NEURONAL HIPERCONNECTIVITY IN PATIENTS WITH AUTISM SPECTRUM DISORDERS

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ABSTRACT

Autism spectrum disorders (ASD) reunite a series of neurodevelopment disorders characterized by difficulties in social interaction, communication and stereotyped behaviors. Most of the current etiological theories regarding ASD identify social interaction deficits as being the hallmarks of these disorders. A new hypothesis, The Intense World Theory, based on neuronal hiperconnectivity, tries to explain that the social deficit in ASD is secondary to a neuronal over activation and to the painful perception of environmental stimuli.

Keywords: autism spectrum disorder, hiperconectivity, neural overactivation

Autism spectrum disorders (ASD) are an umbrella term that incorporates a set of complex neurodevelopmental disorders characterized by varying degrees of impairment in social integration and communication and by different stereotyped behaviors.

They are associated with various disorders of sensory integration deficits. The latest data from the Center for Disease Control (CDC) in the US report a prevalence of 1 in 68. The data show that from the definition of autism by Dr. Leo Kanner, until around the year 2000, the prevalence was relatively constant, ranging from 1.9 to 13.9 cases per 10,000. For example, the study by Victor Latter, in 1967, in NE London, showed a prevalence of autism 4.5/ 10,000, defined based on Dr. Leo Kanner's definition.

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Since 2000, the prevalence has begun to rise leading to a figure of 60/10000 (1 of 166), according to studies conducted by Prof. Dr. M. Rutter and Prof. Dr. C. Gillberg [1]. In the 2000 - 2010 period, the CDC reported a prevalence of ASD in children from 1/150 (2000) up to 1/68 (2010) [2].

According to DSM-IV-TR, pervasive developmental disorders include autistic disorder (classic infantile autism), Asperger's syndrome, childhood disintegrative disorder, Rett's syndrome and pervasive developmental disorders not elsewhere classified (PDD-NOS).

The DSM 5 autistic spectrum disorders receive the same diagnosis code and 3 classification areas are introduced: the need for support, intellectual development and the level of language development.

Rett disorder has been passed as a differential diagnosis, being proven that is a genetic disorder of metabolism.

NEUROPSYCHOLOGYCAL THEORIES THAT ARE TRYING TO EXPLAIN THE ETIOLOGY OF ASD

The etiopathogenesis of ASD is complex and only partially known. The involvement of genetic factors has been demonstrated. 90% of cases are idiopathic ASD and transmission is polygenic. Studies have shown up to 95% heritability [3]. 10% of autism cases are secondary to monogenic disorders such as fragile X syndrome or tuberous sclerosis [4]. Also, the presence of specific personality traits has been identified in parents of children with ASD. Thus, most of these parents have higher education, especially in technical fields such as engineering [1]. It was also found that about two-thirds of relatives of children with ASD, especially fathers, have a predominantly visual or pictorial thinking and a lower performance on verbal tasks [5]. Several theories that attempt to explain the nature of the clinical manifestations of the ASD have been developed. Autism is characterized by a deficiency of the Theory of Mind (ToM). ToM is the ability to assign other individuals beliefs and desires in order to understand their behavior. People have the ability to build models of the mind of others. This process is carried out quickly, unconsciously [1]. The development of these models is made through perception - apperception. The child observes the environment, especially on the social level and draws unconscious conclusions, while developing schemes of apperception. Subsequently, the selection of the details observed in an individual and consequent interpretation will be determined by these schemes apperception [6]. Development of the theory of mind is slow or missing in autism. New studies show that people with ASD have so-called literal perception – they observe the environment, but do not develop interpretations, rather they always "take things as they are" [7]. Two other theories are the hypersistematisation and hypoempathy theory and the extreme male brain theory developed by Prof. Dr. Simon Baron-Cohen from the Autism Research Centre at the University of Cambridge, UK. These theories infer that autism is caused by low levels of empathy associated with increased levels of systematized thinking. Prof. Dr. Simon Baron-Cohen's results have shown that neurotypical men demonstrate a lower level of empathy and increased systematization compared to neurotypical women. People diagnosed with Asperger syndrome have a very high level of systematization and a very low level of empathy. Following neuroimaging studies and prenatal testosterone blood levels, the extreme male brain theory was developed. Two cognitive functions were investigated: social-psychological understanding (folk psychology) and physical understanding (folk physic). A decrease in the activity of mirror neurons was also found. These mirror neurons represent neuronal groups located in the frontal lobe that are responsible for imitation. Another theory that tries to explain ASD is the weak central coherence theory developed by Prof. Dr. Uta Frith, University of London, in late 1980s. This theory refers to the perceptual-cognitive function and states that people with ASD have an increased capacity to process details related to a low capacity to process the full picture. A study on people with ASD showed an increase of activity in the occipital-temporal area (responsible for sensory processing) and a decrease in prefrontal areas activation (responsible for information integration). A deficit of executive functions was also revealed, which would explain the adherence to routine activities. The role of immunological factors in ASD has also been investigated and the presence of maternal antibodies directed against CNS tissue was shown in fetal blood, such as anti-serotonin receptors antibodies. An autoimmune enteropathy has also been described in children with ASD [8]. These theories try to bring a common explanation for the different manifestations of ASD. All these theories have been developed in various clinical and laboratory studies. Many of these explain the nature of ASD by a primary deficit of brain areas responsible for social development. Currently, the new theory states that social difficulties are secondary to the different overall functioning of the brain in ASD.

THE INTENSE WORLD THEORY IN ASD

A new theory that tries to explain brain function in people with ASD is the Intense World Theory. It was proposed by Henry and Kamilla Markram from the Laboratory of Neural microcircuits from the Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Switzerland. In developing the theory, the

authors have developed an animal model of autism by intrauterine exposure to valproic acid (VPA). Their experiments had two steps: 1) studying the behavior; 2) studying the brain. The rat pups exposed to VPA had a diminished social behavior, a higher level of fear reaction to noise stressors and restricted behaviors (they followed the same route every time they were placed in a Y shaped tube) compared to the controls. In the second stage, the rat pups' brain was studied (amygdala and cortex). At these levels, an increased number of synapses was observed, with an amplified electrical reactivity of the postsynaptic neuronal membrane and an increase in the number of synapses in vitro after glutamate stimulation. Thus, the hiperconectivity- hyperreactivity-hiperplasticity model was proposed [9]. Subsequently, based on functional MRI studies in children with ASD, this model was extended to individuals diagnosed with ASD. In 2013, Dr. Jose Perez-Velasquez L., and Dr. Roberto F. Galan presented, in an article published in Frontiers in Neuroinformatics, a study concerning the magnetoencephalography features in children with Asperger syndrome compared with neurotypical children.

Magnetoencephalography (MEG) is a technique for recording brain activity by capturing and measuring the magnetic fields generated by nerve inflows, based on electromagnetic effect. MEG determines the level of neuronal activation entropy and the degree of nerve inflows. The magnetic field is detected by sensors placed on the scalp. The recording was performed in resting state. The study showed that the entropy is not significantly different in children with ASD compared to neurotypical children. In contrast, the activation or production of information was 42% higher in children with Asperger syndrome. Thus, this study demonstrated the presence of basal neuronal hyperactivity in children with ASD [10]. Changes were observed in ASD brain activation, particularly in the neocortex, the amygdala, the white matter of the brain and cerebellum.

The cerebral cortex. Typically, the human cortex is organized into six cell layers: molecular, external granular, external pyramidal, internal granular, internal pyramidal and muriform. The morphofunctional unit of the cortex is the cortical column. The connections are made through two types of fibers: 1) intracortical fibers, short and medium-linking units that form cortical microcircuits, 2) long fibers that are found in the subcortical white matter and connect distant areas and subcortical regions [11]. The development of cognitive processes is based on the balance between inhibitory and excitatory mechanisms of cortical microcircuits and on the balance of connections within these microcircuits and at distance [12]. In autism, there is an overactivation in the cortical columns and microcircuits. It is based on genetic mechanisms, environmental factors and toxicity (epigenetic factors). In Asperger syndrome it is likely that only genetic factors dominate or interfere, while the classic autism results from both genetic factors and extracerebral factors such as the immunological ones. Some authors believe that a child with classic autism would have been genetically "programmed" to have Asperger syndrome, but, due to other factors, developed autism [1]. MRI studies have shown that children with ASD have an increased volume of white matter, both in the cerebral hemispheres and in the cerebellum. The increase is uneven and these white matter density differences were observed in children aged between 2 and 3 years. In older children, MRI appearance is identical to the neurotypical cortex layout. It has been shown that the connections between adjacent cortical areas through short and medium intracortical fibers are overrepresented in ASD, while long connections among distant areas such as the occipito-frontal, have no anatomical changes. Hiperconnectivity in different areas leads to overactivation of microcircuits and maintaining reverberations, which translates into perseverance in activities. During development, microcircuits hyperconnectivity, associated with neural hyper-responsiveness and synaptic hiperplasticity results in an amplification of sensory, cognitive, and specific motor processes, which leads to the development of environment information processing preferences and the overdevelopment of certain areas. For example, cortical microcircuits overdevelopment in the sensory areas,

translates sensory preferences and self-stimulating behaviors. Overdevelopment in other areas leads to the development of specific cognitive abilities. This verifies the hypersistematisation theory of ASD. Thanks to the cortical microcircuits hyperactivation from the local columns, an altered balance between short and long connections appears with hypoconnectivity via distant connections, which translates into relative hipoconectivity between areas [12]. The sensory areas and the occipital cortex are the most frequently hyperconnected areas. In young children with autism, there is general neuronal hiperconectivity, with emphasis on the whole frontal lobe, which results in increased cortical volume. An accelerated growth of the cranial perimeter has been found in children with classic Kanner autism [4]. These imbalances underlying connectivity abstraction deficit are present in varying degrees in both classic autism and Asperger syndrome. Individuals with ASD have difficulty forming abstract categories. They have, however, the ability to form categories, but only based on visual criteria. Neuronal hiperconectivity in different areas, corresponds to increased abilities. As a person with autism ages, certain areas and certain connections between areas develop, while others lag behind. For example, analyzing the biography of Albert Einstein, one may see that he presented many features of autism in childhood and that he started to speak only at the age of 3. Postmortem, his brain was studied, and hiperconectivity areas associated to mathematical calculation were, as were overrepresented connection between these areas and the visual cortex [5]. Overactivation was found in other neural structures as well - the cerebellum had fewer Purkinje cells, that have an inhibitory role, and an increase in white matter density [12].

Amygdala and emotions. The amygdala is located at the extremity of dorsomedial frontal lobe and consists of several nuclei. It receives aferences from the sensory areas and from the thalamus. It has reciprocal connections with the prefrontal cortex through thalamo-frontal circuits and uncus circuits. It also sends efferents to the hypothalamus. The right and left amygdalae are interconnected through fibers of the anterior commissure. The amygdalae regulate social behavior and emotions [11]. Social difficulties in autism are based on amygdala dysfunction. Studies of autism induced by VPA on animal models have shown hiperconnectivity with overactivation and hiperglutamatergia in the amygdala. Studies in adults with Asperger syndrome showed a hypoactivation of the amygdala. However, in children with ASD aged up to 18 months, there was a hyperactivity in the amygdala. In children with high-functioning autism there was a right amygdala activation when they had to look familiar and unfamiliar faces, and of the left amygdala and orbitofrontal cortex at the sight of faces expressing specific emotions. While neurotypical children actively seek the gaze of others and pay attention to social cues, children with ASD perceive social stimuli at an intense and painful level, and develop avoidance behavior. This behavior might be explained by an overdevelopment in the amygdala and frontal cortex. The overactivation of the amygdala also causes a high level of anxiety, so individuals with ASD are prone to phobias and generalized anxiety. According to the Intense World Theory, the deficit of empathy is not primary, but secondary to a painful perception of social stimuli, followed by their active avoidance [12]. In autism primary emotions are intense. They can manifest extremely and transitory. Understanding the complex emotions that underlie social interaction in ASD is difficult or even impossible. From the emotions development perspective, we can say that a person with autism remains at the level of a child [5].

Hiperglutamatergia. Excitatory receptor overactivation, such as NMDA and glutamate receptors, was detected in autism in different brain regions, particularly in the hippocampal circuits and amygdalae. Overexpression of excitatory receptors underlies hiperplasticity and long-term memory. There is an imbalance between inhibitory receptors and excitatory receptors. This underlies the increased risk of epilepsy and inhibits the development of specific areas. For example, by exposure to normal social environment stimuli that activate fronto-amyglalian circuits, overactivation of the circuits in the amygdala and prefrontal cortex in ASD brain is accompanied by an overactivation of glutamate and NMDA receptors leading to synaptic hyperplasticity. This is followed by an excito-toxic effect, the consequence of which is

a marked decrease in the volume of these regions [12].

The role of brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin synthesized at the neuronal level. It has several roles in the typical brain: the survival and differentiation of neurons, dendritic spines development, synaptic plasticity. It is also involved in the maturation of dopaminergic and serotoninergic neurons [13, 14]. BDNF has a molecular weight of 14 kDa and is synthesized from a precursor, pro-BDNF, with the weight of 23 kDa. Pro-BDNF and BDNF have opposite effects resulting in inhibition of neuronal differentiation and the formation of synapses by pro-BDNF. In different regions of the brains of people with autism, such as the fusiform gyrus a high level of both mature BDNF and pro-BDNF has been found [14]. One study also showed significantly increased BDNF levels in serum from children with autism in the first 6 years of life, followed by the subsequent lowering thereof. BDNF levels were directly correlated with the size of the cranial perimeter [13]. BDNF can assist in developing cortical microcircuits connectivity [4].

COGNITIVE CONSEQUENCES OF NEURONAL HIPERCONNECTIVITY

The cognitive consequences of hiperconnectivity are hyperperception, hiper-attention and hypermemory.

Perceptual function in people with autism. Individuals with ASD have different perceptual troubles. They are based on the development of cortical microcircuits in the sensory areas. Many people with ASD notice noises or fine visual details that many people don't [12]. People with autism may have certain ways of perceiving the world. These include "literal" perception, Gestalt perception, fragmented perception distortions, perceptual inconsistency, inhibition of perception, hyper- or hyposensibility to stimuli, film perception, shut-down phenomena, synesthesia. These perceptual experiences and the theory of central coherence differ for each person with autism and for every sensory system in the same person. "Literal" perception refers to observing environmental stimuli without interpreting them. In autism, this is true in particular for social stimuli. People with autism note social cues such as facial expressions change, but do not read between the lines. Gestalt perception means to observe the entire form with all the details without filter. This apparently contradicts the theory of central coherence. Gestalt perception can occur at the level of any sensory system. Some people with ASD are not "fooled" by optical illusions, other memorize an object with all its details and reproduce it exactly. Regarding hearing, Gestalt perception people have difficulties focusing on a speech in the presence of background noise or in retaining verbal instructions from more than one person. In these individuals, the overlapping information may induce a sensory overload. Fragmented perception involves focus on some details, while omitting others. It seems that there is a contradiction between fragmented perception and Gestalt perception, but these two come as a couple. If the information processed as a whole becomes overwhelming, then there is focus on details. This can manifest as selecting the detriment of the overall image for the detail, not recognizing a person when they change clothes, or in pictures, understanding clearly only certain words in a sentence, the rest sounding like "gibberish" or focusing on specific body parts. Sensory overload occurs in many people with autism. This can manifest as fatigue, excessive anxiety, mutism or aggressive reactions after exposure to certain stimuli, such as fluorescent lamps, sun, prolonged standing, noisy and crowded places, night clubs. In many people with high-functioning autism or Asperger syndrome, the film perception phenomenon occurs mainly related to social stimuli. The person with autism pays attention to, is aware of the mouth and the words of the interlocutors and other social stimuli, such as facial expressions, act as "subliminal" stimuli. Direct attention to them can be painful and cause overload. Consequently, some people with Asperger syndrome might say that they have a "telepathic sense" or a "sixth sense" and "notice hidden things". In some cases, sensory overstimulation leads to temporary blocking of perception or mental functions (Shut-down phenomenon). A rare perceptual phenomenon is synesthesia or cross perception. It consists in

triggering a sense path at the perception of a stimulus. The frequency in the general population ranges between 1/2000 and 1/100. It occurs more frequently in individuals with ASD. It can consist in associating sounds with colors, or combination of sounds with a sense of touch. The most common are combinations of figures or letters with certain colors. A certain degree of synesthesia is present in most people, especially children, but in a small number of individuals it is emphasized and lasts for life. Another problem that can occur in people with ASD, is the scotopic hypersensitivity syndrome, or Irlen syndrome, described thus by Helen Irlen, educational psychologist, in 1983. The hypersensitivity syndrome lies in the perception of certain colors in the light spectrum, and the symptoms are very varied. Usually, it associates various difficulties in reading, fatigue, difficulty concentrating. It can be corrected by wearing special colored lenses that block the passage of specific colors [7].

Attention. Attention has 4 functions: support, orientation, response inhibition and switching. One can classify it into spontaneous and voluntary attention. Individuals with ASD have an intense focus on activities. Also, many people with ASD focus on the inner world. During the period in which they focus on an activity, they can hardly respond to environmental stimuli, such as being called by their name. In autism, sustained attention is intact, reorienting and inhibition are low, and it is very difficult to switch focus. Attention difficulties are due to an overactivation in the microcircuits of the prefrontal cortex and lingering reverberations, which translates into perseverance on activities [12].

Memory and intellectual abilities.

Hyperreactivity acting synergistically with synaptic hiperplasticity intervenes in long-term memory. This means that people with autism have long-term memory skills, especially in a particular field. Development of connectivity in certain brain areas by overactivation and hiperplasticity, is responsible for developing specific skills such as numeracy, calendar calculation, drawing, and more [12].

Executive functions include planning, working memory, impulse control, inhibition and cognitive flexibility, initiating and monitoring actions. The frontal lobe is responsible for them. In ASD and ADHD the executive functions are altered. Frequently, ASD is associated with symptoms of ADHD. Behaviors such as solilocvia or stereotypes can be attributed to executive functions alterations. For example, it was found that in children with high-functioning autism, solilocvia during a task improves task-related executive functions [8]. ASD executive functions deficits have a different mechanism compared to ADHD, according to the hiperconectivity theory . A reduction in cortical volume and especially the frontal lobe was identified in ADHD without ASD, [1]. In ASD there is a rapid increase in brain volume, and executive function deficits may be relative, followed by information overload refractory periods. Some authors claim that the full picture of autism disorders is achieved by associating perceptual and executive functions deficit [7].

EMOTIONAL CONSEQUENCES OF HIPERCONECTIVITY IN PATIENTS WITH ASD

Investigation of hiperconectivity through psychological tests. Although demonstrated by neurophysiological means, the presence of hiperconectivity in ASD can be difficult to prove clinically. In order to analyze neuronal hiperconectivity in people with ASD, one can study the clinical effects of hiperconectivity underlining social difficulties and stereotyped behaviors. For example, sensory difficulties can be studied by means of specific questionnaires, such as the Sensory Profile Infant, Pediatric Sensory Profile, or Adolescent / Adult Sensory Profile. Problems of perception and executive functions can be studied using the Stroop effect (named after John Ridley Stroop who described it the first time in 1935). According to the Intense World Theory, people with ASD have exacerbated emotions, and this, in combination with sensory hypersensitivity leads to blocking or slowing the development of the theory of mind. People with ASD should have an excess of emotions associated with a lack of understanding of social indicators.

Empathy Imbalance Theory. A new theory proposed by Prof. Adam Smith, University of Dundee, Scotland, UK, refers to empathy imbalance. The author describes the function of empathy as having two components: affective empathy (AE) and cognitive empathy (CE).

These two components may occur separately. AE underlines parent-child attachment, compassion, friendship relations, moral development, inhibition of violence. CE is the basis of understanding behaviors and intentions of others, negotiation and resolution of conflicts, the principles of educating children, competitiveness and Machiavellian skills. CE is synonymous with the Theory of Mind. CE and AE are two separate elements which act complementary. In some circumstances, it may be necessary to separate the two components of empathy, because high-level expression of AE while exerting CE can be overwhelming. Under normal conditions, the 2 components are in balance. The author has described four cases of empathy imbalance: 1) high AE and low CE - is manifested by considerable confusion in social situations and meets ASD features; 2) high CE and low AE - in manipulators, lack of conscience and antisocial personality characteristics; 3) both AE and CE low- Schizoid personality appears; 4) both EA and EC increased - Williams syndrome occurs [15]. ASD appears therefore as an increase in EA leading to blocking EC development. This is stated in the Intense World Theory. The child who will develop ASD or Asperger syndrome is overly sensitive to social stimuli so that he or she tends to block the action of stimuli. The amygdala hiperconectivity plays a special role in this mechanism. Raised EA is a direct marker of neuronal hiperconectivity. These new theories contradict the extreme male brain theory. The low values of the coefficient of empathy in people with Asperger syndrome may lead to a low self-image related to social values and to confusion in social situations. The questionnaire that assesses empathy relates more to CE and indirectly to AE [16].

Data that check the empathy imbalance in ASD. There are several researches that revealed the presence of elevated AE in individuals with ASD. For example, one study showed that children with high-functioning autism (HFA) have a positive emotional pattern more intense than neurotypical children in front of funny videos. This can demonstrate the presence of increased AE in autism. Another study conducted on a group of young adults with HFA, assessed the amplitude of the movements made to mimic the images of people expressing primary emotions, using electromyography. The results showed a smaller amplitude of movements in HFA compared with the control group. This phenomenon can be explained by the mirror neurons overcharging, followed by blocking. Electrodermal response measurement showed higher levels in people with HFA compared with the control group, when viewing certain images. People with HFA report intense emotions. Another way to highlight hiperconectivity and AE is to study the Stroop effect. It consists of an interference between two contradictory stimuli, applied simultaneously. Stroop tests measure the response time to the two stimuli. In the emotional Stroop test the 2 stimuli include black and white images that are coated with background color. The image expresses positive or negative emotions, and the individual must designate colors. By applying this test to a lot of people with Asperger syndrome, they responded more quickly to items that included negative emotions and slower to those harboring positive emotions compared to the control group. This may explain the fact that people with Asperger syndrome may perceive negative emotions painfully and will want to " quickly escape " these stimuli, while it is possible to have a strongly positive emotional response to positive facial expressions [16]. A study where two tests were applied, Interpersonal Reactivity Index and Eyes Test for Children on a group of preteens with Asperger syndrome and a control group demonstrated a self-reported AE similar to the control group, but a low eye test score. This discrepancy might lead to the fact that those with Asperger syndrome become the bullying target of their classmates [17]. Another study that used the Interpersonal Reactivity Index questionnaire, revealed a higher AE reporting in those with HFA compared with the control group [16].

BRAIN DEVELOPMENT IN ASD – SPECIFIC PATTERNS OF BRAIN DEVELOPMENT IN CHILDREN WITH ASD

Studies have shown a rapid development of the brain in infants who develop ASD, especially in the first 1-2 years of life. Accelerated brain growth is associated with an

increase in cranial perimeter. In children with poorly functioning autism , increased brain volume is higher [5]. Increased brain mass is due to the rise in the number of synapses. Because hiperconectivity is associated with hiperglutamatergia, a higher hiperconectivity in early years, will lead to more severe symptoms and subsequent cognitive deficits due to glutamate excitotoxicity [5, 12].

Brain overspecialization. In all individuals there is a certain degree of specialization of functions, so each person is talented in different areas and less talented in others. Temple Grandin described, in terms of her autism, 3 types of human thinking: visual thinking, thinking in and verbal logical thinking. Every person meets these 3 types, but one or two of them predominate [5]. In people with ASD, the degree of specialization of the brain is more pronounced. In autism, as the brain develops, functional fragmentation occurs, developing very specific areas and lagging behind in others. The process of specialization of the brain is determined by both genetic factors and the continued stimulation from the environment [12]. Autistic spectrum disorders are classified according to the level of systematization in Asperger syndrome, high-functioning autism, medium functioning autism and poorly functioning autism [1]. The level of specialization of the brain is correlated with the level of systematization. In all autistic spectrum disorders, the triad hiperconectivity - hyperreactivity - hiperplasticity occurs in the early years. The degree of hiperconectivity and synaptic overactivation determine the severity of autism. In highly functional forms of autism, it is difficult to differentiate between HFA and Asperger syndrome. Although differentiation is made, usually based on the history of language development disorders, modern studies have demonstrated the presence of specific EEG patterns in autism or Asperger syndrome [18]. The difference may also be made according to the thinking pattern. The actual Asperger syndrome is characterized by hiperconectivity in cortical areas responsible for language and development in areas of the left hemisphere, with a right lateral ventricle enlargement. Imaging studies describe a hypotrophia in the amygdala, prefrontal cortex, cerebellar hemisphere and left hemisphere, and hypertrophy in the right inferior parietal lobe and right fusiform gyrus. Many people with Asperger syndrome have an accelerated development of the language with hiperlexia, but have difficulties in visual spatial processing. People with high-functioning autism have hypotrophy in the cerebellum, dorsal hippocampus and median temporal gyrus , and bilateral hypertrophy of the prefrontal cortex, caudate nucleus and ventral region of the temporal lobe. People with HFA often have a history of language disorders, good visual-spatial skills and, despite a high level of systematization of thought, they can hijack the mechanisms for social systematization, developing theory of mind based on cause-effect relationships [1, 5, 19]. Medium and low functional autism are characterized by an increased overspecialization of the brain, with large atrophic brain areas and small regions with high synaptic density. These include autistic patients with scholars syndrome, who develop some very high cognitive performances, such as calendar calculation or memorizing a large number of pages, but who have low communication skills and self-management [5].

ASPECTS REGARDING THERAPY IN CHILDREN WITH ASD

The autistic spectrum disorders therapy uses several methods, such as ABA, PECS method and TEACCH method. Therapy must be initiated as early as possible. Most studies and clinical observations show that starting therapy at younger ages associated with an intensive therapy program leads to significantly better results than otherwise. Diperconectivity and hiperplasticity are marked during early childhood and therapeutic intervention helps develop microcircuits [1]. However, given the heightened risk of excitotoxicity due to environment overstimulation it is necessary to avoid sensory overstimulation, such intense emotional events, around the child (these can lead to a withdrawal of the child in their inner world). It is necessary to create a predictable environment. The exposure to stimuli must be progressive [12].

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