Frequently Asked Questions About Our Work in Mapping Brain Connectivity in Autism.

With the release of Temple Grandin & Richard Panek's Book The Autistic Brain: Thinking Across the Spectrum (April 30, 2013) and the reports of 60 Minutes programs October 23, 2011 and July 15, 2012 we have had may requests for information Below is a summary of the frequently asked questions and the answers we have provided. This is an ongoing research program and much remains to be learned. Even so, we are optimistic that the combined research efforts of multiple laboratories will provide a detailed understanding of how developmental disorders, such as autism, produce atypical brain connectivity and how measuring the size of the brain tracts or cables might in the future help guide treatment to establish communications.. If you have questions, send a note to walters@pitt.edu and we will try to answer them. See also information on the web sites http://HDFT.info & http://schneiderlab.lrdc.pitt.edu/

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Frequently asked questions

1. **What is High Definition Fiber Tracking (HDFT) and how might it be used to diagnose Autism Spectrum Disorders (ASD; Autistic Disorder, Pervasive Developmental Disorder, Not Otherwise Specified, Asperger Disorder)?** High Definition Fiber Tracking (HDFT) is new MRI based technology that can make a circuit diagram of the connections in an individual's brain. The goal is to provide a biomarker for differentiating between the various subtypes found within Autism Spectrum Disorder (ASD) based on the brain connectivity differences. In brain connectivity image, the tracts or cables of the language portion of a child's brain with ASD can be inspected and contrasted to those of a typical brain. Knowing what is atypical will aid in targeting treatment. We identify what links have been compromised and how to most effectively use therapy to establish functional abilities which compensate for the uncharacteristic links in

each child's brain. Quantifying the extent of these connective differences will facilitate research to develop more effective future treatments**.**

2. **What does an HDFT scan show you?** HDFT visualizes the brain cables or tracts in exquisite detail (see Figure 1 below). For example, we can map a child's language system to quantify the size of cables which support various language functions. The development of the X-ray scans transformed diagnostic abilities in orthopedics by providing non-invasive images of the bones. HDFT may do the same for developmental connection disorders. This technology will allow clinicians to observe and compare the integrity of 40 tracts in the brain. These tracts, much like the bones, are the support structures for brain functioning. In the past, these tracts or brain cables could rarely be detected or seen with any clarity. Now, with HDFT, we can provide the high definition image of millions of brain connections.
3. **How might this help lead to better diagnosis?** With clear pictures of connection problems, we can better target specific therapies. For example, by quantifying the integrity of each link in the brain's language network, we expect to find that some children will show missing, reduced and over connected tracts that may account for differential language ability. We hypothesize that the subtypes of ASD (e.g., preverbal - no single words, stereotyped and echolalia and difficult speech - single words/phrases) each have different patterns of reduced connections (see answer #5).
4. **How might HDFT affect treatment?** It is important to establish effective communication with children early in life to approximate a normal developmental path. Depending on which link is compromised, different modes of communication might be extremely difficult or even impossible to achieve. The parents and treatment teams must decide what priority to give in the training of communication skills. For example, whether to best prioritize goals with regard to speech production, speech comprehension or use of augmentative communication systems (e.g. use of Picture Exchange Communication System, Dynavox, IPad and other devices). Knowing how children with different connection anomalies developed the most effective communication will support better decision making, and ultimately lead to better treatment. We are currently engaged in research to collect such data (see #10).
5. **You did an HDFT map of Temple Grandin's brain – what did you see and what did you conclude?** Temple was kind to allow us to create an HDFT map of her brain and has given us permission to talk about what we found in the language parts of her brain. We are still collecting data; as we seek to understand structural differences between the brain of individuals with ASD vs. the "neurotypical" brain. We did virtual dissections of Temple's language system (see Figure 1 below). We found key connections in Temple's brain to be out of the typical range in the major language tract which is called the arcuate fasciculus. Interestingly, we found most links were similar to a control brain but some links were dramatically increased and some decreased in Temple's brain relative to a control brain (e.g., the volume of the axons from the left hemisphere projecting from the area of visual object information to the frontal and motor cortex is ten times that of the control, in contrast the volume of the axons that connect between speaking what you hear and speaking what you see is one tenth that of the control) We think this pattern of increased and decreased connectivity might account for Temple's high visual skills, combined with the difficulty of acquiring language as a child. We note these are early tentative interpretations and much work must still be done. It could be that these differences in Temple's brain resulted from living with autism, and finding new ways to see the world. It could also be that they were there at birth. It is encouraging to find that this new HDFT technology can visualize and quantify such

differences. We believe applying this technology to more cases will lead to insights and understanding of the brain mechanisms of ASD.

Figure 1. Virtual dissection of sub tracts of language network. Left shows the full actuate fasciculus (major language tract and connecting tracts. The right shows four sub networks and the far right the individual subtracts. The amount of axonal volume can be quantified and compared across individuals to look for atypical connectivity patterns.

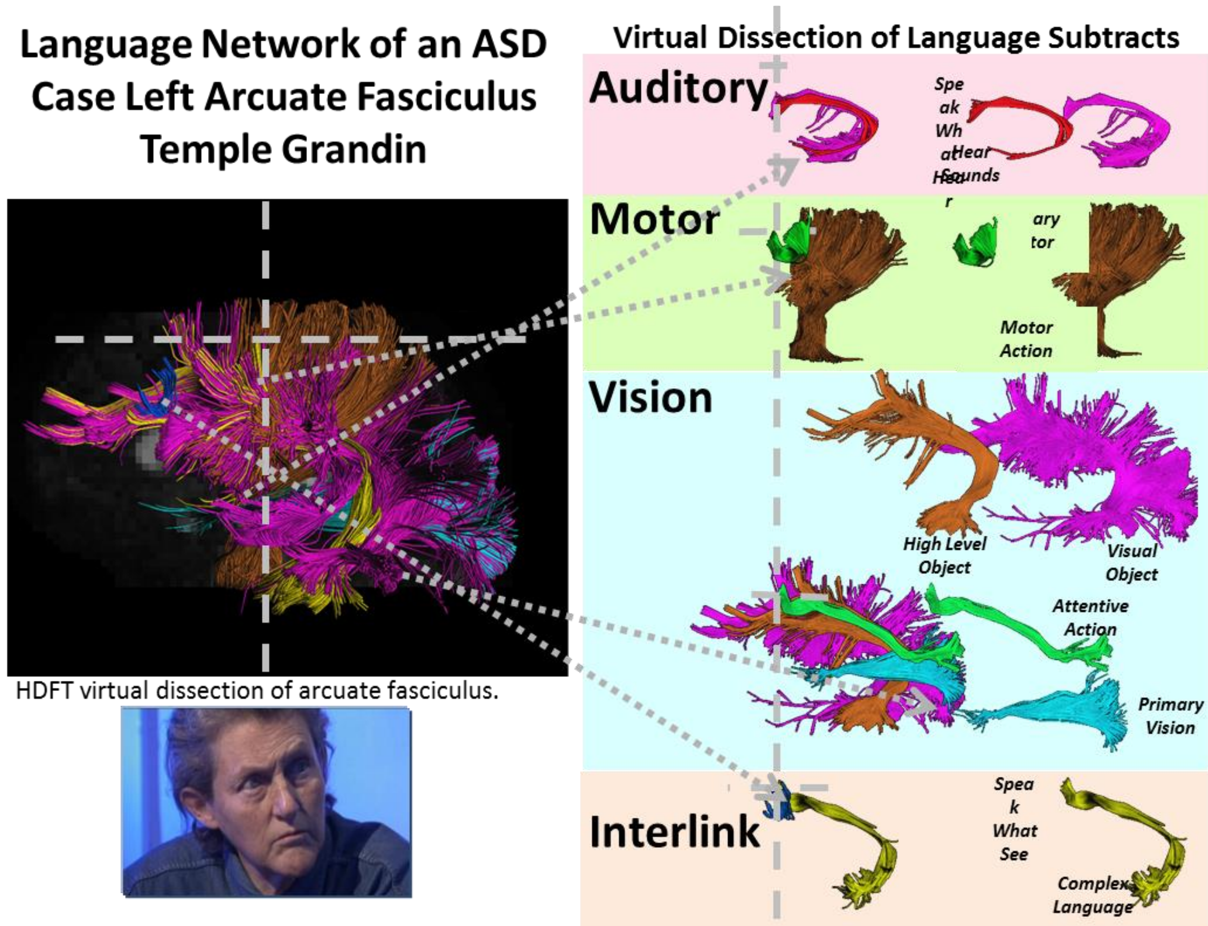
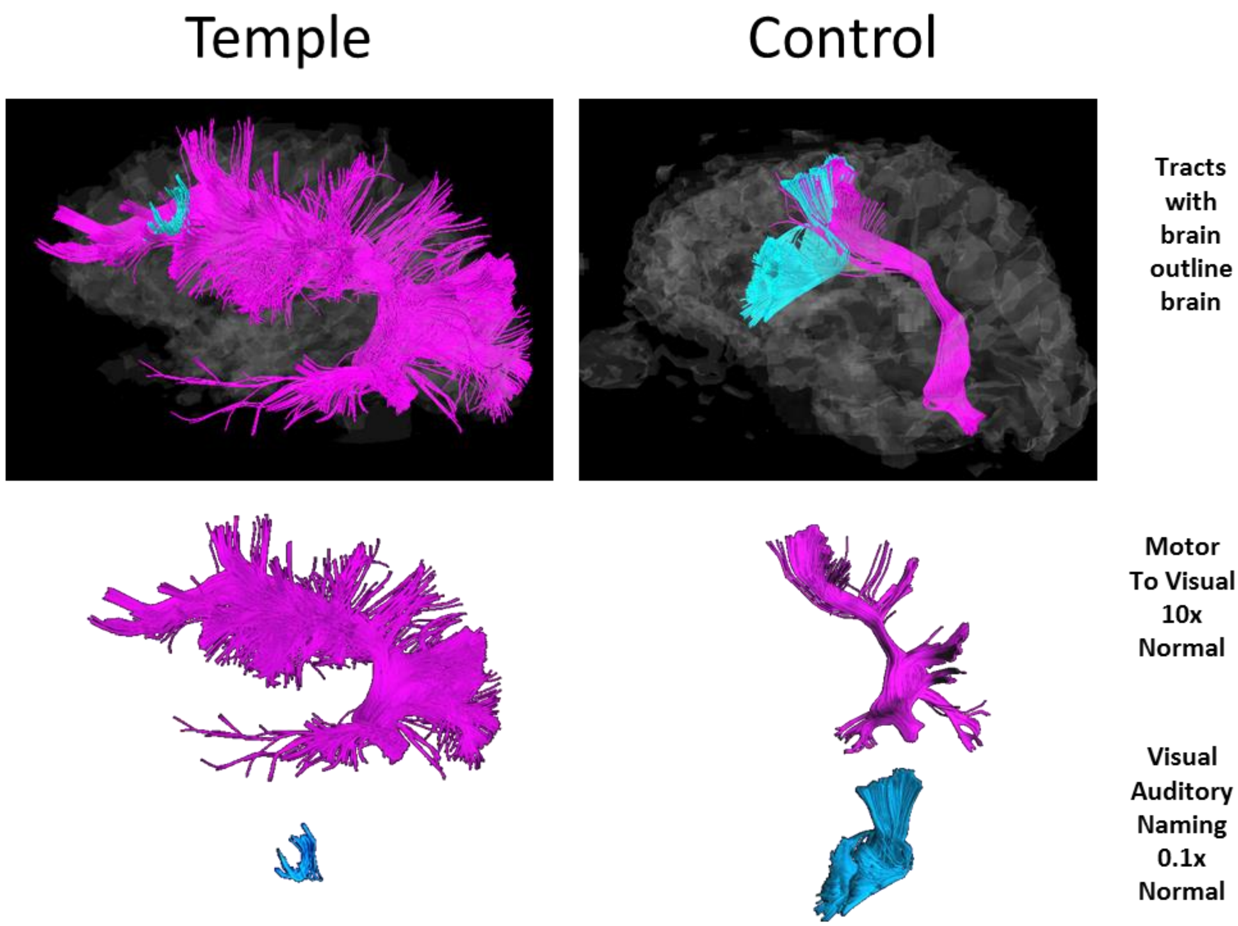
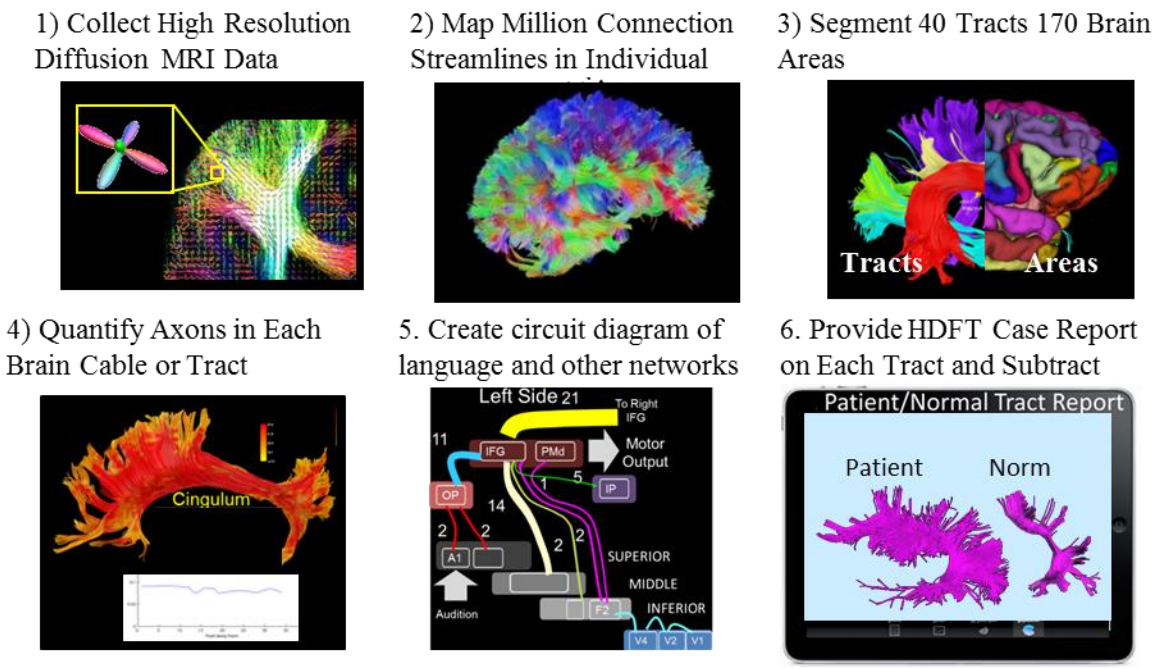


Figure 2. Two component tracts within the language system. In Temple, the tract connecting from the visual object to motor and frontal cortex is ten times the volume of the control. The tract that connects speaking what we hear to speaking what we see is one tenth of the volume of the control tract.



6. **What are the steps involved in getting an HDFT analysis of brain connectivity in autism and other disorders?** Figure 2 shows the steps of an HDFT connectivity analysis applied to language mapping in ASD. Step 1 involves collecting high resolution diffusion MRI information using state of the art equipment (3T MRI scanners with 32 channel head coils, novel pulse programming). Step 2 utilizes sophisticated computational techniques to accurately map the path of axons connecting different brain areas. Step 3 involves segmenting the brain into specific tracts and areas (40 tracts and 150 areas per brain). Step 4 quantifies the left and right side differences or differences compared to normal control brains. Step 5 involves creating a person-specific circuit diagram of the connectivity. For autism, we quantify 40 major tracts but then do a detailed mapping within sub-tracts of the language network doing virtual dissection of clusters of fibers of the arcuate fasciculus (the major language tract of the brain). Step 6 involves providing an HDFT case report, which is currently implemented as an iPad application. This case report provides the clinical treatment team and the parent a detailed quantification, visualization and interpretation of any connectivity anomalies.

Figure 3. Steps in HDFT Analysis Quantify and Visualize Atypical Brain Tracts



7. **How have parents and children reacted to seeing the connective differences in a brain where ASD has been diagnosed?** We have received many favorable remarks from parents who appreciate "seeing" connection disruptions. We had one case of a child with autism looking at the images of the tracts and explaining to the parent they now understood how they were different. The mother wrote me stating "*As a mother of a son with Asperger's Syndrome, I thought you might be interested to know that at the age of 8 my son … was able to describe for me how his brain functions. I recently watched a 60 Minutes interview in which you demonstrated your HDFT technology with the results from Temple Grandin's brain scan. I was shocked to see that the pictures showed what my son had described to me… My son was relieved to find out that his atypical behaviors were not his fault. As I was driving down the street, he exclaimed his eureka moment from the back seat of our van. He said, "I know why it is! People who are normal have straight lines in their brains. I have autism and I have bumps in my lines ... and, on the really crazy days, my brain is ... plaid!!"*

One of the problems in dealing with ASD is coping with a diagnosis that tells you nothing specific about the brain. You naturally want to learn what makes your loved one different. We now have the technology to show key tracts and quantify differences. In the years ahead we hope to be able to explain what each of those tracts does so the child and parent can understand the differences. They can then begin the process of teaching their child how to communicate. Getting early communication is dealing with life and building bonds within a family.

8. **How long does an HDFT scan take and where can it be done, what are the risks?** The HDFT scanning technology continues to advance and the scan times are reducing. HDFT requires high performance scanning on high end 3T MRI machines outfitted with specialized brain coils and using new software to collect and analyzed the data. The analyst methods are currently only available at the University of Pittsburgh Medical Center. The HDFT scan time is about ten minutes but is part of a full clinical scan taking about thirty minutes. MRIs are very safe, there are no injected agents. It is important that the child can remain still during the scan. The child can watch videos during the scan.
9. **Can my child get an HDFT scan for ASD?** HDFT scanning is still a research protocol. It is not covered by insurance programs. We are collecting the data that will facilitate getting approvals in the years ahead. The research must be carefully done and it is a slow process. It will likely take several years. There are some limited opportunities to sign up for research protocols.
10. **How is HDFT used in mapping other brain connectivity problems such as traumatic brain injury, tumors and vascular problems?** Our HDFT work is being applied to a variety of clinical connection disorders (see Summary). We are currently scanning about a hundred traumatic brain injury (TBI) and neurosurgery patients a year. Our clinical research protocols include examination of broken connections in TBI (see paper), connections disrupted by brain tumors, strokes, and vascular problems (see paper) and neurodegenerative diseases, including Alzheimer's and Huntington's. We believe HDFT diagnoses methods can make a difference in all these areas. Our TBI and neurosurgery are the most advanced efforts at this point. You can view a 3 minute video on how HDFT is applied in TBI. We are adapting the technology we use for TBI and neurosurgical diagnosis for autism (see answer #10).
11. **What should I read to learn about HDFT and ASD connection disorders?** There are many good resources for general information on ASD (e.g., see Autism Speaks, Autism-Society , NIH, and CDC). The book by Temple & Panek ***The Autistic Brain: Thinking Across the Spectrum*** provides a readable account of the technology for the general reading. I think the best academic review of autism as a connection disorder is by Schipul, Keller, & Just: 2011 *Inter-regional brain communication and its disturbance in autism* that appeared in Frontiers in Systems Neuroscience (Link). For more about HDFT see my web page, or see the information on our HDFT.info web site.
12. **What are the next steps in the research?** We are starting a protocol to scan 4-year-old children with ASD and with various types of language problems to determine if they show different patterns of connectivity using HDFT. We will follow the children through treatment to determine what levels of language function developed and what rehabilitation therapies were most effective. It will be several years before we have enough results to identify clear patterns.
13. **Are these problems in connections genetic, environmental or both? How might HDFT help to clarify those relationships?** There are many research groups using a wide range of methods to understand ASD. It is likely that both genetic and environmental factors contribute to the disrupted connectivity in ASD. An HDFT map of tract anomalies shows the combined effects. It is important to note that genetics and environment interact in complex ways. We will use HDFT data to quantify different connective states and then seek to find genetic and environmental factors that correlate with these connective subtypes.

(Comments updated April 30, 2013)