Although there have been enormous advances in several fields of neurology, progress in our understanding of the neurobiology of some neuropsychological disorders, including autism, and in the translation of basic science discoveries into effective treatments for these conditions, is still considerably limited. Between 1 in 500 and 1 in 2,500 Americans suffer from autism, a brain disorder that begins in early childhood and impairs thinking, feeling, language, and the ability to relate to others. Families coping with this devastating illness are desperate for answers about its causes, diagnosis, prevention, and treatment. In the mid 1970s, autism was seen as a rare condition, thought to affect between two and four children per 10,000. But recent studies suggest that this figure has grown by an average of 40%. Most autism researchers think that changes in the way the condition is defined and diagnosed explain this rise in recorded cases. But that is of little consolation to the parents of affected children. They want to know what is happening to the minds of their children and whether anything can be done to treat the condition.

Recently, the National Institutes of Health (NIH) launched a research plan for autism, hoping to cut the condition’s prevalence in the United States by a quarter by 2013. The NIH autism ‘roadmap’ aims to identify the genetic, environmental and neurological factors underlying the disorder. It represents the biomedical research agency’s first concerted push to tackle the condition. Similarly, 2003 was designated European Year of People with Disabilities, the objective of this special year being to bring us closer to the achievement of equal rights for people with disabilities, including autism. There are 37 million people with disabilities in the European Union, and thus 37 million good reasons to become involved in this project.

The disorder currently has no known biological basis. No genes or circuits have been identified; there are no workable animal models, and thus no tools to develop new treatments. This is in striking contrast to the point scientists have reached in the rest of medicine. Knowledge of autism is at a stage similar to that we were at ten years ago with Alzheimer’s disease, or 20 years ago with Huntington’s. Autism is a complex neuropsychiatric disorder, in which multiple genetic and environmental factors may interact, producing a clinical continuum. The genetic component is best described by a multi-locus model that takes into account epistatic interactions between several susceptibility genes. In the past ten years, enormous progress has been made in identifying chromosomal regions showing linkage with autism, but progressing from chromosomal regions to candidate genes has proved to be tremendously difficult. Neuroanatomical findings point to early dysgenetic events taking place in the cerebral cortex, cerebellum, and brainstem. At cellular level, disease mechanisms may include altered cell migration, increased cell proliferation, decreased cell death, or altered synapse elimination. Neurochemical findings in autism point to involvement of multiple neurotransmitter systems. The serotonergic system has been intensively investigated in autism, but other neurotransmitter systems (e.g., the GABAergic and the cholinergic system) are also coming under increasingly close scrutiny. The role of environmental factors is still poorly characterised. It is not yet clear whether environmental factors act merely as precipitating agents, always requiring an underlying genetic liability, or whether they represent an essential component of a pathogenetic process wherein genetic liability alone does not lead to the full-blown autism phenotype. A third potential player in the pathogenesis of autism, in addition to genetic and environmental factors, is developmental variability due to “random” factors, e.g., small fluctuations of gene expression and complex, non-deterministic interactions between genes during brain development. These considerations suggest that a non-deterministic conceptual framework is highly appropriate for autism research.

Neuroscientists involved in studying autism have focused, in particular, on at least three major fields: brain imaging, genetics and developmental neurobiology. Non-invasive brain imaging techniques, such as MRI (magnetic resonance imaging),...
offer great potential for advancing understanding of the neural basis of emotional and intellectual deficits in autism and other childhood neuropsychiatric disorders. However, scientists currently have at their disposal few data on normal brain function and development to compare with data from individuals with autism. Such norms have been lacking for brain imaging studies, leading to non-comparable findings and excessive duplication in the scanning of control subjects. A study of normal brain development should catalogue the structural development of the brain, by age and sex. Initial scans should be followed up with additional scans and clinical and behavioural reassessments at 2-year intervals. This would permit the normal growth curves of brain structures to be charted, revealing the development of circuitry for language, thinking, and other functions. Individual brains differ so much that only broad generalisations can be made from comparisons of different individuals at different ages. The promise offered by a normative brain database of this kind is that it will turn up clues about childhood brain disorders. In a recent longitudinal structural MRI study that set out to track individual children’s developing brains, the researchers were surprised to discover a second wave of overproduction of grey matter occurring just prior to puberty. Possibly related to the influence of surging sex hormones, this thickening peaks at around age 11 in girls and 12 in boys, after which the grey matter actually thins some. Prior to this study, scientists had thought that the brain overproduced grey matter for a brief period in early development (in the womb and for about the first 18 months of life) and then underwent just one bout of pruning. This grey matter growth spurt predominates in the frontal lobe, the seat of the “executive functions” (planning, impulse control and reasoning) that are impaired in childhood-onset schizophrenia, a rare (1 in 40,000 children) psychotic disorder that is sometimes confused with autism. In teens who had developed psychosis prior to puberty, the MRI scans revealed four times as much grey matter loss in the frontal lobe as normally occurs.

In other brain imaging studies, researchers using MRI and magnetic resonance spectroscopy (MRS) have been seeking to identify brain anatomical and biochemical abnormalities that may underlie impaired social communication in children with autism. One fMRI study has been investigating malfunctioning brain circuits associated with impaired thinking about human relationships, a problem seen in autism. Yet another series of MRI studies has been trying to pinpoint the brain structural abnormalities associated with severity of attention deficits in people with autism. Researchers have, for example, shown that decreased volume in an area of the brain’s parietal lobe correlates with the degree of impairment of the ability to detect stimuli located outside a principal focus of visual attention.

While it is known that heredity plays a major role in complex behavioural disorders like autism, the identification of specific genes that confer vulnerability to such disorders has proved extremely difficult. Detecting multiple genes, each contributing only a small effect, requires large sample sizes and powerful technologies that can associate genetic variations with the disorder and pinpoint candidate genes. And even after human disease vulnerability genes are found, sophisticated tools are needed to find out what turns them on, what brain components they code for, and how they affect behaviour. Although by no means assured, the prospect of acquiring such molecular knowledge offers great hope for the engineering of new therapies.

Recently, five research teams published results from genome scans in autism. Regions on chromosomes 1, 2, 4, 5, 6, 7, 10, 13, 15, 16, 17, 18, 19, X, and 22 were identified as possible locations for disease vulnerability genes. These pooled data are now being analysed. Although all the studies pointed to one chromosomal region (7q) as being involved, no specific linked gene has yet been identified. Variants of a particular gene in the 7q region, expressed in the human thalamus, may be associated with susceptibility to autism. In addition to its suspect location, this gene is also a member of a family of genes that influences brain development.

If there is a developmental abnormality in autism, due to a gene defect or gene/environment interaction, then it is likely that some genes turn on too much or too little, or in the wrong place. This may interfere with the migration and wiring of embryonic brain cells during early development, or with the way cells function. A vital resource for validating this hypothesis will be the joint scientific infrastructure called the BMAP (Brain Molecular Anatomy Project). The goals of this multidisciplinary effort are to catalogue the genes that turn on in various parts of the brain at different developmental stages, and to make this information readily available to investigators via the Internet. This body of information will include maps revealing a gene’s location and detailed breakdowns of its chemical components. One important initial focus of attention of the BMAP is the mouse brain. A web-based digital mouse brain atlas will offer 3-D and 2-D views of this biological blueprint, covering different strains and ages of animals. A gene library of mouse brain tissue, optimised to detect rare gene variations, will speed along studies of how specific genes act in both animals and humans. Studies will characterise gene expression patterns in precise brain regions in response to the disorder, and to pharmacological or environmental influences. In addition to advancing basic knowledge, the BMAP database promises to enhance both clinical science, providing new leads for studying gene expression in post-mortem tissue and for the identification of candidate genes, and capacity to screen for individuals who might be at risk of developing brain disorders.