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Autism Post-Mortem Neuroinformatic Resource: The Autism Tissue Program (ATP) Informatics Portal

Michael B. Brimacombe · Richard Pickett · Jane Pickett

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Abstract The Autism Tissue Program (ATP) was established to oversee and manage brain donations related to neurological research in autism. The ATP Informatics Portal (www.atpportal.org) is an integrated data access system based on Oracle technology, developed to provide access for researchers to information on this rare tissue resource. It also permits sorting of existing cases based on donor ante-mortem history as well as agonal states and post-mortem tissue conditions. Phase II of development established administrative tracking of registrants intending to donate, as well as management of tissue requests and the awarding and tracking of tissue. Phase III is the ongoing assimilation of data sets derived from research on a core group of donors with searchable access by investigators.

Keywords Autism · Neuroinformatics · Brain imagery · Neurology; Autism Tissue Program (ATP)

M. B. Brimacombe (✉)
Department of Preventive Medicine, New Jersey Medical School, UMDNJ, 185 S. Orange Ave (MSB F-647), PO Box 1709, Newark, NJ 07101-1709, USA
e-mail: brimacmb@umdnj.edy

R. Pickett
University of San Diego, San Diego, CA, USA

J. Pickett
Autism Tissue Program, National Alliance for Autism Research (NAAR), Princeton, NJ, USA

Introduction

Informatics as a broad, integrated approach to investigation is a new field of research. Even with the severe computational burdens that are typical in this field, it has engendered successful research environments, especially through the linking of medical, genetic and other information (Weimer et al., 2003; Wong et al., 2004). Much of the current impetus in the area of neuroinformatics stems from the federally funded Human Brain Project and the advances it has brought to imaging and image data (Brinkley & Rosse, 2002).

Autism, Asperger, Rett and Childhood Disintegrative Disorder are pervasive developmental disorders (PDD), often referred to today as autism spectrum disorders (ASD) (DSM-IV-TR, American Psychological Association, 2000). These disorders are characterized by varying degrees of impairment in communication skills, social interactions, and restricted, repetitive and stereotyped patterns of behavior. With no known cause, lack of effective treatment and increasing numbers of diagnosed children, research on autism has become a national priority.

Various studies in the United States and abroad estimate that ASD occurs at a rate of 2–6 per 1,000 births (Yeargin-Allsop et al., 2003). Epilepsy co-occurs with autism with rates up to 33% (Tuchman & Rapin, 2002) and there is a reported increase in mortality associated with autism (Shavelle, Straus, & Pickett, 2001). Other conditions such as fragile X and mental retardation are known to co-occur as well in individuals with autism (Kielinen, Rantala, Timonen, Linna, & Moilanen, 2004).

Autism affects multiple organs and systems of the body, but is believed to be primarily a disorder of the

brain and subsequent behavioral development. An approach to identifying the cause of autism has therefore been to look for basic underlying neurological causes. Brain volume and abnormal growth patterns have also been identified by MRI in living subjects and corresponding post-mortem investigations are underway (Courchesne, 2004; Schumann et al., 2004). Early post-mortem surveys reported structural abnormalities (Bauman and Kemper, 1994). A review of neuropathology structural and neurochemical studies from 1980 to 2004 summarized abnormalities in limbic structures, cortex, basal forebrain, brainstem and the cerebellum and pointed out that this area of study suffered from a lack of brain tissue (Palmen, van Engeland, Hof, & Schmitz, 2004). Investigators generally work independently; however, they are often using tissue samples from the same donor brain; a single brain has been studied by as many as 19 laboratories. Thus, a neuroinformatics approach using an accessible database platform is necessary to interpret results. Disease-specific neuroinformatic environments remain rare and the use of a common set of autism and control subjects to generate data in the Portal raises possibilities for integrated, multi-disciplinary research when the database and environment is carefully developed (Gupta, Ludascher, Grethe, & Martone, 2003).

Background

The Autism Tissue Program (ATP) was created in 1998 to coordinate a national effort to accelerate autism neurologic research by providing a needed and scarce resource; human brain tissue. Combining brain tissue acquisition and a tissue request–review process via an impartial scientific advisory board, the program, by the end of 2004, had distributed over 500 brain tissue samples from 130 autism or control donor brains to 40 peer-reviewed investigators.

To facilitate data-sharing and research collaboration, research data from these studies, often visual in nature, along with phenotypic and genotypic data on the donor, reside in an integrated relational database, the ATP Informatics Portal. The integration of contributed research data into the existing Portal creates a uniquely sourced utility for targeted neurological and neuroinformatic research. Researchers examining various aspects of how the autistic brain differs from non-autistic brains are currently using many advanced informatic software tools and examining research data of many types. These include various visual neurologic data types such as post-mortem MRI, digitalized stained hemibrain sections as shown in Fig. 1A, stereologic measures of cells and dendritic structure of various brain regions thought to be relevant to autism.

Stereologic tools of relevance include software programs to run cortical 'nearest neighbor' cell analyses for changes that relate to neurodevelopment

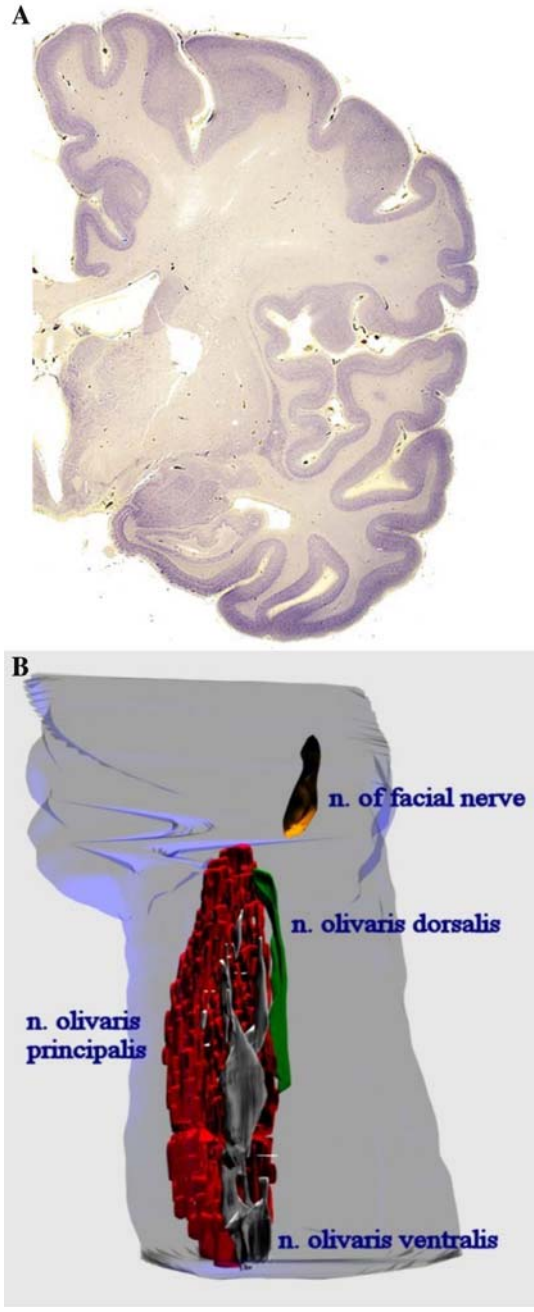

Fig. 1 (**A**) Example of cresyl violet stained hemispheric section for the ATP brain atlas project. (**B**) 3-D reconstruction using serial stained sections of the brainstem of the 23-year-old man diagnosed with autism illustrating the size, shape and spatial relationships of the three subdivisions of the nucleus olivaris inferior (prinicpalis, dorsalis and medialis) and the nucleus of facial nerve

(Schmitz & Hof, 2005), gray-level indexing to measure cortical minicolumns architecture (Casanova, Buxhoeveden, Switala, & Roy, 2002) and 3-D reconstructions of stained serial sections as seen in Fig. 1B (Bobinski, de Leon, & Wegiel, 2000). Some typical research focuses on relative brain region size via MRI (Schumann, Buonocore, & Amaral, 2001; Schumann et al., 2004), stereologic and detailed visual data relevant to design-based stereologiy (Schmitz & Hof, 2005) and data related to the distribution of neurotransmitter receptors in various brain regions (Perry et al., 2001).

Immunohistochemistry (IHC) and genetic projects generate vast amounts of data, especially when one considers that for this resource, laser cell microdissection allows for detailed molecular analysis of gene expression by specific cell type. Tissue array methodology, where up to 99 brain samples can be embedded and sectioned into 150–200 slides for various investigations (Eberhart, Copeland, & Abel, 2006; Samaco, Nagarajan, Braunschweig, & LaSalle, 2004), multiplies the possible IHC measures and requires attention to handing such data. These arrays in particular and availability of tissue samples in general allow testing of many autism gene candidates as well as the evaluation of signal receptors and processes such as brain immunoreactivity, suggested to be relevant to the onset of autism (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005).

In recent years, focusing on specific, measurable traits, or endophenotypes, in the autism population has helped refine and focus analysis. In autism, some of these traits are face recognition, processing emotional visual or auditory stimuli, visual tracking, eye gaze shifting and 'insistence on sameness'. This last trait describes the extreme difficulty of some but not all autistic children to exhibit repetitive compulsions and have extreme difficulty with changes to their daily routine. Many of these attributes of the brain donors are quantified on the Autism Diagnostic Interview—Revised (ADI-R), a standardized diagnostic assessment (Lord et al., 2000) adopted for research and used by ATP clinicians on home visits with donor families. Discrete measures from this instrument are available for clinico-pathologic analysis.

Portal System Design & Status

The ATP Informatics portal is designed to provide researchers with an easily searchable repository of all

Case	Age	Ethnicity	Control	Disorder	Diag Notes	Updated	Download
B-6143	45	African American	N	Autism		24-AUG-04	29-AUG-05
B-6184	18	English-White	N	Autism	Was diagnosed by a physician at 11	17-JAN-05	29-AUG-05
B-6184	18	English-White	N	Chicken Pox	Mild	17-JAN-05	29-AUG-05
B-6184	18	English-White	N	Epilepsy	at age 8	25-JAN-05	29-AUG-05
B-6184	18	English-White	N	Hearing problems	BER waveforms study concluds hearing within normal	01-FEB-05	29-AUG-05
B-6184	18	English-White	N	Other - describe in notes	Was never vaccinnated; malabsorption problems, sympyomatomatic,	01-FEB-05	29-AUG-05
B-6184	18	English-White	N	Seizures	Petit mal, grand mal, had first seizure at 8	25-JAN-05	29-AUG-05
B-6202	48	English-White	N	Abnormal gait		08-MAR-05	29-AUG-05
B-6202	48	English-White	N	Asthma	Had 5 severe asthmas - like attacks before age 2. none since. Cause never	08-MAR-05	29-AUG-05

Fig. 2 Example of structured data and text notes relating to medical disorders of donor information. columns can be sorted by clicking column header and the entire table of 499 records can be downloaded to an Excel sheet

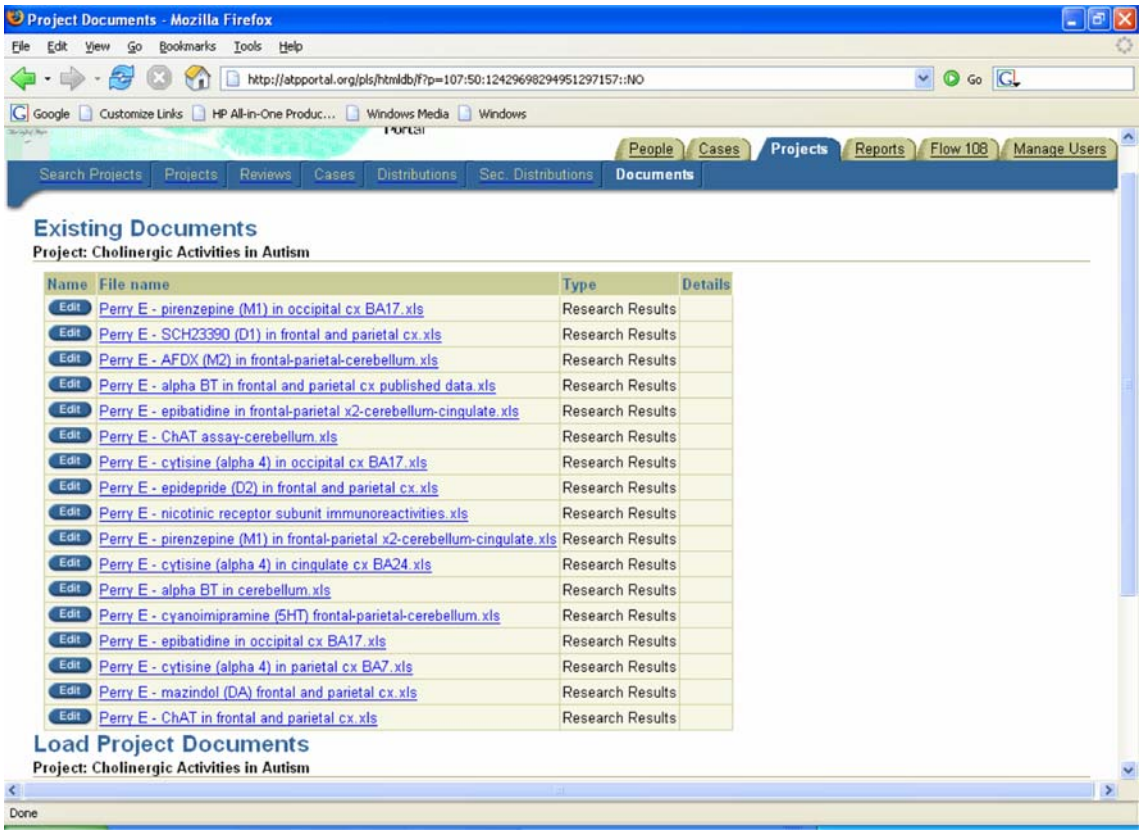

Fig. 3 Example of unstructured research data. Shown here is a partial list of excel files with data from various IHC binding experiments associated with a project by investigator Elaine Perry in Great Britain

information collected by the ATP on donated brain tissue using the latest in relational information technology. Guests are invited to visit the portal at www.atpportal.org. A guide on the welcome page gives an overview of the portal layout and functions. The system stores both structured (Fig. 2) and unstructured data (Fig. 3) and can easily accommodate additional resources such as new imaging and software tools for investigators.

The infrastructure now includes an Oracle 10 g Relational Database and Oracle 10 g Application Server software utilizing Linux as the operating system on a Hewlett-Packard ML350 G3 Server. These platforms, developed for integrated data settings, allow for excellent integration of the various types of data into the Portal.

Discussion

The ATP Informatics Portal is progressing to becoming a widely used, comprehensive neuroinformatic research environment. When considering the development of informatic research environments, the sheer size and scope of the database and related possibility of spurious results when testing hypotheses in these settings implies the need for *informed* planning and development of the underlying databases. Naïve integration of databases and subsequent use of sophisticated statistical clustering and modeling techniques in these settings can be misleading. The huge files and issues associated with the visual data can be daunting as described in a paper entitled; Neuroimage Databases: the good, the bad and the ugly, by Toga (2002).

To encourage the level of collaboration necessary for further development, it is imperative for informatic resources to be developed in a collaborative manner, reflecting the interests and needs of participating researchers. This creates a practical and useful setting for data sharing and the further development of the integrated informatic environment. In the case of the ATP Informatics Portal, an international data steering committee consists of actively participating principal investigators and brain bank administrators directly involved in decisions regarding data standardization, integration and processing and any potential exami-

nation of interdisciplinary associations and hypotheses. In the specific case of autism, the basic goal of ATP related research remains the identification of the neurological cause(s) and symptoms of this unexplained spectrum of disorders.

Data comparability challenges for the ATP Informatics Portal are numerous and include differences in lab assay procedures, time related factors affecting tissue quality and comparability, common file types and data coding practices affecting comparability of data. Prior to merging collected data, some assessment must be made regarding comparability of the various datasets and variables. Data dictionaries must be provided by researchers along with general descriptions of lab procedures. These need to be integrated and made available to other researchers to allow for proper interpretation of the collected data. Interpretation of brain structure related results necessarily involve assessment of brain tissue quality and whether the quality has remained stable across labs and over time.

A unique resource such as the ATP Informatics Portal serves as a potential template for future informatic efforts in disease specific research areas other than autism and we welcome inclusion of brain data from all autism neuropathy studies and from autism-related disorders. Hopefully, this collaborative effort will result in breakthrough identification of cytoarchitectural, neurochemical and genetic changes associated with autism that will pave the way for improved diagnosis and treatment.

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