

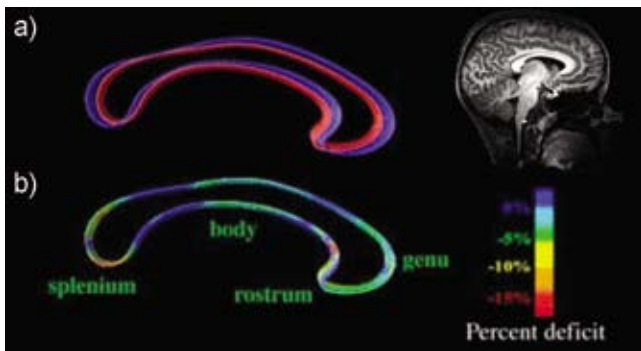
# Brain Structure and Chemistry of Children with Autism

by Timothy DeVito, recipient of 2003-04 ASO Research Studentship (OMHF)

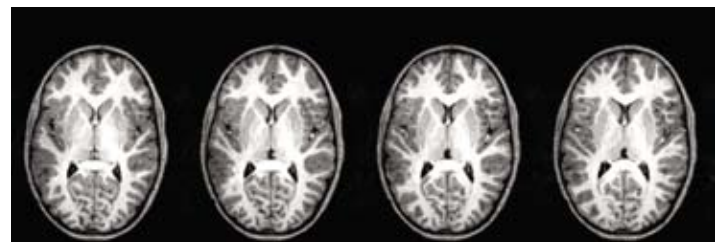
While results from recent studies in various fields point to a neurobiological basis for autism, the full extent and nature of brain abnormalities and how they ultimately affect development remains unknown. Identifying abnormalities in brain structure and chemistry are essential steps in the effort to identify the origin and developmental time-course of autism, and modern neuroimaging techniques offer tremendous promise for discovering and understanding biological irregularities of the brain. Under the supervision of psychiatrist Dr. Rob Nicolson and physicist Dr. Dick Drost, I have been involved in a unique neuroimaging research project investigating brain structure and chemistry of children with autism that has revealed some interesting insights about the nature of this debilitating disorder.

This research uses one of the most flexible and rapidly expanding methods of neuroimaging: magnetic resonance imaging, or MRI. MRI has unparalleled flexibility; it can be used to image brain structure in fine detail, to form images of brain function, to visualize the “wiring” of the brain, and even to measure the levels of certain neurochemicals in a safe and non-invasive manner. MRI doesn’t require the injection of a tracer compound, nor does it expose the patient to potentially harmful radiation, as in x-ray imaging or nuclear medicine. This makes MRI suitable for studying children, and for repeated follow-up exams. Our research specifically focuses on three aspects: examining the size and shape of specific parts of the brain, assessing the density of different brain tissues, and measuring the concentration of numerous chemicals throughout the brain. We acquire all three types of image in the same hour-long scanning session. To date, we’ve imaged over 30 school-aged and adolescent children with autism and roughly the same number of typically developing children for comparison.

Examining the size and shape of various parts of the brain requires high-resolution, three-dimensional images with excellent contrast between different brain structures. This is one of the greatest strengths of MRI, which can produce exquisite brain images with unsurpassed contrast, allowing for the segmentation of distinct subunits of the brain. The volume and shape of each region can be measured and comparisons made between the patient and control groups, highlighting in a very precise manner where anatomical differences exist between groups. These specialized analysis techniques were developed at the Laboratory for Neuro-Imaging at UCLA, and we actively collaborate with that group to analyze our anatomical data. One of the most striking differences we’ve identified concerns the corpus callosum—the conduit that allows communication between the left and right halves of the brain. Figure 1(a) shows that on average, this structure is smaller in the group of children with autism. Figure 1(b) shows more precisely in what regions and to what extent the corpus callosum is thinner in the autism group. It has been proposed that autism is associated with reduced connectivity between brain regions, which could lead to disruption of psychological or neurological functions that depend on the coordination or integration of different brain regions—sometimes referred to as “under-connectivity.” In fact, many of the core symptoms of autism involve cognitive processes that require the integration of input from many brain regions, e.g., language processing and social interaction. Disruption of normal development of the corpus callosum may contribute to these functional deficits common to autism. We have also identified abnormalities in the gross structure of the hippocampus, a region of the brain involved in memory, learning, social functioning and emotion. Given the symptoms of autism, abnormalities of the hippocampus are of obvious interest. Numerous additional



▲ Fig. 1 (a) Average corpus callosum cross-section is smaller in autistic patients (red) than in the control group (blue). (b) Regional thinning is localized mostly to the front (genu) and rear (splenium) of the structure. The MR Image at the top right shows the position of the corpus callosum relative to the rest of the brain.



▲ Fig. 1(b) A few slices from a high-resolution (1.2 mm) 3-D data set of one of our participants. Note the excellent contrast between white and gray matter achieved in these images.



▲ *The 3.0 Tesla head-only MRI system used in our research, located at the Lawson Health Research Institute, St. Joseph's Health Centre, London, ON.*

brain regions are presently being analyzed, including cortical regions specific to language functioning, and total brain volume. Through re-scanning of our participants every few years, we hope to clarify the time-course of these structural abnormalities. This will shed light on when the abnormalities manifest themselves, and give clues to potential developmental insults that may trigger them.

Secondly, MRI is used to quantify the density of various brain tissue types. This protocol provides an additional angle from which we can assess the character and health of brain tissue in autistic patients. The analysis of this portion of the project was carried out by Janet Hendry, another graduate student in our research group. Our results indicate widespread abnormalities in white matter in the autism group. The white matter can be thought of as the wiring of the brain—the means by which the brain's electrical signals get from one part of the brain's gray matter to another, allowing rapid integration and coordination of information. Our findings suggest that the wiring itself may be compromised. While it is uncertain exactly what aspects of the white matter are disturbed at the cellular level, the abnormalities are concentrated in regions involved in sensory processing and integration, and may be associated with the hypersensitivity to sensory stimuli often seen in autism (e.g., aversion to loud sounds, touch). We plan to augment our MRI protocol in the future to delineate more precisely what cellular components of the white matter are abnormal. This will further help in identifying the developmental origin of the deficit.

A large amount of effort has been invested in the third arm of our research, measuring regional levels of brain chemicals. The various chemicals that we can measure with this technique each tell us something different about the brain region being examined. Two of the most important compounds we measure allow us to infer the density of functioning neurons and specific neurotransmitter levels. We observed significantly reduced levels of both of these compounds in the gray matter of the autism group compared with controls. This suggests widespread cortical dysfunction—that is, our group of autistic patients may have fewer healthy, functioning brain cells on average than the typically developing children. In addition to this, the reduced levels of the neurotransmitter glutamate that we observed in the patient group may indicate a global reduction in excitatory signaling in the brain of patients. Interestingly, numerous genetic studies have found that certain genes that code for various components of the glutamate system are abnormal in

autistic patients. This suggests that our observations of reduced glutamate levels may be secondary to genetic anomalies, with direct functional consequences. These findings are also consistent with the notion of under-connectivity. The wiring of the brain adapts during development largely in response to demand and usage—globally reduced signaling during development may lead to a state where proper connections do not form, ultimately leading to an under-connected network with poor ability to integrate and coordinate brain activity. Again, it is imperative that our research participants are followed up at multiple time points in order to clarify how these characteristics change during development, how they are related to white matter changes, and importantly, at what point in development they arise.

This is a truly multi-disciplinary project that combines many disparate fields of study and requires the input from numerous experts in their respective fields, focusing our resources toward the common goal of furthering our understanding of autism. I have had the pleasure to work with psychiatrists, physicists, mathematicians, anatomists, radiologists and psychologists to pursue this goal. It is an honour to have been granted this prestigious province-wide award. I am particularly grateful for the opportunity to present some of our findings to a group of parents, clinicians and therapists at the 2004 Autism Society Ontario Annual Conference in Windsor. This was my first opportunity to discuss our work with devoted family members and professionals who are directly involved in the struggle to understand and cope with this debilitating disorder. Finally, we owe a great debt of thanks to the children who participated in our research and to their parents for their enthusiasm, generosity and patience. These volunteers make this work possible, and their contribution will ultimately bear fruit for all affected by autism.