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Neuroscience Theories, Hypothesis and Approaches to ASD Physiopathology. A Review

Castejón OJ[1,*]

[1]Instituto de Investigaciones Biológicas "Drs. Orlando Castejón and Haydee Viloria de Castejón" e Instituto de Neurociencias Clínicas, Fundación Castejón, San Rafael Clinical Home. Maracaibo. Venezuela.

Abstract

According to the results of our laboratory the theory of immune dysfunction, the theory on the genetic architecture of ASD, the disrupted cortical connectivity theory and the theory on the contribution of cerebellum to ASD have shown fundamental experimental evidences to support the core symptoms of the complex and enigmatic autism spectrum disorder. The following hypothesis, such as hypothesis of mirror neuron networks, on oxytocin and vasopressin in ASD, and the neurogenesis in the amygdala are interesting and stimulating approaches that deserve further basic and clinical research.

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Corresponding author: Orlando J. Castejón, Instituto de Investigaciones Biologicas "Drs. Orlando J. Castejón and Haydée Viloria de Castejón". Facultad de Medicina. Universidad del Zulia, Apartado 526, Maracaibo. Venezuela, Phone Cell 58 414 621 8209, E-mail: ocastejo@cantv.net

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Introduction

In a previous paper [1] (Castejón et al.,2019) we have reported a clinical study on 75 infant patients from 3 to 15 years with autism spectrum disorder in a developing country. These patients exhibited disconnected brain with social isolation (80%), hyperconnected children (5%), creative child, (Asperger syndrome) (10%), stereotypic movements of hands and body (10%), psicomotor retard (5%), behavioral changes such as aggresivity and autoagressivity (10%), crisis of tears (1%), separation anxiety (1%), mood disorders (3%), photofobia (1%), loss of weight, (1%), routinised patterns of though and fantastic thoughts (2%), language disorders such as delay in the onset of language or early vocalization, regressive changes of language, mutism, gestual language, escatologic language, digital language (5%), learning and memory deficit (10%). The following associated comorbidities: perinatal hypoxia, low weight at birth, behavioral abnormalities, anxiety, auto- and heteroaggressivity, language disorders, hiperphagia, learning and memory deficit, hearing disorders, mainly hiperacusia, Social isolation, cognitive deficit, sleeping disorders and parenteral abuse of child. Some non-nervous system comorbidities, such as pulmonary diseases and allergic reactions also were found. Some locomotor abnormalities as genus valgo and flat feet were also observed. The mothers exhibited the followings diseases during pregnancy: urinary infections, behavioral disturbances like anxiety, fobias, hyperactivity, toxoplasmosis and Zika virus infections, hyperemesis, oligohydramnios and lost of amniotic fluid, twin pregnancy, pre-eclampsia, aging placenta, cesarean, high blood pressure, maternal sepsis, diabetes, hepatic coma, hipotiroidism, viral hepatitis, parent obesity, and social problems, such as excessive work, low economy and poor social conditions, environmental contamination and labor and conjugal stress. We emphasized different phenotype subtypes of ASD related with the environmental changes of developing countries and the multiple maternal pathology as risks factor for ASD.

In the present review we made a neuroscience approach to the study of ASD describing the following hypothesis and theories based on clinical data in an attempt to explain the complex physiopathology of the autistic brain.

The Hypothesis of Abnormal Neuron and Glial Cell Migration During Development

A large amount of evidence suggests that pathological processes taking place in early embryonic neurodevelopment might be responsible for later manifestation of autistic symptoms. This dysfunctional development includes altered maturation/differentiation processes, disturbances in cell-cell communication, and an unbalanced ratio between certain neuronal populations. All those processes are highly dependent on the interconnectivity and three-dimensional organizations of the brain [2] (Ilieva et al., 2018). As experimental evidence emerges in recent years, it becomes clear that although there is broad heterogeneity of identified autism risk genes, many of them converge into similar cellular pathways, including those regulating neurite outgrowth, synapse formation and spine stability, and synaptic plasticity. These mechanisms together regulate the structural stability of neurons and are vulnerable targets in ASD [3]. Lin et al. (2016)

Dendritic spines receive a majority of the excitatory synaptic inputs to cortical neurons and are critically involved in synaptic plasticity and learning. Therefore, abnormalities in dendritic spines have long been associated with cognitive dysfunction and neurodevelopmental delay Therefore, abnormalities in dendritic spines have long been associated with cognitive dysfunction and neurodevelopmental delay [4] (Castejón et al., 2004)

Altered Modular Organization of Structural Cortical Networks

ASD and ADHD are functional alterations of the cerebral cortex, which present structural anomalies in the arrangement of neurons, in the pattern of connections of cortical columns and in the structure of dendritic spines. These anomalies affect mainly the prefrontal cortex and its connections (ASD and ADHD) are functional alterations of the cerebral cortex, which present structural anomalies in the arrangement of neurons, in the pattern of connections of cortical columns and in the structure of dendritic spines. These alterations affect mainly the prefrontal cortex and its connections. [5]. (Martinez-Morga et al., 2018).

Shi et al. [6] (2013) described three modules in autistic children with similar patterns. Compared with

controls, autism demonstrates significantly reduced gross network modularity, and a larger number of inter-module connections. However, the autistic brain network demonstrates increased intra- and inter-module connectivity in brain regions including middle frontal gyrus, inferior parietal gyrus, and cingulate, suggesting one underlying compensatory mechanism associated with brain functions of self-reference and episodic memory. This alteration of correlation strength may contribute to the organization alteration of network structures in autistic brains.

Disrupted Cortical Connectivity Theory and Autism Spectrum Disorders

This theory suggests that weaker functional connections among brain areas in those with ASD hamper their ability to accomplish complex cognitive and social tasks successfully. These theory support the following hypotheses 1) underconnectivity in ASD is manifested mainly in long-distance cortical as well as subcortical connections rather than in short-distance cortical connections; 2) underconnectivity in ASD is manifested only in complex cognitive and social functions and not in low-level sensory and perceptual tasks; 3) functional underconnectivity in ASD may be the result of underlying anatomical abnormalities, such as problems in the integrity of white matter; 4) the ASD brain adapts to underconnectivity through compensatory strategies such as overconnectivity mainly in frontal and in posterior brain areas [7]. (Kana et al., 2011).

Neuroimaging and electroencephalographic studies have found evidences suggesting that connectivity patterns are altered in ASD. The converging findings of functional connectivity abnormalities and white matter abnormalities in autism suggest that alterations in neural connectivity and the communication between different brain regions may be involved in behavioral and cognitive deficits associated with autism [8]. (Palau-Baduell et al., 2012).

The dominant theory regarding brain connectivity in people with ASD is that there is long distance under-connectivity and local over-connectivity of the frontal cortex. Consistent with this theory, long-range cortico-cortical functional and structural connectivity appears to be weaker in people with ASD than in controls. However, in contrast to the theory, there is less evidence for local over-connectivity of the frontal cortex [9]. (Vissers et al., 2012).

Recent findings of neurological functioning in autism spectrum disorder (ASD) point to altered brain connectivity as a key feature of its pathophysiology. According to the Just et al. [10] the cortical underconnectivity theory of ASD provides an integrated framework for addressing these new findings. This theory suggests that weaker functional connections among brain areas in those with ASD hamper their ability to accomplish complex cognitive and social tasks successfully

The crucial role played by the disruption of global connectivity in a parallel distributed cortical network, which might result in impairment in integrated cognitive processing, such as impairment in executive function and social cognition. On the other hand, the reduced inter-regional collaboration could lead to a disinhibitory enhancement of neural activity and connectivity in local cortical regions. In addition, enhanced connectivity in the local brain regions is partly due to the abnormal organization of the cortical network as a result of developmental and pathological states. This enhanced local connectivity results in the specialization and facilitation of low-level cognitive processing.

The disruption of connectivity between the prefrontal cortex and other regions is considered to be a particularly important factor because the prefrontal region shows the most influential inhibitory control on other cortical areas [11] (and Kato, 2008)

Many functional connectivity studies (fcMRI) have reported underconnectivity in ASD, but results in others have been divergent. Underconnectivity reflects reduced efficiency of within-network communication in ASD, diffusely increased functional connectivity can be attributed to impaired experience-driven mechanisms (e.g., synaptic pruning) [12] (Muller et al., 2011). However, there are notable inconsistencies, with some studies reporting overconnectivity. Improved awareness of their implications appears indispensible in fcMRI studies when inferences about "underconnectivity" or "overconnectivity" in ASD are made [13]. (Nair et al.,2014).

Mohammad-Rezazadeh et al. [14]. (2016) also consider that the results of more recent studies do not

unanimously support the traditional view in which individuals with ASD have lower connectivity between distant brain regions and increased connectivity within local brain regions. Moreover, further investigations of connectivity with respect to behavior and clinical phenotype are needed to probe underlying brain networks implicated in core deficits of ASD.

A recent theory attempting to reconcile conflicting results in the literature proposes that hyper-connectivity of brain networks may be more characteristic of young children with ASD, while hypo-connectivity may be more prevalent in adolescents and adults with the disorder when compared to typical development (TD) [15, 16]. (Uddin et al., 2013, Nomi and Uddin (2015). Cohorts of individuals with ASD and typical development (TD) individuals demonstrates that functional connectivity atypicalities in the disorder are not uniform across the lifespan.

According to Abbott et al., (2016) [17], predominant overconnectivity was found at the posterior cingulate seed and right inferior parietal seed, predominant underconnectivity was found for right anterior insula seed and left inferior parietal seed. In the ASD group, reduced integrity was associated with sensory and sociocommunicative symptoms. Atypical connectivity in ASD is network-specific, ranging from extensive overconnectivity to extensive underconnectivity.

Cauda et al. [18] (2017) distinguished two alteration clusters. Cluster 1, includes the anterior insular, anterior cingulate cortex, ventromedial prefrontal cortex, and frontopolar areas, which are parts of the cognitive control system. Cluster 2, presents occipital, temporal, and parietal alteration patterns with the involvement of sensorimotor, premotor, visual, and lingual areas, thus forming a network that is more associated with the auditory-visual, premotor visual somatic functions. In turn, ASD appears to be uniformly distributed in the two clusters.

Carper et al. [19] (2015) analyzed the corticospinal tract anatomy and functional connectivity of primary motor cortex in autism and postulated that their findings, implicating both functional and anatomical connectivity of the primary motor cortex, suggest that network anomalies in ASD go well beyond sociocommunicative domains, affecting basic motor execution. They also suggested that even in right-handed adolescents with ASD, typical left hemisphere dominance is reduced, both anatomically and functionally, with an unusual degree of right hemisphere motor participation.

Melillo and Leisman [20] (2009) conceptualize that if the problem of autistic spectrum disorder is primarily one of desynchronization and ineffective interhemispheric communication, then the best way to address the symptoms is to improve coordination between areas of the brain. To do that the best approach would include multimodal therapeusis that would include a combination of somatosensory, cognitive, behavioral, and biochemical interventions all directed at improving overall health, reducing inflammation and increasing right hemisphere activity to the level that it becomes temporally coherent with the left hemisphere. They hypothesize that the unilateral increased hemispheric stimulation has the effect of increasing the temporal oscillations within the thalamocortical pathways bringing it closer to the oscillation rate of the adequately functioning hemi-sphere.

Recent brain neuroimaging studies point to anatomic and functional abnormalities of the superior temporal lobe in autistic children [21]. (Golse and Robel, 2009). The superior temporal lobe is currently at the focus of intensive research in infantile autism, a psychopathologic disorder apparently representing the severest failure of access to intersubjectivity, i.e. the ability to accept that others exist independently of oneself. Access to intersubjectivity seems to involve the superior temporal lobe, which is the seat of several relevant functions such as face and voice recognition and perception of others' movements, and coordinates the different sensory inputs that identify an object as being "external".

According to Levy [22] (2007) when the developing brain encounters constrained connectivity, it evolves an abnormal organization, the features of which may be best explained by a developmental failure of neural connectivity, where high local connectivity develops in tandem with low long-range connectivity, resulting in constricted repetitive behaviors.

The Hypothesis of Mirror Neuron Networks in Autism Spectrum Disorder

Adolescents with ASD showed atypically increased functional connectivity involving the mentalizing and mirror neuron systems, largely reflecting greater cross talk between the 2. This finding is consistent with emerging evidence of reduced network segregation in ASD and challenges the prevailing theory of general long-distance underconnectivity in ASD. This excess ToM-MNS connectivity may reflect immature or aberrant developmental processes in 2 brain networks involved in understanding of others, a domain of impairment in ASD. Further, robust links with sociocommunicative symptoms of ASD implicate atypically increased ToM-MNS connectivity in social deficits observed in ASD [23] (Fishman et al.,2014).

It seems possible that different sub-populations of mirror neurons, located in several regions, contribute differentially to social cognitive functions. It is hypothesized that mirror neuron coding for action-direction may be required for developing attentional sensitivity to self-directed actions, and consequently for person-oriented, stimulus-driven attention. Mirror neuron networks may vary for different types of social learning such as "automatic" imitation and imitation learning [24]. (Williams, 2008).

Oberman and Ramachandran [25].(2007) studied the role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders and propose that internal simulation mechanisms, such as the mirror neuron system, are necessary for normal development of recognition, imitation, theory of mind, empathy, and language. Additionally, the authors suggest that dysfunctional simulation mechanisms may underlie the social and communicative deficits seen in individuals with autism spectrum disorders.

The Hypothesis on Oxytocin, Vasopressin, and ASD.

Insell et al. [26] (1999) reviewed evidence from animal studies demonstrating that the nonapeptides, oxytocin and vasopressin, have unique effects on the normal expression of species-typical social behavior, communication, and rituals. Based on this evidence, they hypothesize that an abnormality in oxytocin or vasopressin neurotransmission may account for several features of autism. As autism appears to be a genet-ic disorder, mutations in the various peptide, peptide receptor, or lineage-specific developmental genes could lead to altered oxytocin or vasopressin neurotransmission.

The Hypothesis of Neurogenesis in the Amygdala as a Contributing Cause of Autism

Since the childhood psychiatric condition of autism involves deficits in "social intelligence", it is plausible that autism may be caused by an amygdala abnormality. The amygdala is therefore proposed to be one of several neural regions that are abnormal in autism [27] (Baron-Cohen et al., 2000). Several studies have associated the amygdala to the autism. This key structure is a complex cerebral region which has been associated with social behaviors and the emotional significance of the daily experiences. It is known that new neurons are not well responsive to GABA stimulation, allowing the long-term potentiation necessary for the learning process. Based on these evidence it is tantalizing to hypothesize that the sociability impairment seen in some individuals with autism may partly be assigned to impaired regulation of the GABAergic system and to the impact of this impairment on the adequate functioning of the amygdala and on its capacity to store new experiences and to modulate the plasticity of the corticostriatal connections [28]. (Mercadante et al.,2008). The key brain structures that have been implicated in the social cognition deficits in autism are: (1) the amygdala, (2) the superior temporal sulcus region, and (3) the fusiform gyrus [29]. (Pelphrey K et al., 2004).

According to Amaral [30,31] recent data from studies in our laboratory on the effects of amygdala lesions in the macaque monkey are at variance with a fundamental role for the amygdala in social behaviour. If the amygdala is not essential for normal social behaviour, as seems to be the case in both non-human primates and selected patients with bilateral amygdala damage, then it is unlikely to be the substrate for the abnormal social behaviour of autism. However, damage to the amygdala does have an effect on a monkey's response to normally fear-inducing stimuli, such as snakes, and removes a natural reluctance to engage novel conspecifics in social interactions. These findings lead to the conclusion that an important role for the amygdala is in the detection of threats and mobilizing an appropriate behavioural response, part of which is fear. If the amygdala is pathological in subjects with autism, it

may contribute to their abnormal fears and increased anxiety rather than their abnormal social behavior.

Theory of Immune Dysfunction on ASD

Dysregulation in immune responses during pregnancy increases the risk of a having a child with an autism spectrum disorder (ASD). Asthma is one of the most common chronic diseases among pregnant women, and symptoms often worsen during pregnancy [32]. (Vogel Ciernia et al., 2018).

Two main immune dysfunctions in autism are immune regulation involving pro-inflammatory cytokines and autoimmunity. Studies showing elevated brain specific antibodies in autism support an autoimmune mechanism. Viruses may initiate the process but the subsequent activation of cytokines is the damaging factor associated with autism. Virus specific antibodies associated with measles virus have been demonstrated in autistic subjects. Maternal antibodies may trigger autism as a mechanism of autoimmunity. MMR vaccination may increase risk for autism via an autoimmune mechanism in autism [33]. (Cohly and Panja, 2005).

Epidemiological studies have shown a relationship with maternal immune disturbances during pregnancy and ASD. Moreover, decades of research have identified numerous systemic and cellular immune abnormalities in individuals with ASD and their families. These include changes in immune cell number, differences in cytokine and chemokine production, and alterations of cellular function at rest and in response to immunological challenge. Many of these changes in immune responses are associated with increasing impairment in behaviors that are core features of ASD [34-36]. (Careaga and Ashwood, .2012, Hsiao, 2013, Noriega and Savelkoul, 2014). Individuals diagnosed with ASD have alterations in immune cells such as T cells, B cells, monocytes, natural killer cells, and dendritic cells. Also, many individuals diagnosed with ASD have alterations in immunoglobulins and increased autoantibodies. Finally, an important portion of individuals diagnosed with ASD has elevated peripheral cytokines and chemokines and associated neuroinflammation [37] (Bjorklund et al., 2016). Scientific research studies emerging within the past two decades suggest that immune dysfunction and inflammation have pathogenic influences through different mechanisms, all leading to both a chronic state of low grade inflammation, and alterations in the central nervous system and immune response, respectively [38]. (Dipasquale et al., 2017). Neuro-inflammation and neuro-immune abnormalities have now been established in ASD as key factors in its development and maintenance [39] (Siniscalco et al., 2018). Inflammation in the brain and CNS has been reported by several groups with notable microglia activation and increased cytokine production in postmortem brain specimens of young and old individuals with ASD [40] (Gesundheit et al., 2013).

The Theory on the Genetic Architecture of ASD

The genetic architecture of ASD has become increasingly clear and increasingly complex with estimates of at least 1000 genetic alterations associated with the risk for ASD [41]. (Beversdorf, 2016). In the last 10 years, there have been significant advances in understanding the genetic basis for ASD, critically supported through the establishment of ASD bio-collections and application in research. Collectively, these include mapping ASD candidate genes, assessing the nature and frequency of gene mutations and their association with ASD clinical subgroups, insights into related molecular pathways such as the synapses, chromatin remodelling, transcription and ASD-related brain regions [42]. [Reilly et al., 2017]. Multiple lines of evidence from genetic linkage studies to animal models implicate aberrant cortical plasticity and metaplasticity in the pathophysiology of autism spectrum disorder (ASD) and fragile X syndrome (FXS) [43]. (Oberman et al., 2016).

Data from whole-genome screens in multiplex families suggest interactions of at least 10 genes in the causation of autism. Thus far, a putative speech and language region at 7q31-q33 seems most strongly linked to autism, with linkages to multiple other loci under investigation. Cytogenetic abnormalities at the 15q11-q13 locus are fairly frequent in people with autism, and a "chromosome 15 phenotype" was described in individuals with chromosome 15 duplications. Among other candidate genes are the FOXP2, RAY1/ST7, IMMP2L, and RELN genes at 7q22-q33 and the GABA(A) receptor subunit and UBE3A genes on chromosome 15q11-q13.[44]. (Muhle et

al.,2004).

Prior structural MRI studies demonstrated atypical gray matter characteristics in siblings of individuals with autism spectrum disorder (ASD). However, they did not clarify which aspect of gray matter is related to the endophenotype (i.e. genetic vulnerability) of ASD. This proof-of-concept study suggests that an ASD endophenotype emerges in sulcal depth SD and that neural bases for ASD diagnosis can be discerned from the endophenotype when accounted for the difference between TD siblings. [45]. (Yamagata et al., 2019).

The Hypothesis of Mitochondrial Dysfunction in Children with ASD

The different clinical symptoms found in ASD patients as observed in the present study suggest the dysfunction of a cell energy organelle as mitochondria. Rose et al. [46]. (2018) systematically review the literature on human studies of mitochondrial dysfunction related to ASD. Clinical aspects of mitochondrial dysfunction in ASD include unusual neurodevelopmental regression, especially if triggered by an inflammatory event, gastrointestinal symptoms, seizures, motor delays, fatigue and lethargy.

Recent researches have revealed the influence of mitochondrial physiology on the development of ASD. Several research groups have identified defects in respiratory complexes, coenzyme-Q10 deficiency, increased oxidative damage, decreased of superoxide dismutase (SOD2). A study on the influence of mitochondrial physiology on the development of ASD can provide new alternatives and challenges. The increment of mitochondrial DNA, high oxidative stress, and high expression of the *MFN2* gene could help as a scanner of the mitochondrial function in children with ASD [47]. (Carrasco et al., 2019).

The Dopamine Hypothesis of ASD

Pavăl (2017) [48] has proposed a dopamine hypothesis of autism spectrum disorder postulating that autistic behavior arises from dysfunctions in the midbrain dopaminergic system and that a dysfunction of the mesocorticolimbic circuit leads to social deficits, while a dysfunction of the nigrostriatal circuit leads to stereotyped behaviors. This hypothesis is based clinical studies of dopamine antagonists which seem to have improving effects on autistic behavior

The hypothesis on Synaptopathology in ASD

Multiple studies have revealed that mutations in genes like *NRXN, NLGN*, *SHANK*, *TSC1/2*, *FMR1*, and *MECP2* converge on common cellular pathways that intersect at synapses. These genes encode cell adhesion molecules, scaffolding proteins and proteins involved in synaptic transcription, protein synthesis and degradation, affecting various aspects of synapses including synapse formation and elimination, synaptic transmission and plasticity. This suggests that the pathogenesis of ASD may, at least in part, be attributed to synaptic dysfunction [49]. (Guang et al., 2018). Most ASD genes are implicated in neurogenesis, structural maturation, synaptogenesis and function [50]. (Gilbert and Man, 2017). SHANK3 is a synaptic scaffolding protein localized in the postsynaptic density and has a crucial role in synaptogenesis and neural physiology. Deletions and point mutations in SHANK3 cause Phelan-McDermid Syndrome (PMS), and have also been implicated in autism spectrum disorder (ASD) and intellectual disabilities, leading to the hypothesis that reduced SHANK3 expression impairs basic brain functions that are important for social communication and cognition.

Maussion et al. [51] (2019) found an increased expression of BDNF mRNA in the frontal cortex of autistic patients based on a candidate genes approach. The Authors present the expression data of 4 transcripts of interest (BDNF, CAMK2a, NR-CAM and RIMS1) located at the synapse in two regions of interest in the context of the ASDs; the lobule VI of cerebellum and the Brodmann area 46.

'Theory of Mind' and the Contribution to ASD

The ability to attribute mental states to others ('theory of mind') pervades normal social interaction and is impaired in autistic individuals. The Happé studies in Asperger syndrome (1996) [52] suggest that a highly circumscribed region of left medial prefrontal cortex is a crucial component of the brain system that underlies the normal understanding of other minds. Experimental evidence shows that the inability to attribute mental states, such as desires and beliefs, to self and others (mentalizing) explains the social and communication impairments of individuals with autism. Brain imaging

studies in normal volunteers highlight a circumscribed network that is active during mentalizing and links medial prefrontal regions with posterior superior temporal sulcus and temporal poles. The brain abnormality that results in mentalizing failure in autism may involve weak connections between components of this system [53]. (Frith, 2001). Specifically, the ability to decode others' mental states from observable cues (such as facial expressions) may rely on contributions from the orbitofrontal/medial temporal circuit within the right hemisphere. In contrast, the ability to reason about others' mental states may rely left medial frontal regions. We conclude by reviewing evidence suggesting that the developmental roots of autism might lie in abnormal functioning of the orbitofrontal/medial temporal circuit which may, in turn, underlie the abnormal development of social-cognitive skills among individuals with autism [54]. (Sabbagh, 2004).

The Theory Contribution of Cerebellum to ASD

During the past decades results from neuroanatomical, neuroimaging and clinical studies have substantially extended the functional role of the cerebellum in a variety of cognitive processes, such as executive functioning, memory, learning, attention, visuo-spatial regulation, language and behavioral-affective modulation to cognitive and affective regulation [55,56]. (Barrios and Guàrdia, 2001, Baillieux et al., 2008).

A special focus of recent research have been made on the striatum and the cerebellum, two structures known not only to control movement but also to be involved in cognitive functions such as memory and language. Dysfunction within the motor system may be associated with abnormal movements in ASD that are translated into ataxia, abnormal pattern of righting, gait sequencing, development of walking, and hand positioning, There is evidence that the frontostriatal motor system and/or the cerebellar motor systems may be the site of dysfunction in ASD. Indeed, the cerebellum seems to be essential in the development of basic social capabilities, communication, repetitive/ restrictive behaviors, and motor and cognitive behaviors that are all impaired in ASD. Cerebellar neuropathology including cerebellar hypoplasia and reduced cerebellar Purkinje cell numbers are the most consistent neuropathologies linked to ASD [57,58].(Fucillo,2016, Jaber 2017,)

Disruptions in specific cerebro-cerebellar loops in ASD might impede the specialization of cortical regions involved in motor control, language, and social interaction, leading to impairments in these domains. Consistent with this concept, structural, and functional differences in sensorimotor regions of the cerebellum and sensorimotor cerebro-cerebellar circuits are associated with deficits in motor control and increased repetitive and stereotyped behaviors in ASD. Communication and social impairments are associated with atypical activation and structure in cerebro-cerebellar loops underpinning language and social cognition. Finally, there is converging evidence from structural, functional, and connectivity neuroimaging studies that cerebellar right Crus I/II abnormalities are related to more severe ASD impairments in all domains [59,60] (D'Mello and Stoodley 2015, D'Mello et al., 2015). Differences in cerebellar development and/ or early cerebellar damage could impact a wide range of behaviors via the closed-loop circuits connecting the cerebellum with multiple cerebral cortical regions. Based on these anatomical circuits, behavioral outcomes should depend on which cerebro-cerebellar circuits are affected.[61-64] (Becker and Stoodley 2013,.Stoodley, 2014, 2016, Stoodley et al., 2017),

Postmortem studies have revealed neuropathological abnormalities in cerebellar cellular architecture while studies on mouse lines with cell loss or mutations in single genes restricted to cerebellar Purkinje cells have also strongly implicated this brain structure in contributing to the autistic phenotype [65]. (Hampson and Blatt, 2015).

One major component that appears highly impacted in autism is the GABAergic system. It is now apparent that there are widespread significant effects in many distributed regions in the autism brain revealed by histochemical, autoradiographic, and biochemical studies. The key synthesizing enzymes for GABA, glutamic acid decarboxylase type 65 and 67 (GAD65 and GAD67), are decreased in the cerebellum and closer examination of mRNA levels revealed that it is largely due to decreases in Purkinje cells and a subpopulation of larger dentate neurons as measured by in situ hybridization studies. Other cell types had either normal

GAD levels (Golgi cells, smaller dentate interneurons, and stellate cells) or increased levels (basket cells). GABA receptor density, number, and protein expression are all decreased in the cerebellum and in select cortical areas. These Authors suggest suggests a disturbance in the intrinsic cerebellar circuitry in the autism group potentially interfering with the synchronous firing of inferior olivary neurons, and the timing of Purkinje cell firing and inputs to the dentate nuclei. Disturbances in critical neural substrates within these key circuits could disrupt afferents to motor and/or cognitive cerebral association areas in the autistic brain likely contributing to the marked behavioral consequences characteristic of autism. Taken together, data from these studies suggest that there is a marked dysregulation of the inhibitory GABA system in the autism brain affecting particular biomarkers localized to specific cell types and lamina likely influencing circuitry and behavior [66-68]. (Yip J (2007), Soghomonian and Blatt, 2007, Yip et al, (2009) and Blatt and Fatemi.(2011).

Conclusions

According to the results of our laboratory the theory of immune dysfunction, the theory on the genetic architecture of ASD, the disrupted cortical connectivity theory and the theory on the contribution of cerebellum to ASD have shown fundamental experimental evidences to support the core symptoms of the complex and enigmatic autism spectrum disorder. The hypothesis above described are stimulating and interesting approaches that deserve further systematic basic and clinical neuroscience research.

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