INTRODUCTION TO AUTISM

Autism is a neurodevelopmental disorder clinically defined by limited social interactions, abnormal use of language and stereotyped patterns of behavior, interests, and activities [1,2]. It has a prevalence of affecting 1 in 110 children with a 4.5:1 male to female ratio [1,3]. The first behavioral signs of social impairment present themselves usually between 1 and 2 years of age and the final diagnosis is usually made by 2-4 years of age [4].

Although the etiology of ASD is still not precisely defined, growing scientific evidence shows a diversity of morphological, functional, genetic, and neurotransmitter systems alterations. However, there are several important obstacles to advances in the search of ASD etiology. As the pathological changes of ASD are developmental, it is imperative to study very young children, preferably in their first three years of life. This is difficult because most children with ASD do not present with definite signs of social impairment until 24 to 36 months of age, making a precise earlier diagnosis almost impossible [4]. Apart from technical difficulties in forming large-scale study groups of infants and toddlers with precise IQ, age and gender-matched controls, ASD is a very heterogeneous group of disorders, ranging from severely impaired, low-functioning patients to mildly affected children with Asperger’s syndrome. According to the current classification, there are three main types of ASD: autistic disorder, Asperger’s syndrome, and pervasive developmental disorder - not otherwise specified (PDD-NOS) [5]. Autism is often further subclassified into high-functioning autism (HFA) and low-functioning autism (LFA), based on the IQ level, using an IQ below 70 as the cut-off for LFA and above 70 for HFA [6]. This heterogeneity may explain a great quantity of non-matching research data, most importantly among structural imaging and neuropathologic studies of autism [7,8].

MORPHOLOGICAL FEATURES OF AUTISM

Early brain overgrowth

Early brain overgrowth is one of the most important morphological abnormalities of the autistic brain. The dynamics of the extensive growth of gray and white matter were precisely demonstrated by Courchesne and Pierce in 2005 [9]. At birth, the head circumference of autistic children is normal or slightly smaller than average [9]. After several months, however, the head circumference grows rapidly with an increase of 2 standard deviations or more in 59% of ASD children in contrast to only 6% of normal infants [10]. Also, this acceleration of growth was found to be a good predictor of the severity of clinical outcome and abnormal cerebral and cerebellar volumes in 2 to 5-year-old toddlers [10]. Interestingly, after early increase of brain volume, this process seems to decrease or stop completely, resulting in adult brain volumes of average size [11,12]. The disruption...
of brain development at an early age has serious implications for the formation of precise circuitry and consequential normal function. At the microstructural level, abnormal cell division and apoptosis regulation, excessive glial growth and inflammation have all been hypothesized as substrates for the disruption of brain development. At the genetic level, there are several genes directly linked with autism, known for their cell growth and migration regulation. The most implicated of these are the PTEN and RELN genes [76, 86-88] (See Table 1).

Minicolumns
There is important evidence of abnormal minicolumnar structure [13,15] in frontal, temporal, and anterior cingulate cortices. Minicolumns are basic units of cortical information processing, developing and specializing in response to inputs from the environment [14]. The minicolumnar volumes of ASD patients are reduced, but the cell number per minicolumn seems to be normal [14]. This might be explained by a too fast and precocious minicolumnar formation, leaving a shorter time-window for experience-dependent inputs to influence the development of pyramidal neurons of origin of long-distance connections and of their dendritic arbors [9]. Also, an underdevelopment of inhibitory neurons, such as chandelier and basket cells, has been reported, important for isolating specific information processed by a single minicolumn [9]. Lack of inhibition of this kind could lead to hyperactivation of neighboring minicolumns resulting in hyperstimulation by simple outside stimuli which would normally activate one or a small group of minicolumns. On the clinical level this would result in weakened awareness of surrounding context and hyperexcitation by seemingly minor external influences, both often reported as a feature of autism.

Conversely, Casanova et al. in 2006 [15] reported an excess of minicolumns, packed closer together. These findings implicate founder cell divisions responsible for the process of cortical expansion during encephalization [16], placing the time of neurodevelopmental disruption responsible for autism as early as embryonic day 40 [17].

The integrative brain regions
Autism is a disorder primarily affecting higher-order integration processes, such as complex social interactions, associative thinking, and appropriate emotional reactions. This has led researchers to focus on brain regions associated with these functions: the frontal and temporal cortex, anterior cingulate cortex (ACC), fusiform gyrus (FG), the amygdala, and the cerebellum.

The frontal cortex
The frontal cortex, specifically its dorsolateral and medial parts, grows disproportionally larger than the rest of the cortex [6] in the first years of life. Afterwards, from 2 to 9 years of age, this portion of the cortex shows an enlargement of only 10% in autistic children opposed to 48% volume increase in the control group [6]. This time coincides precisely with the development of dendritic arbors of pyramidal neurons in layer III, their complex synaptogenesis and the process of myelination [9]. For comparison, there is no evidence of disrupted microarchitecture in the visual cortex, a portion of the brain that finishes development at a dramatic speed in the first months of life [9], leading to a conclusion that the portions of the brain most affected in autism are the same ones that take longest to develop. It is probable that the rapid brain growth in the first year of life prevents later experience to influence the synaptogenesis, cell survival and myelination essential for the formation of higher order functions. Repeating words, social situations or facts shapes and remodels the circuitry of the toddler brain and represents the basis of learning.

Interestingly, the theory of impeded plasticity of integrative brain centers is somewhat in contradiction with the hypothesis of the early disruption of founder cell divisions that form the basis of minicolumnar anomalies found in the frontal and temporal cortices, but not the visual cortex. Namely, the gross number of minicolumns is formed by the early phase of gestation in both frontal and visual cortices alike. The extensive early brain growth might only be a result of a pathological occurrence in early embryonic development and the substrate for the hampered plasticity preventing later advancement. New approaches are needed to research the prenatal brain development, the most feasible being the research of mouse model embryo brains.

Superior temporal and inferior frontal gyri
Investigations of impaired language processing, one of the core deficits of autistic children, have led to several important discoveries. Normally, language processing is a function lateralized to the left hemisphere, involving perisylvian

Table 1. The list of selected genes associated with the autistic spectrum disorders.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Recent relevant studies</th>
</tr>
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<tbody>
<tr>
<td>RELN</td>
<td>Regulates neuronal migration and positioning in the developing brain by controlling cell–cell interactions</td>
<td>Fatemi, 2010 [66]</td>
</tr>
<tr>
<td>PTEN</td>
<td>Tumor suppressor gene, regulating the cell cycle</td>
<td>Ey et al. 2011 [76]</td>
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<td></td>
<td></td>
<td>McBride et al. 2010 [88]</td>
</tr>
<tr>
<td>SHANK3</td>
<td>Mediates synapse formation and dendritic spine maturation, connects neurotransmitter receptors</td>
<td>Bangash et al. 2011 [77]</td>
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<td></td>
<td></td>
<td>Peça et al. 2011 [78]</td>
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<td></td>
<td></td>
<td>Bozdagi et al. 2010 [79]</td>
</tr>
<tr>
<td>NL3</td>
<td>Mediates synapse formation and remodeling</td>
<td>Ellegood et al. 2011 [80]</td>
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<td></td>
<td></td>
<td>Gutierrez et al. 2009 [81]</td>
</tr>
<tr>
<td>NL4</td>
<td>Mediates synapse formation and remodeling</td>
<td>Etherton et al. 2011 [82]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ey et al. 2011 [76]</td>
</tr>
<tr>
<td>FMR1</td>
<td>Regulation of synaptic plasticity</td>
<td>Testa-Silva et al. 2011 [83]</td>
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<td></td>
<td></td>
<td>Hagerman et al. 2011 [84]</td>
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<tr>
<td>GABRB3</td>
<td>Part of GABA-A receptor</td>
<td>DeLorey et al. 2011 [85]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatemi et al. 2009 [72]</td>
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</tbody>
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regions of the brain: the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) [18]. A sleep fMRI study performed by Redcay and Courchesne in 2008 [19] showed anticipated reduced activation in the left STG in response to speech in comparison to mental age-matched subjects, explained by underdevelopment of long-distance connections of this region. Unexpectedly, while listening to a bedtime story, ASD subjects showed greater recruitment of the right STG and IFG in comparison to chronological age controls. Several studies replicated these findings, proving them to be a constant and early feature of autism [20,22]. Toddlers with autism exhibited significantly weaker interhemispheric synchronization (i.e. weak “functional connectivity” across the two hemispheres) in putative language areas; the abnormal right-lateralized language processing was found to be present at as early as 14 months of age [21]. The discovery raises hope that this invariable early characteristic could permit early identification of infants at risk and perhaps be used as a first neurologic functional biomarker for early diagnosing of ASD [20].

The precise substrate for the inverse lateralization of language processing is yet unproven, and it is unclear whether this “wrong-sided” specialization impedes normal language acquisition or is a consequence of an unknown factor preventing development of the left-side lateralization of language. Also, it is possible that the impaired learning of social skills, another core feature of autism, is a result of superseding of the centers for shared attention and gestures, normally centered at the right perisylvian regions [20,22]. Future research, focused on sleep fMRI, will hopefully be able to explain the etiology of these findings.

Weakened emotional processing, one of the most important features of autism, has led researchers to focus on cortical and subcortical regions related to this function, namely the FG, ACC, and amygdala.

**Fusiform gyrus**

The functional MRI research of the FG has not yet concluded irrevocable results, but most of the findings report present but significantly diminished FG activation in response to face and emotion recognition [23]. For example, in a study by Corbett et al. (2009) measuring FG activation in reaction to emotion processing, a significant hypoactivation of both FG was found in the ASD group. In the same study, a “limit” hypoactivation of the FG was found in reaction to face recognition [24]. In differently arranged testing by Pierce and Redcay (2008), hypoactivation of the FG was found only in response to unknown faces, while presenting of familiar faces triggered normal FG activity [25]. This interesting finding has led Pierce to form “the threshold theory” suggesting that ASD patients dispose of normal task-activated networks, but need additional stimuli to activate them [20].

The results of cytoarchitectural research of the FG are also ambiguous. A study, using a rigorous stereologic design, reported reduction in the mean neuron density and mean neuron number, as well as decreased pyramidal cell volumes in layers III and V of FG [26], while others, using a non-stereologic and less systematic approach did not find such changes in this region [27].

**Anterior cingulate cortex**

The study of ritualistic behavior and impaired social restriction in autism has led researchers to focus on the ACC, a part of the limbic system known for its role in response inhibition tasks, exact delineation between the perception of self and others and error detection [28].

A hypoactivation of the ACC was repeatedly found across task-related fmRI studies such as making judgments about self and others [29], controlling the urge to look towards a suddenly appearing stimulus [30], identifying a wrong letter in an alphabet stream [31] and reacting to unexpected auditory stimuli [32]. Morphological research has also shown substantial aberrations in gray [33] and white matter [34].

ACC is one of the major localizations of von Economo neurons (VEN) in the human brain [35-37]. VENs, or spindle neurons, are large bipolar neurons hypothesized to play a particular role in regulating self-awareness, empathy and understanding of social context, and as such have been implicated in autism pathophysiology [37]. A decreased quantity of VENs has been reported in other disorders affecting emotional conduct and social integration such as frontotemporal dementia [38,39], agenesis of the corpus callosum [40], and early onset schizophrenia [41].

There have been several studies of VENs in autism, and conflicting results have been found. Simms et al. (2009) reported two subgroups of autistic patients. Of the 9 autistic patients examined, 3 had substantially elevated VEN density, while 6 others showed a depletion of VENs in the ACC [33]. Another stereologic study by Santos et al. (2010) quantified VENs in the ACC and the frontoinsular cortex (FI) of four autistic children [42]. This study unexpectedly failed to show a similar decrease in VEN numbers. Conversely, an elevated VEN to pyramidal neuron ratio, and an almost significantly higher VEN number was found. Due to a very small number of studied patients, further research will be needed to support these findings. To explicate these counterintuitive results, the authors developed an original outlook on autism, sustained by recent functional imaging data. Autism may not be characterized by severe social isolation and ignorance of social cues, but in fact an impairment of dividing the consciousness of self and others. Surprisingly, both conflicting interpretations result in the same clinical presentation. This theory is supported by the finding that autistic patients show activation of the ventromedial prefrontal cortex in performing self-referential processing [29,43]. This new interpretation of autism symptoms will perhaps alter the course in autism research.

**Amygdala**

The amygdala plays an important role in the mediation of social behavior such as, among others, facial and emotional recognition, enhancement of memory for emotionally significant events, predicting reward values [44], and as such has been one of the structures thoroughly studied in autism. In autistic patients, volumetric analyses show amygdala enlargement as early as age 2, followed by a cessation of growth not proportional, however, to the overall cerebral volume changes [45,46]. Schumann et al.
(2004) found that although the amygdala in the typically developing boys grows by 40% between 8-18 years of age, the autistic boys present a stagnation of growth [47]. Therefore, even though the amygdala volumes differ significantly in the young age between ASD and control groups, the volumes equalize in the adolescent and adult age groups because of different growth patterns among these two populations. An important correlation was found between the severity of clinical presentation and amygdala volume. Current results also imply that amygdala enlargement is related to a higher degree of anxiety [48] and worse social and communication abilities [49]. Furthermore, different left and right amygdala enlargement was found in correlation with the degree of mental retardation [47]. On the microstructural level, the findings in the amygdala are not consistent [50]. While Shumann and Amaral (2006) found a ~15% decrease in total neuron number in a stereological study of the amygdala [51], prior neuropathological findings reported an increased neuron density [52]. Here too, more stereological studies will be needed to elucidate these contradicting results.

Cerebellum
There has been much research on the cerebellum in autistic patients. Even though the ASD patients do not present typical motor signs of cerebellar dysfunction, knowing that the cerebellum is also involved in cognitive functions, such as language, imitation, attention, and mental imagery [53] has led researchers to designate the cerebellum as an area of interest in autistic patients. Most of the volumetric findings report an augmented size of the cerebellum proportionate to the overall brain volume [50]. The size of the vermis has been reported both as larger and as smaller than normal [54,55] which could be due to the heterogeneity of ASD [56]. In addition, numerous questions have been raised about the method of volumetric measurement of the cerebellar vermis [50], which has been suspected to be subjective and imprecise [57].

Postmortem studies revealed significant abnormalities in the Purkinje cells, particularly in the hemispheres, reporting smaller cell size and decreased cell-packing density [50,57]. Even though the Purkinje cell irregularities are one of the most consistent morphological findings in autism thus far, these reports have not yet been confirmed by stereological research. Furthermore, in most of the postmortem studies, the brains were obtained from individuals with mental retardation associated with ASD, while most of the volumetric studies have been performed on high-functioning individuals with autism [50].

White matter
Studies of cerebral white matter in ASD patients report changes in organization, maturation rate, and structural integrity [12,58-60]. Some of these studies use the technology of diffusion tensor imaging (DTI), a MRI technique that enables the measurement of the restricted diffusion of water in tissue in order to produce neural tract images. To assess the fiber density, axonal diameter and myelination stage, a parameter called fractional anisotropy (FA) is measured. In a recent study by Shukla et al. (2010) [61] structural changes in FA were observed in several cortical regions involved in social cognition and information integration as well as in interhemispheric and corticocortical white matter tracts such as the corpus callosum, anterior and posterior limbs of the internal capsule, cingulum, anterior thalamic radiation, and corticospinal tract. Most studies of white matter in ASD are consistent with the finding of decreased FA in regions performing higher cognitive functions, interpreted as lower fiber density, smaller axonal diameter and uneven myelination phases. One of the studies found the largest aberration FA values in the anterior cingulate cortex [34], a region associated with anticipating conflicting information and interpretation of subtle emotional subtexts [28]. In contrast, Noriuchi et al. (2010) [34] also found an excess of white matter in cerebellar vermis lobules, a region also known for its abnormal cytoarchitecture in autism (see above).

NEUROCHEMICAL FINDINGS
In a search for a specific and sensitive biomarker of autism, a great quantity of research has focused on the study of neurotransmitters, measuring their blood concentrations, marking receptor density and quantifying the production and degradation of specific neurochemicals. The proton magnetic resonance spectroscopy imaging (1H-MRS), a technique permitting non-invasive quantification of endogenous neurochemicals, has provided useful information, none of which unfortunately provided a firm and conclusive theory.

However, one of the most important neurochemical theories of autism supported by diverse different research approaches is the excitation/inhibition imbalance theory. Based on extensive evidence of glutamate- and GABA-related abnormalities found in the autistic brain, it has been hypothesized that a complex lack of local inhibition and long-distance excitation during development and later in life could be a common factor to the diverse developmental findings in autism.

One of the first findings that pointed to an excitation/inhibition dysregulation in autism was the fact that around 30% of patients with ASD develop epileptic seizures during their lifetime and approximately 60% have epileptiform EEG activity during sleep [62,63]. Also, as noted above, an underdevelopment of inhibitory neurons, allowing the processing of individual stimuli, has been found in several brain areas [9].

There is evidence of glutamate dysregulation in the ASD population, although none point to a single gene or protein in the glutamate signaling system, but indicate a complex pathophysiology in the functioning of this neurotransmitter in general. Aldred et al. (2003) measured glutamate blood levels in ASD patients and their families and found higher than normal concentrations [64]. In the same study the peripheral levels of phenylalanine, lysine and asparagine were also elevated, while glutamine concentration was reduced. Moreno-Fuyenmayor et al. (1996) also found lower blood levels of glutamine [65] but Shinohe et al. (2006) [66] failed to observe reduced glutamine concentration. Both studies found higher glutamate blood levels, and the latter reported a significant correlation between the glutamate upregulation and the
severity of clinical presentation. In conclusion, the peripheral levels of glutamate are definitely altered in relation to autism, but measuring neurochemical blood levels is perhaps too dependent on pre-medication, nutrition and comorbidity as to be a reliable marker of autism.

Secondly, the research of glutamate system related genes has shown some substantial aberrations. An upregulation of AMPA receptor subunits GluR1, GluR2 and GluR3 were found through cDNA and mRNA quantification in post-mortem cerebellar and hippocampal tissue, but interestingly, a lower overall post-mortem cerebellar and hippocampal glutamate quantification was found to the whole ASD population [73].

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Glutamate decarboxylase (GAD), an enzyme that metabolizes glutamate into GABA, was also found to be significantly reduced in the parietal cortex and cerebellum of ASD patients [74], thus showing that both neurotransmitter systems are inseparable in the etiology of autism.

A recent 1H-MRS study by Bernardi et al. (2011) has measured concentrations of neurotransmitters in varying brain regions in high-functioning, non-medicated adults with autism and controls. Unfortunately, 1H-MRS cannot yet distinguish between glutamate, glutamine, and GABA signals, so these compounds are measured together and termed Glx. However, a significant depletion of Glx concentration was found in ACC in this study, providing important evidence for the glutamate-GABA dysregulation theory. Although only high-functioning patients were used in the study, no IQ correlation was noted, implicating that this finding can be generalized to the whole ASD population [75].

Further neurochemical imbalances were found in other 1H-MRS studies, such as widespread and localized reductions of N-acetyl-aspartate, choline-containing compounds and myo-inositol concentrations, but more studies of this type will be needed to support these findings. The precise 1H-MRS technology will surely prove to be very useful in the future.

A large quantity of genetic research has also implicated that the genes involved in some ASD cases are also connected to the excitation/inhibition imbalance. There is a subgroup of genes conclusively linked to autism, which, through regulation of synaptic plasticity and receptor expression, mediate the metabolism of glutamate and GABA, thus resulting in ASD-like symptoms. The genes most implicated are SHANK3, neurexin 3 (NL3) and 4 (NL4), GABRB3 and FMR1 [72,76-88] (See Table 1).

Serotonin
Serotonin (5HT) dysregulation has been mentioned as a possible etiology of autism, based on consistent findings of higher than normal blood levels of 5HT [89]. Hyperserotonemia has been reported in about a third of all the autistic patients, but a correlation between severity of clinical presentation and levels of 5HT has not been established. The elevated blood levels of autistic patients seem to be age-independent, while normally developing children show a progressive decrease in 5HT blood levels [89]. The increased concentration of 5HT is also found in parents and siblings of ASD patients with hyperserotonemia [89,90]. Some findings report a negative influence of high 5HT levels on language learning [91] and self-injuring behavior [92] as well as IQ levels [89]. Symptoms of autism comorbidities such as depression, irritability and obsessive-compulsive disorder have been shown to improve with selective 5HT reuptake inhibitors (SSRI) therapy [68]. 5HT plays an important role in early brain development when serving as a growth factor and regulating proliferation and maturation, both key events known to be disrupted in autism, which makes it a possible primary defect in ASD etiology [68].

Dopamine
Research on dopamine in autism was motivated based on clinical evidence showing reduced aggressive, hyperactive and self-destructing behavior in patients under treatment with dopamine D2 receptor antagonists. This amelioration of symptoms has been attributed to D2-mediated glutamate release, again pointing to the excitation/inhibition imbalance theory [75]. The peripheral quantification of homovanillic acid (HVA), a metabolite of dopamine, has proven to be insignificantly altered in autism. Furthermore, central HVA measurements were inconstant, showing evidence of elevated, normal or lowered concentrations. Studies of endogenous opioids and norepinephrine in autism have also failed to show conclusive results [68].

Neuropeptides
Finally, two neuropeptides, vasopressin (AVP) and especially oxytocin (OT) have been suspected to be involved in the pathophysiology of ASD. OT and AVP are similar nonapeptides produced in the hypothalamus and secreted from the pituitary. Oxytocin plays crucial roles during child birth, breastfeeding and sexual arousal [93-95]. Perhaps even more importantly, research performed on knock-out OT mice has confirmed it to be vital in mother-child bonding, pair-bonding, as well as in social recognition and attachment behavior (trustfulness) in general, thus giving OT dysregulation a possible role in the etiology of autism [96-98]. The hypothesis that autistic children are affected by a prolonged exposure to OT during birth leading to a downregulation of OT receptors has been refuted [99]. However, decreased plasma concentration of OT in ASD patients has been reported, providing an interesting explanation of the male:
female ratio in patients with autism. A higher female sensitivity to OT could prevent the development of autistic traits in females, while the same decrease of OT concentration could be easily mistaken for another syndromic disorder or isolated retardation. On the other hand, high-functioning autism and Asperger’s syndrome are the object of an ongoing dispute. Some postulate that an apprehension syndrome are the object of an ongoing discussion. The diversity of ASD can explain the contradictory findings of morphological, neurochemical, and genetic research. This fact invokes an urgent need to synthesize all present findings into a coherent compendium of knowledge and try to accurately define all the permutations of this complex disorder, a task begun by the Autism Genetic Resource Exchange. A fast progressing understanding of genes implicated in synaptogenesis and plasticity, such as SHANK3, NL3 and NL4 or NEUREXIN1 provides evidence that autism is a disease with high potential for improvement with active behavioral therapy. The investigation of different genes associated with neurotransmitter systems, for example GABRB3 and FMR1, has already started to produce promising results at the level of pharmacological therapy.

Even though there is no cure yet available for autism, there has been a lot of effort put into early diagnosing of ASD patients. This is a difficult project because normal and affected infants do not necessarily differ in the first year of development. In addition, a high comorbidity rate in autism patients, as well as the diversity of clinical presentation complicates precise and timely identification.

Lately, there has been an important development of early screening for ASD. A new version of Autism Diagnostic Observation Schedule (ADOS) has been adapted for children between 12 and 30 months of age, promising precocious recognition of ASD patients and a possibility of early intervention. Moreover, a One-year Well Baby Check-up Approach has been developed for screening in the general population, showing a encouraging positive predictive value of 0.75. Future research should be oriented to providing a specific and sensitive biomarker of ASD patients which, paired with screening behavioral tests, could easily lead to an accurate early diagnosing of ASD. Abnormal lateralization in response to language, a measurement of blood amino acids and neurotransmitters or a discovery of another distinctive ASD trait will hopefully find its role in clinical assessment of autism in the future.

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