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Abstract

Autism was first described as the earliest form of schizophrenic psychosis. It is now considered to be a biologically based pervasive neurodevelopmental disorder affecting, from the first days of life, social communication and adjustment to the environment. Advances in the understanding of its clinical, neurofunctional and genetic aspects have progressively modified conceptions and practices for diagnosis, exploration and therapeutics.

Keywords

Asperger syndrome · Autism · Cerebral modulation insufficiency · Checklist for autism in toddlers (CHAT) · Endophenotypes · Extreme male brain theory ·

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Neurofunctional models, autism · Theory of mind · Theory of weak central coherence · Voxel-based morphometry

Brief History

In two distant parts of the world at almost the same time, two eminent neuropsychiatrists, Leo Kanner in Baltimore in 1943 and Hans Asperger in Vienna in 1944, published articles describing children presenting disorders they named “autism.” The father of the expression “early infantile autism,” Leo Kanner, put forward the hypothesis of an innate inherited biological disturbance of affective contact:

We must, then, assume that these children have come into the world with innate inability to form the usual, biologically provided affective contact with people, just as other children come into the world with innate physical or intellectual handicaps.

Kanner and Asperger had borrowed the term “autism” from two adult neuropsychiatrists, Emil Kraepelin and Eugen Bleuler, who used it to describe the escape from reality and withdrawal seen in schizophrenia. Therefore, for several decades, infantile autism was classified, in reference to schizophrenia, under the heading “infantile psychosis” and linked to a psychogenic explanation of its origin suggesting that pathological maternal behavior triggered early distortion of self-other relationships.

During the 1970s, neurobiological concepts began to greatly outweigh the psychodynamic tendencies. When, in 1980, the category “pervasive developmental disorders” (PDDs) was introduced in the American classification, an international debate arose. The hypotheses put forward on links between peculiar behaviors and maternal deprivation or brain development resembled discussions in the early nineteenth century on the psychopathology of feral children fostered by Doctor Jean Itard’s efforts in educating the wild boy, Victor of Aveyron.

The innovative neurobiological concepts influenced pathophysiological hypotheses and therapeutic intervention. The first results in neuropathology and brain imaging were published. In France, the pioneer Lelord proposed the hypothesis of “cerebral modulation insufficiency.” According to his work, abnormalities of the filtering and modulation of sensory, emotional, and motor perception could explain the characteristics of autism. From this period on, large international epidemiological studies were launched. In the United States and Europe, cohorts and data banks were built up. Technological progress offered new tools, video recording of behavior, molecular biology, and functional brain imaging and enabled studies linking cognitive particularities to neurophysiological mechanisms.

The international medical and scientific communities now consider that autism is the result of a neurodevelopmental disorder that pervasively alters the affected children’s capacities to interact with their environment and to develop means of

communication with others. This leads rapidly to a particularly disconcerting form of behavioral and social dysfunction and a lifelong handicap.

Autism Is a Behaviorally Defined Syndrome

Babies with autism do not seem to react to their mother's voice; they do not make eye contact. Their face expresses little emotion. Their muscle tone and posture are abnormal; sometimes they seem floppy like a rag doll; at other moments, they are stiff and taut. Caresses may seem to cause them pain. They do not stretch their arms toward adults to be picked up out of their crib.

By the age of 3 years, the autistic syndrome is defined by significant impairments in three behavioral domains:

- *Social Relationships*: Children with autism seem alone in their own world. They play alone and often appear to be deaf, reacting to people as if they were objects, making unusual eye contact, and showing few expressions. Sharing emotion is difficult for them.
- *Communication*: Some children with autism do not speak. If language is present, it is not used to exchange information or converse with others.
- *Adaptation (Restricted Interests, Repetitive Movements)*: Children with autism are attached to sameness in the environment. The slightest change or unexpected event may provoke anxiety or aggressiveness. Their range of activities and interests is narrow and repetitive. Stereotypic behaviors such as flapping, spinning, or rocking all or parts of the body may appear when some children are alone or even with others.

These qualitative abnormalities are the basis of the diagnostic criteria used in international classifications: the American Psychiatric Association Manual of Psychiatric Diseases, fourth edition text revision (DSM-IV-TR) and the World Health Organization's (WHO) International Classification of Diseases, tenth edition (ICD-10) (see Table 1). In these manuals, autistic disorder is described under the heading "pervasive developmental disorders" of which it constitutes the most typical form. The diagnosis is clinical and based solely on behavior. No reliable biological markers have been found, and the cause of autism remains unknown.

If parental concern is often expressed before their child's first birthday, it always indicates a probable risk. Large-scale epidemiological studies and retrospective studies of family films have guided the elaboration of a screening instrument called the CHAT (Checklist for Autism in Toddlers) composed of a series of absolute signs of concern in simple questions to be asked at the child's 18-month medical checkup. These signs concern essential precursors of communication: reaction to

Table 1 World Health Organization ICD-10 criteria for childhood autism

| ICD-10 criteria for “childhood autism” |
|--|
| A. Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas: |
| 1. Receptive or expressive language as used in social communication |
| 2. The development of selective social attachments or of reciprocal social interaction |
| 3. Functional or symbolic play |
| B. A total of at least six symptoms from (1), (2), and (3) must be present, with at least two from (1) and at least one from each of (2) and (3) |
| 1. Qualitative impairment in social interaction is manifest in at least two of the following areas: |
| (a) Failure adequately to use eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction |
| (b) Failure to develop (in a manner appropriate to mental age and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities, and emotions |
| (c) Lack of socioemotional reciprocity, as shown by an impaired or deviant response to other people’s emotions; or lack of modulation of behavior according to social context; or a weak integration of social, emotional, and communicative behaviors |
| (d) Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., a lack of showing, bringing, or pointing out to other people objects of interest to the individual) |
| 2. Qualitative abnormalities in communication as manifest in at least one of the following areas: |
| (a) Delay in or total lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gestures or mime as an alternative mode of communication (often preceded by a lack of communicative babbling) |
| (b) Relative failure to initiate or sustain conversational interchange (at whatever level of language skill is present), in which there is reciprocal responsiveness to the communications of the other person |
| (c) Stereotyped and repetitive use of language or idiosyncratic use of words or phrases |
| (d) Lack of varied spontaneous make-believe play or (when young) social imitative play |
| 3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities are manifested in at least one of the following: |
| (a) An encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus |
| (b) Apparently compulsive adherence to specific, nonfunctional routines or rituals |
| (c) Stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting or complex whole body movements |
| (d) Preoccupations with part objects of nonfunctional elements of play materials (such as their odor, the feel of their surface, or the noise or vibration they generate) |

the human voice, pointing a finger toward a desired object, and the first elements of language. The questionnaire allows detection of at-risk children and appropriate early intervention. But, by definition, a diagnosis of autism must be confirmed before age 3.

Clinical Assessment Has to Be Completed for Each Subject with Autism

Autism is frequently associated with other abnormalities, disorders, or diseases. Their identification does not question the diagnosis of autism, but provides invaluable indications concerning intervention and outcome.

Mental retardation of variable severity is classically described in almost 80% of cases, and 50% of the children do not develop functional language. These percentages are now much lower because milder forms of the disorder are more often diagnosed. Delay, whether it be mild or severe, is characterized by marked contrast between weak social-communication abilities and better nonverbal cognitive performance. This “disharmony” typical to autism often disconcerts therapists and teachers.

It is also important to investigate associated neurological diseases: epilepsy, diagnosed in over one third of children with autism and mental retardation, motor coordination disorders, and sensory impairments.

Most cases of autism are nonsyndromic (of unknown etiology). However a genetic or metabolic etiology is identified in 10–20% of affected children. The most frequent are fragile X syndrome, tuberous sclerosis, neurofibromatosis type 1, Down syndrome, Angelman or Prader-Willi syndrome, and phenylketonuria. With rapid progress in neurogenetics and in molecular biology, these percentages are constantly increasing.

The Broadening Definition of the Disorder Has Led to the Concept of Autism Spectrum Disorders

Today, the concept of autism spectrum disorders (ASDs) is progressively replacing the diagnostic categories of autism and PDD. Indeed, in the population meeting the criteria for a diagnosis of PDD, there are many different clinical profiles. This is not only due to variations in the severity of the disorder but also to varied early clinical developmental trajectories, for example, the absence of language delay in Asperger syndrome or the later onset of childhood disintegrative disorder. Recently, the definition of PDD has also been broadened to include even milder forms of the disorder.

Are these different forms of PDDs separate entities or points on a single spectrum? This is under discussion. It is probable that future classification systems such as the American Psychiatric Association’s forthcoming DSM-V and the new version of the WHO’s ICD will adopt the term “ASD” so as to focus on the specificity of the disorders of social development and on the considerable variations of symptoms among individuals. In spite of the great diversity of clinical presentations, all individuals with autism have common characteristics:

- Their limited capacity for empathy may be expressed as social detachment or an unusual, unilateral, or even intrusive manner of relating to others.

- Language is absent or limited or when present includes unusual content such as echolalia, neologisms, or pronoun reversal. Their repertory of emotional expressions is poor.
- Their incapacity to develop internal representations affects their aptitude to predict what is going to happen next. They often have personal, narrow, and atypical centers of interest.

Many individuals with autism have hypo- or hypersensitivity to tactile, auditory, or visual stimuli; they may also have unusual reactions to heat, cold, and/or pain.

Anxiety, sleep problems, eating disorders that may lead to gastrointestinal problems, violent tantrums, and self-aggression are among other frequent characteristics often associated with autism.

Is there an “epidemic” of autism? Indeed, prevalence rates have risen in recent years from 1–4 in 10,000 births in the 1980s to 1–4 in 1,000 in 2000. The most recent figures published report 1 in 100. The change is due to the broadening spectrum of autism. Also heightening awareness and better training among health professionals has enabled them to identify even mild forms of autism at all ages of the life span.

Neurofunctional Models Are Rooted in Clinical Observations

Over the last 30 years, the neurodevelopmental hypothesis has been expanded through clinical observations and studies in anatomy and anatomical pathology (see Fig. 1). In developmental psychopathology, several hypotheses have been put forward. They do not exclude each other; some even share common conceptual components. Abnormalities in functioning of neural networks play an essential role in this disorder of the perceptions of others, of their intentions, emotions, and reactions. The neural theories of autism can be linked to models proposed by cognitive psychologists who have described particular intellectual and social functioning in the syndrome. The aim of many studies is elucidating the cerebral bases of deficits in empathy, theory of mind, executive functions, and central coherence.

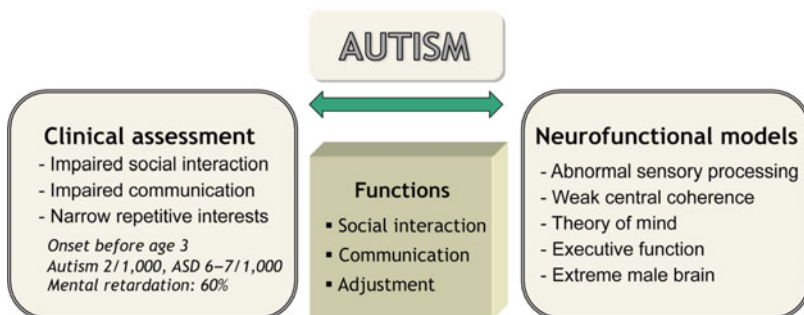


Fig. 1 Neurophysiological hypotheses are rooted in clinical observations

The principal theories and eventual underlying neurophysiological dysfunctions are summarized here.

Unusual responses to sensory input (hyper- or hyposensitivity, distortions, cut-offs, shutdowns) observed in all sensory channels, and also particular social functioning, could be linked to impaired processing of auditory and visual stimuli and especially stimuli with social content such as voices or faces. Data from functional brain imaging and neurophysiological measures have also evidenced particular sensory systems functioning. Nevertheless and especially in the auditory domain, unusual activation patterns are also found with neutral stimuli without social content (tones). A left temporal hyporeactivity was first thus described in the first electrophysiological studies and further studied using brain imaging. Interest grew for a specific temporal area (the superior temporal sulcus) in recent years with the hypothesis that this area responds specifically to the human voice. Advances in functional imaging techniques and further studies evidenced a wider activation of a network of brain regions. Particularities of visual processing and multimodal auditory-visual processing were also observed. Visual stimuli with social content such as faces were intensively studied, and a hypoactivation of the fusiform gyrus in response to faces was observed in autism. Concurrent to these studies of cortical sensory processing, observations of particular ocular behavior (circular gaze, absence of focus on the eyes, absence of strategies taking into account ocular dominance) were explored using eye tracking systems.

According to the theory of *weak central coherence*, atypical processing of sensory stimuli, privileging local processing to the detriment of global processing that integrates separate elements into a coherent whole, could be implicated. Rather than a genuine impairment, this particular type of information processing could be the expression of a distinct cognitive style. This hypothesis could be linked to abnormalities of long-distance cerebral connectivity concurrent to hyperreactivity of local connectivity. The behavioral domains affected in autism (communication, socialization, and restricted interests) require rapid integration of various pieces of information coming from different brain regions distant one from another. Minor, though scattered, dysfunction of neurotransmission, on a synaptic level, for example, could easily disrupt this type of integration.

A specific impairment of *theory of mind*, the capacity to attribute mental states to one's self and to others, could be implicated in autism. On a physiological level, the "social brain" is constituted by neural networks specialized in processing information on others' appearance, behavior, and intentions. Although an ensemble of different regions could be involved, areas such as the superior temporal sulcus, the fusiform gyrus, and the orbitofrontal cortex are more particularly devoted to processing social stimuli. Dysfunction of this social brain network could underlie unusual social behavior. Particularities of the mirror neurons that are activated when a significant movement is perceived could also be linked to impaired treatment of social stimuli. Among recent imaging studies, a study using diffusion tensor imaging (DTI) shows a decrease in anisotropy of white matter adjacent the prefrontal cortex, the anterior cingulate gyrus, and the superior temporal sulcus, evoking disturbance of white matter tracts involved in social information processing.

Within the inhibitive, flexible, and generative processes (spontaneous production of a new behavior in a new context) involved in planning, flexibility seems to be most severely impaired. *Executive function deficits* evidenced in young teens and adults with autism would correspond to more complex development patterns in young children considering the late maturational processes involved.

The *extreme male brain theory* makes reference to cognitive and emotional phenotypes characterizing the normal population. The “empathizing” phenotype (more frequent in women) corresponds to the capacity to attribute mental states to others and to have an appropriate emotional reaction, whereas the “systemizing” phenotype (more frequent in men) is defined by the capacity to understand and predict abstract, technological, or biological systems’ functioning. A weakness of the first cognitive style, combined with an unusually frequent use of the second, could explain the behavioral phenotype of certain individuals with autism. This hypothesis leads to the extreme male brain theory, according to which individuals with autism function essentially in the systemizing mode, driven by a high level of the hormone testosterone.

Autism Results from Abnormal Brain Development

The origin of pervasive developmental disorders is neurodevelopmental, which means that one or several stages of brain development are disrupted, as opposed to a neurodegenerative disorder in which mature nerve cells are progressively lost. There are nine different stages of brain development: neurogenesis, neural migration, differentiation, axonal growth, dendritic growth, myelinogenesis, synaptogenesis, synaptic selection, and apoptosis (programmed cell death). All of these stages could be candidates for disturbance in autism, but recent studies (supported by results in genetics) focus more frequently on development and conservation of synaptic connections, also on axonal growth and the establishment of tracts connecting different brain areas.

One of the most robust and frequently replicated findings in the neuroanatomy of autism is that the mean volume of the brain of patients with autism is larger than average. Twenty percent of these patients present a macrocephaly, as defined by head circumference over the 98th percentile, in contrast to only 2% of the general population. Studies of brain volume using measurement of head circumference, anatomical magnetic resonance imaging (MRI), and anatomical pathological analysis have evidenced a particular pattern of brain growth: overgrowth during the first 2 years of life followed by a deceleration. The underlying pathophysiological mechanisms involved remain unexplained and their exact chronology unknown. Data on head circumference at birth are contradictory; some studies have reported an enlargement, others a decrease, but in general, recent studies report an average head circumference at birth. Anatomical brain imaging studies concern both white matter and gray matter; several studies evidence the involvement of radiate white matter. This increase has been found, according to various studies, in the cerebellum and in different cerebral lobes. Some studies find an anterior to posterior gradient,

whereas others evidence a significant increase of brain volume in temporal, parietal, and occipital, but not in the frontal lobes.

The first anatomical imaging data published in the early 1980s made a major contribution to the emergence of the neurodevelopmental hypotheses in autism. In 1988, Courchesne and his colleagues, using the first MRI data, evidenced hypoplasia of cerebellar vermal lobules VI and VII in autism. Using conventional MRI, a high prevalence of nonspecific abnormalities of white matter is also found in autism as compared to the general population. Concurrently data support brain enlargement and the unusual brain growth pattern previously described, and new techniques allowing fine-grained analyses of brain structure are now being applied in autism. Data obtained by DTI allow studies of white matter tracts, and analysis by VBM (voxel-based morphometry) allows detailed studies of brain structure. Preliminary work with these techniques has evidenced decrease or increase of white matter density in different brain areas of children with autism compared to normal controls.

In parallel with these macroscopic data, studies in anatomical pathology and their description of cytoarchitectural organization of brain tissue have also provided arguments in favor of the neurodevelopmental hypotheses. The small size of the samples studied, possible methodological bias, and frequent comorbid mental retardation or epilepsy limit these studies. Nevertheless, the most frequently replicated findings concern a decrease of Purkinje cells and signs of an altered organization of the cortical minicolumns. Increased number and decreased width of minicolumns could reflect modifications in the GABAergic systems. These results support the hypothesis of a connectivity disorder, showing a local hyperconnectivity to the detriment of long-distance connections between different brain regions underlying integrative processes. Recent studies evidenced a glial reaction, an increase in immune markers such as TNF-alpha that could sign an inflammatory process. Nevertheless, these markers are also involved in synaptic developmental processes and apoptosis; they could therefore simply reflect the neurodevelopmental disorder.

The role of environmental factors in autism pathophysiology or in phenotype variations has been suspected for many years. Observations have linked exposure to certain pre- or perinatal factors, such as cytomegalovirus, rubella, thalidomide, and valproic acid, to autism but rarely and principally in cases where this exposure has first caused brain damage. Recent epidemiological studies have shown that vaccines are not a causal factor in autism.

Moreover, studies in anatomical pathology have evidenced astroglial and neuroglial reactions, suggesting the implication of neuroinflammatory phenomena. Various factors, such as genetic susceptibility, maternal factors, and exposure to prenatal factors, could account for these neuroglial reactions. High blood levels of cytokines have also been observed.

Oxidative stress phenomena could also be involved, as shown by studies of antioxidant substances in platelets levels (decrease in levels of superoxide dismutase and transferrin) or oxidative stress markers (lipid peroxidation).

Lastly, another research domain concerns the presence in the serum of mothers of children with autism of autoantibodies that could react with fetal brain proteins. A recent study has found an unusual profile of these antibodies in mothers of children

with autism, but in the results of another study using serum, samples taken systematically in midpregnancy are not significant. Nevertheless, studies using animal models of intrauterine of exposure to this type of antibodies could be an interesting lead in research.

Autism Could Be Linked to Abnormal Neurotransmission and Neuromodulation

Among the monoaminergic hypotheses, the theory concerning a disturbance of serotonergic transmission has been further developed in autism, whereas dopaminergic hypotheses are more frequently advanced in schizophrenia. The role of neurotransmitters in the central nervous system is linked not only to synaptic function but also to cerebral developmental and maturational processes. One of the most frequently replicated findings concerns plasmatic hyperserotonemia (concerning essentially the serotonin level in platelets) eventually linked to hyperactivity of the platelet serotonin transporter. Concurrently, genetic studies have shown an association between autism and a polymorphism of the SLC6A4 gene encoding the serotonin transporter. In clinical observation, certain repetitive behaviors evoke forms of OCD (obsessive-compulsive disorder), and the efficacy of selective serotonin reuptake inhibitors in certain cases is another argument in favor of this theory. Lastly, imaging studies using positron-emission tomography (PET) and single photon emission computed tomography (SPECT) have recently evidenced in children with autism the absence of a peak in serotonin synthesis (observed normally in well children around age 2), as well as a decrease 5-HT_{2A} receptor binding in the cerebral cortex.

Parallel to this monoaminergic hypothesis, glutamatergic and GABAergic pathways have gained interest. This interest is focused not only on synaptic transmission but also on eventual involvement of these systems in neurodevelopment. It is, for example, well known that activation of GABAergic and glutamatergic receptors is involved in neuronal migration, especially in radial and tangential migration. Moreover, balance between excitatory (glutamatergic) and inhibitory (GABAergic) transmission is essential for normal cerebral development and functioning. Implication of these neurotransmitters in the pathophysiology of autism and PDD is supported by findings in genetics and anatomical pathology. Certain association studies of candidate genes encoding glutamatergic and GABAergic receptors have evidenced association with autism. Studies of cerebral tissue have also shown an increase of the expression of certain genes associated with glutamatergic pathways and a decrease in GABAergic receptors.

Since 2003, several studies in genetics have evidenced functional mutations in genes encoding for proteins localized at the glutamatergic synapse in patients with autism (and/or mental retardation). The first studies concerned genes of the neuroligin family (NLGN4, NLGN3), cell-adhesion molecules, and then their pre-synaptic partners, the neurexins. These molecules are involved in synaptic development and conservation, playing an important role in the balance between excitatory

and inhibitory transmissions. Other studies have also pointed to genes encoding proteins localized at the glutamatergic synapse such as the SHANK3 protein that binds with the neuroligins enabling membrane proteins to bind to the cytoskeleton of the synapse and the KCNMA1 gene involved in a postsynaptic channel regulating neuronal excitability. The hypothesis of a deficit in synaptic development and functioning is now at the frontline in pathophysiology research on autism.

Brain activity is modulated by neuropeptides and neurohormones such as oxytocin and melatonin. Targeting oxytocin, which plays a role in social behaviors, in specific stages in development could be promising. The link between melatonergic dysregulation and sleep disturbances common in ASDs also opens new pathways for therapeutic intervention.

Autism Is a Strongly Genetic Disorder

There is now no doubt that genetic factors are a major component of the cause of autism. Research was undertaken on the basis of strong clinical and epidemiological arguments in favor of this hypothesis, particularly twin studies finding much higher concordance rates for the syndrome among monozygotic than dizygotic twins. The risk of reoccurrence was also much higher in siblings of children with autism.

Over 60 chromosomal abnormalities were identified in candidate regions particularly on chromosomes 2, 7, and 15. These regions each comprise large numbers of genes involved in central nervous system development and functioning and in various neurodevelopmental pathologies: autism, schizophrenia, and mental retardation. Considering the great heterogeneity of ASDs, it is necessary to define homogenous subgroups of affected children regarding clinical and biological phenotypes such as head circumference, presence of developmental regression, epilepsy, sleep problems, or plasmatic levels of serotonin. Electrophysiological characteristics measured using cortical evoked potentials could also prove to be potential phenotypic markers.

The exact pathophysiological mechanisms involved remain unknown. Some cases are sporadic, corresponding to *de novo* genetic abnormalities. In others, several members of a same family are affected by neurodevelopmental disorders involving the expression of inherited genetic factors.

Autism being a highly inheritable disorder, it seemed probable that genes linked to the disorder would be rapidly identified. Even though these hopes were not fulfilled, research undertaken in the field has been fruitful. Identification of genes involved in disorders linked to autism such as Rett syndrome, fragile X, and tuberous sclerosis, or rare mutations linked to cases of autism (in particular NLGN, NRXN, and SHANK3 genes), suggests that pathophysiological pathways common to various forms of the ASDs may be found.

Each mutation discovered accounts for at the most 1% of cases suggesting that many genes are involved, each with a limited effect. Finally, the identification of abnormalities common to several conditions such as copy number variations (CNVs), or the fact that certain mutations are also present in nonaffected individuals,

evokes interaction between these abnormalities and other genetic, developmental, or environmental factors.

Future research strategies must take these findings into account by diversifying their approaches. Thus, a dimensional framework based on specific traits or phenotypes instead of diagnostic categories appears promising. Longitudinal studies in at-risk families could help define endophenotypes or environmental factors linked to onset of the disorder. Moreover, innovative brain imaging techniques allowing identification of cerebral signatures present among individuals with autism should be used concurrently with molecular biological or genetic analysis. Approaches combining clinical observation, neuroimaging, and molecular genetics will allow identification of critical periods of cerebral development and neuronal functioning to target.

Treatment of Autism Is Essentially Based on Behavioral Methods and Education

No cure for autism exists to this day. Autistic children growing up without support and without specific teaching of basic communication skills and means of making sense of their environment are at risk of developing challenging behaviors, a source of exclusion and of additional handicaps (see Fig. 2). Treatment focuses on improving core deficits in social communication, as well as improving functional engagement in appropriate activities. Principal treatments include behavioral interventions and special education. Early intervention is paramount, cerebral plasticity being

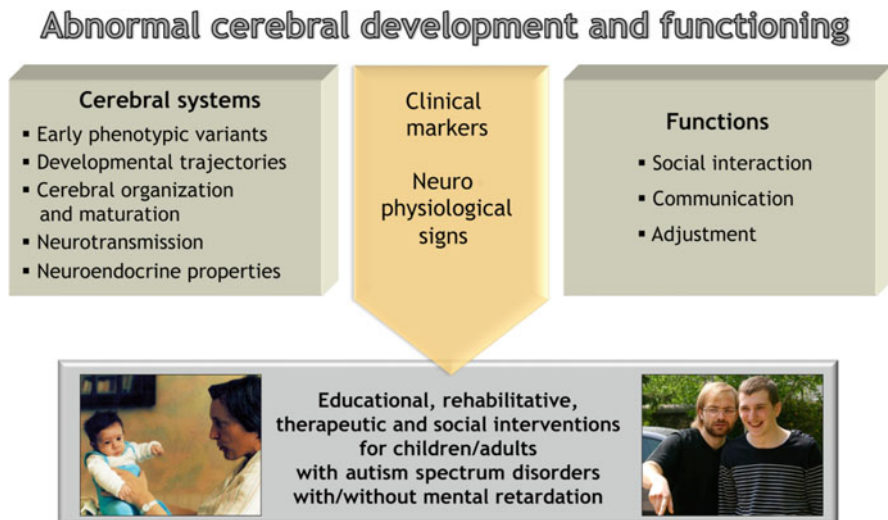


Fig. 2 Behavioral interventions and special rehabilitations are based on clinical and neurophysiological analysis

highest before the age of 4. Early treatment helps toddlers master basic neurophysiological functions such as attention, perception, association, intention, and imitation. During sessions in a rewarding environment, the therapists adjust support to the children's intellectual and emotional level, helping them to progressively develop adequate means of action and communication. Exchanges between the children and adults are increasingly synchronized growing into genuine sequences of social interaction and shared pleasure. This is a necessary prerequisite for further development of nonverbal and verbal communication skills.

Medical treatments comprise a variety of pharmacologic agents and address specific symptoms associated with the disorder such as epilepsy, anxiety, attention difficulties, or sensory problems.

Outlook

Systematic studies from birth on of younger siblings of children with autism, at higher risk for ASDs than the general population, are promising. They will not only allow a detailed description of very early signs but also the identification of early phenotypic variants in single families. Scientific training of future professionals involved in health services for babies and toddlers is crucial for early detection of the disorder. Studies of atypical developmental trajectories of at-risk children and links between certain forms of epilepsy with language disorder are potential fields for pathophysiological studies. Advances in the understanding of the clinical, neurofunctional, and genetic aspects of autism have progressively modified conceptions and practices for diagnosis, investigation, and therapeutic interventions. But the exact pathophysiology of autism remains unknown. This lifelong complex disorder presents major challenges. The body of data collected in multiple research fields (clinical observation, imaging, electrophysiology, biochemistry, genetics) supports the idea of a heterogeneous group of neurodevelopmental disorders probably with different pathophysiological pathways. The unusual pattern of cerebral growth and the involvement of the frontal and temporal lobes are among the most frequently replicated findings. The corpus of results reinforces the hypotheses that a disturbance in neurocortical organization leads to impairment of information treatment processes at various levels of the nervous system, from the synapse to structural and functional neural networks. Future work will require concurrent investigation of clinical, biological, genetic, and imaging markers both in large populations and in single case studies in order to progress toward identification of the pathophysiological cascades involved.

Indeed, each individual with ASD has a unique profile that varies among individuals over the life span. There is no standard protocol of treatment for this social communication disorder. Nevertheless, several fundamental principles underlie educational, rehabilitative, therapeutic, and social interventions: early intervention, accessibility of appropriate services, and diversity of means and methods. The family is, from the beginning and all through their child's life, an active partner in a flexible, continuous, and coherent system of multidisciplinary intervention.

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