her neurological examination continued to progressively improve. She is able to perform her activities of daily living with minimal to no assistance.

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Robert Friedlander, MD, with brainstem cavernoma patient Ashly Hunt.

Monaco to Receive Leksell radiosurgery Award

PGY-6 resident Edward A. Monaco, III, MD, PhD, has been selected to receive the 2012 Leksell Radiosurgery Award by the AANS/CNS Section on Tumors. The award, in recognition for Dr. Monaco’s paper “The risk of leukoencephalopathy after whole brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer,” will be presented at the 2012 AANS Annual Scientific Meeting in Miami, FL, in April.

Study Ranks Pitt at Top for Stereotactic Research

The British Journal of Neurosurgery published findings online in November of a bibliometrics study showing the University of Pittsburgh ranking first in the world in scientific production in stereotactic-related research. The study, using data from 1993 through 2008, “to provide insights on the characteristics of the stereotactic related research patterns, tendencies, and methods that might exist in the papers, as well as in leading countries and institutes.” According to the paper, “the results analyzed by this bibliometric method can show to what extent and by research performance, significant events and major inventors, those attributed to stereotactic neurosurgery, and trend of stereotactic related research.”

In the Media

• Robert Friedlander, MD, with brainstem cavernoma patient Ashly Hunt.

Intraoperative photographs (upper and lower right) to be compared with the preoperative (upper left) and postoperative (lower left) HDFT reconstructions. The information provided by the HDFT study was used to plan the trajectory and entry point into the brainstem (lower right and left figures).

The preoperative HDFT reconstruction of the motor tracts showed the posterior displacement and decreased number of fibers of the left tract (red) when compared to the right tract (green). Postoperatively, the left motor tract (red) recovered most of its normal position and volume of fibers, and the right tract (green) also showed a volume increase as a consequence of the surgical treatment.
Solving Enigmas:
the Anatomy of Language

HDFT provides a unique opportunity to study the connectivity of certain brain areas and functions that are largely unknown. Our studies on the arcuate tract, which is a major fiber system that interconnects different speech centers, have revealed an intriguing arrangement of the language circuitry: an inner semicircumferential tract that interconnects both primary speech centers (expressive or Broca’s and receptive or Wernicke’s), and a pair of outer parallel semicircumferential tracts that interconnect secondary or supplementary speech areas (figure at right). There is no doubt that a better delineation of the intricate structure of the human brain will improve our understanding of its complex functions, such as language, and the treatment of disorders of the human brain.

HDFT reconstruction (right) and anatomical fiber microdissection (left) of the left arcuate tract. With HDFT we can investigate the structural connectivity between multiple areas of the human brain. The arcuate tract is considered the “language” tract because interconnects distant language centers. Our investigations have revealed a complex network formed by several cortical centers interconnected by multidirectional pathways, organized in a concentric and parallel fashion. The inner or primary circuit (purple) is thought to be mostly related to the phonological aspect of language, while the outer circuits (red, yellow) are in charge of the semantic aspect of language. Further investigation is needed to ascertain the complete structure of the language system in the human brain.