Analysis of the specific neurodevelopmental patterns that lead to the development of ASD in individuals

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Abstract:- Approximately 1 out of every 59 children in the United States (16.8/1000) has autism spectrum disorder (ASD). ASD is a neurological and neurodevelopmental disorder that affects the way individuals interact within a social context, communicate, and behave. . The first researcher that is credited with the first detailed description of autistic behavior is Leo Kanner in 1943 . He noted that the outstanding common feature of all children is the presence of parental personalities, such as obsessiveness and lack of warm-heartedness. This perspective corresponded with Asperger's report in 2014, which described the main features of ASD as a series of developmental deficiencies: recognition, communication and understanding. Regardless of the researchers' reports addressed, ASD is in any case considered peculiar and difficult to treat. These difficulties underlie potential nuances and inconsistencies in the current method of research for ASD. In fact, researchers in the history of this disorder mainly focused on its features in terms of social impairments and investigated the consequences of this altered behavior. However, ASD research lacked an essential focus on the origin and physiological processes that contributed to the features of this disorder, which is essential in order to understand its enormous complexity.

Key words: neuroscience, autism spectrum disorder, hypermyelination, social impairment, amygdala, neurodevelopment

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1 Introduction, social cognition

The human brain has evolved to become more highly specialized in social interaction and communication than the brains of any other species. . Social recognition starts maturing early in life and quickly becomes highly complex by building on fundamental processes such as basic sensory integration and emotion recognition. . Later in development, social behavior incorporates higher-order processes, such as mental state attribution, involving integrated activity in several regions across the whole brain. These regions make up the "social brain," which has recently been defined by a meta-analysis of neuroimaging studies in social neuroscience, that comprise 36 distinct regions . These can be further grouped into 4 main clusters: high-level subnetworks (involving attention, memory, and executive function), intermediate-level networks (responsible for cohesion of information in the social context), and visual-sensory and limbic networks (responsible for perception and integration of relevant cues) .

Anomalies in social cognition and communication are a core characteristic of autism spectrum disorder (ASD). However, impairments in ASD are not directly the result of social cognition dysfunctions, but are sometimes the consequences of other neurodevelopmental abnormalities.

In particular, social cognition refers to "the ability to perceive and process information from others, from one's self and interpersonal knowledge" . Therefore, this statement indicates that social cognition is strongly based on information-processing. So, this definition might suggest that altered social behavior can be a consequence of impairments in information processing. Abnormalities in functional connectivity within many of the regions composing the social brain further support this idea.

In particular, functional connectivity is intended as "the strength to which activity between a pair of brain regions covaries or correlates over time" . In this instance, experimental data associates ASD deficits to

process facial features with altered connectivity in the fusiform gyrus and in the Mirror Neuron System . In fact, the function of the MNS (emotional and physical states' recognition) is relevant to understand that altered social behavior in ASD might arise due to an inability to recognize emotions.

However, the nature and extent of social brain anomalies associated with ASD vary considerably within individuals. Although autism is partly diagnosed on the basis of social and communication impairment, the phenotype encompasses much broader differences in perception and early neurodevelopmental patterns that contribute to the core features of the condition. In fact, the variability of ASD symptoms can extend also to altered immune responses or to impairments in auditory and memory stimuli processing.

Recently, several accounts supported by research on children and adults with autism have shifted the focus away from social impairment. In particular, the enhanced perceptual functioning model of autism proposes that superior function and increased independence of auditory and visual perceptual processes are responsible for the distinct pattern of cognitive and behavioral performance observed in ASD. . This indicates that social impairments in this condition might be the result of abnormalities in perceptual processes that are distinct from the social brain.

More recently, a predictive coding account has been applied to autism . In Neuroscience, predictive coding is a theory of brain function in which the brain is constantly generating and updating a mental model of the environment. The role of this coding is to generate predictions of sensory input that are compared to actual sensory input. In particular, the predictive coding theory of autism proposes that an autistic person's brain does not form accurate predictions or that sensory input overrides these internal predictive models. As a result, the autistic individual is overly sensitive to external input. Biologically, the brain adjusts precision by the modification of its proportions of chemical messengers as dopamine or glutamate. In the case of ASD, the brain is slower to recalibrate precision. It remains attuned to details but finds it difficult to generalize. This account may explain how brain differences in autism lead to a bias favoring local over global processing.

More specifically, hypersensitivity in visual or auditory processing may underlie symptoms such as altered social engagement and speech delay. These alternative accounts have also indicated that islands of enhancement, in addition to deficits, may better characterize some aspects of the phenotype . Furthermore, ASD symptoms also include altered memory and auditory information processing, altered stress and anxiety levels and difficulty in imitation or recognition of emotional/physical states. . Overall, these perspectives suggest that viewing autism in terms of a focal impairment in the social brain is overly simplistic. In fact, the previously listed symptoms might all contribute to altered behavior in the case of social situations. However, the origin of these features could be more complex and extended than previous ASD research believed. A more complex pattern of interactions between social and perceptual systems may in fact underlie the pattern of symptoms or individual differences observed in ASD.

1.2 Pre-existing ASD research

Based on its definition, "ASD is a neurological and neurodevelopmental disorder that affects the way individuals interact within a social context, communicate and behave", this disease appears to be mostly concerned with social perception and individual behavior within a social context. In fact, as previously mentioned, the Austrian-American psychiatrist Leo Kanner in 1943, represented in his studies the common public perception of ASD as a disease that involves "extreme autistic loneliness" or "Anxiously obsessive desire for the maintenance of sameness" . This perspective therefore refers to ASD primarily as a social and behavioral condition, rather than focusing on physiological abnormalities such as hypermyelination and cortical enlargement. This restricted and over-simplistic perspective might potentially have arisen due to a lack of appropriate technical equipment to analyze widespread symptoms in ASD.

More recently, the atypical features of social perception and cognition observed in individuals with a diagnosis of ASD have been explained in two different ways. The first

perspective accounts for domain-specificity, which is a theoretical position in cognitive science that argues that aspects of cognition are supported by specialized learning devices . In this instance, domain-specific accounts assume that end-state symptoms as behavioral impairments and language disturbances result from specific impairments within component structures of the social brain network. Secondly, domain-general accounts hypothesize that rather than being localized, atypical brain structure and function are widespread. Then, they hypothesize that the apparent social brain differences are the consequence of adaptations to earlier occurring widespread changes in brain function . This central dogma of ASD therefore influences the manner researchers address this disorder, and understanding this dilemma would permit scholars to deduce the neurodevelopmental origins of ASD and the relevance of specific cerebral areas in the development of the symptoms.

Critical evidence for resolving this basic issue comes from longitudinal studies of infants at risk for later diagnosis. Scholars highlight selected studies from the newly emerging literature on infants at familial risk for autism to shed light on this issue (. Despite multiple reports of possible alterations in brain function in the first year of life, often behavioral symptoms do not emerge until the second year. . However, the fundamental question of why the social brain network is differentially affected remains unanswered. This restricted view on social symptoms, overlooking the origins, therefore strongly influences the way ASD is identified and the period of time in which the diagnosis is suggested.

2 Methodology

This paper will address that social impairments in individuals with ASD are occasionally determined by neurodevelopmental and physiological anomalies, such as a dysfunction in the Mirror Neuron System, hypermyelination, hypermetabolism, enlarged amygdala and enlarged cortical area. Moreover, the paper will further discuss the relevance of these abnormalities to the core symptoms of ASD. This explanation will therefore permit a more extensive perspective of ASD, that perceives the development of the core features as a consequence, not a cause, of early neurological impairments.

2.1 Mirror Neuron System

Based on the information presented in section 1.2, researchers are prone to diagnose autism on the basis of social and communication impairment, but this method may overlook anomalies in the patients' levels of perception and cognition. In fact, the results of several studies on children and adults with autism indicated anomalies other than social impairment. More recently, Pellicano and Burr applied a predictive coding account to ASD. According to these researchers, perception is based on the integration of stimulus information and regulation of information based on previous experience. However, previous experience information may distort perception away from the true stimulus characteristics, since it can involve pre-existing opinions that may draw away from a veridical perception of reality . Furthermore, Pellicano and Burr indicated that autistic individuals on average have less consolidated prior information (based on previous experience) compared to the typically-developing population.

Therefore, individuals with ASD are less influenced by previously integrated contextual information, and hence perceive reality more accurately, as their perception is less modulated by experience . Therefore, since the stimuli in autistic patients are differently modulated compared to those in typically-developing individuals, there are more complex features that might lead to altered social behavior. A more complex pattern of interactions between social and perceptual systems may underlie the pattern of symptoms or individual differences observed in this condition.

In particular, scholars revealed that altered recognition of emotional and perceptual stimuli in ASD patients is related to the dysfunction of the mirror neuron system (MSN). Rizzolatti and Gallese have initially identified the MNS as area F5 of the premotor cortex in the monkey and assessed that the neural connections in this region are active not only when an individual is undertaking an action, but also in the process of observing another individual performing a

movement. Therefore, although the neural substrate's microsimulation revealed that F5 is primarily involved in the control of hand movements , activation of the same cortical area in the observation of an action indicated that the MNS is involved in socioemotional processes, and therefore might have a role in ASD.

To confirm that imitation of physical movements and emotional sensitivity are connected to the development of ASD in infants, several studies assessed that physical emulation involves the processing of another individual's state. Therefore, an inconsistency in MNS might lead to an impairment in perceiving emotional conditions. Scholars assessed that the specificity, nature, and pervasiveness of imitation inconsistencies are present in early stages in the development of ASD and therefore imitative and empathic deficits in ASD might arise from a dysfunction in the MNS.

Furthermore, in order to compare the impairments in imitation abilities of individuals with ASD and typically-developing patients, scholars Rogers, Hepburn, Stackhouse and Wehner conducted an experiment on 24 autistic subjects (mean age 34 months). This experiment indicated that autistic subjects experienced significantly more impairments in imitation abilities and oral-facial imitations compared to typically-developing individuals (15 total subjects assessed). The results of this study therefore indicate that since autistic patients have an imitation impairment, they may not process an individual's emotional state accurately. This may lead to an impairment in socio-emotional abilities and can be identified as "social impairment". However, these findings on the role of the Mirror Neuron System in ASD indicate that more specific factors related to perception are the base to understand autism. This therefore indicates a potential dogma of researchers that address ASD, that is whether physiological impairments (as language and social impairment) are a cause or a consequence of neurodevelopmental patterns.

2.2 Hypermyelination

Therefore, researchers further investigated the relation of linguistic impairments and revealed that dysfunctions in language development in ASD is not related to the functioning of the Mirror Neuron System, but instead to hypermyelination: a permanent excess in myelin deposition. Myelin is an insulating layer that forms around nerves . Its role is to permit electrical impulses to transmit rapidly and efficiently along the nerves. . In order to analyze the way that hypermyelination impacts the development of ASD features, scholars have conducted white matter parcellation and divided cerebral white matter into an outer region containing the radiate compartment and an inner area containing sagittal and bridging system compartments . White matter parcellation is a method that analyzes diffusion magnetic resonance imaging fiber to produce a quantitative description of cerebral connections. In particular, this analysis involves fiber clustering strategies that group white matter fibers according to their geometric trajectories. Therefore, this method is relevant in the case of ASD studies, as it permits to analyze the specific location of hypermyelination, and the brain areas involved. The findings suggested that an unexplained white matter enlargement caused increased brain volume in ASD, and scholars reported a similar phenomenon in developmental language disorder (DLD) . As ASD impacts brain connectivity, the white matter that interconnects discrete cortical regions is an area of interest

Scholars recently conducted a review of DTI (Diffusor Tensor Imaging) longitudinal studies that demonstrated increased fractional anisotropy (anisotropy refers to exhibiting properties with different values when measured along axes in different directions) . In particular, positron emission tomography studies (PET) denoted the presence of hypermetabolism (an abnormal increase in metabolic rates) within the internal capsule, corpus callosum, and frontal and temporal lobes of adult subjects with ASD. Since the internal capsule is a white matter structure composed of myelinated fibers, hypermetabolism in this area denotes an enlargement in the number of neural connections. In particular, the role of the corpus callosum is to connect the information from the right and left sides of the brain. Some of the functions of the right side of the brain are logical-reasoning, analytical abilities, and mathematical/scientific competences. Then, the

roles of the left side of the brain include intuition, creativity, imagination, emotion, and face recognition.

Therefore, hypermetabolism in this area leads to an increased number of connections between these areas that can lead to the association of functions that were not supposed to interrelate. As an example, the recognition and understanding of emotional states might be impaired because of an excessive involvement of logical reasoning. This might impact the ability to empathize in the case of individuals with ASD, and therefore leads to altered behaviors in social contexts. In the case of the frontal and temporal lobes, they are relevant when considering ASD since they are involved in processing of memory input and auditory stimuli . Since auditory impairment is a feature of ASD, the role of beta-APP metabolites (substances produced when the body breaks down chemicals) is an area of investigation, since it might contribute to increased white matter in autism . However, other factors such as neuroinflammation (including astrogliosis and microgliosis) may induce white matter enlargement in autism . Researchers of ASD initially discarded this hypothesis as they assumed until 2005 that autism did not involve an inflammatory process. In fact, there were no reports of gliosis (a non-specific reactive modification of glial cells in response to an inflammation in the central nervous system) or replicable inflammation in neuropathologic studies or brain MRI .

However, Vargas employed immunochemistry and cytokine proteins (proteins that serve as molecular messengers between cells) and denoted an increase in CSF level cytokines (macrophage chemoattractant protein 1) and microglia-astroglial activation in the medial frontal gyrus and cerebellum in children and adults with autism. Further studies identified microglial pathology in autism and an increase in primed microglia (associated with chronic inflammation) . The role of microglia is to release inflammatory cytokines that amplify the inflammatory response by activating and recruiting other cells to the cerebral lesion. Therefore, an increase in microglia indicates an altered immune response, which is a prevalent feature of ASD.

Sokol (2019) then further discussed the potential contribution of myelination to increased white matter in autism. Myelin permits rapid synaptic transmission, provides metabolic support, and reduces the cost of neuronal energy . In order to comprehend the origins of myelination and the specific impairments that might lead to ASD, the researcher Simons analyzed the production of myelinating oligodendrocytes during development. Since oligodendrocytes are cells that are primarily responsible for maintenance and generation of the myelin sheath that surrounds axons, the analysis might in fact have been useful to investigate the course of hypermyelination in ASD. In the initial phase, OPCs (Oligodendrocyte Progenitor Cells) generate oligodendrocytes within the subventricular zone of the germinal matrix in the cortex. OPCs then proliferate through the entire nervous system and migrate within the CNS in adulthood where they continue to generate new oligodendrocytes routinely. This generation further impacts the myelination levels . Then, scholars evaluated and analyzed the role of MBP (Myelin Basic Protein), a component of CNS myelin that promotes myelination by deactivating actin . Several studies have then noted increased levels of autoantibodies to MBP in the cerebellum of children with ASD .

These researchers therefore concluded that an increase in MBP would lead to an excessive production of myelin and cerebral white matter, and this hypothesis could potentially explain the mechanism of hypermyelination in ASD. As previously investigated, hypermyelination is responsible for an increased number of connections between neurons. In the case of the specific brain areas analyzed (hippocampus, frontal and temporal lobes), hypermyelination and hypermetabolism could be related to altered emotional responses or processing of auditory and memory stimuli (since these specific brain areas are involved in these functions). In conclusion, these alterations could impact behavioral responses in the case of social situations.

Hypermyelination then further supports the study's idea that ASD social features are a consequence of complex physiological abnormalities, and that the focus of research should be on the significance of these abnormalities to the development of ASD.

2.3 Cortical enlargement

As numerous findings indicated increased white matter levels in ASD, consistent assessment in the neuropathology of ASD then gave insight into the basis of cortical abnormalities in autism. In fact, increased myelination and white matter levels could have potentially led to an enlarged prefrontal cortex . The authors measured head circumferences at birth and during early childhood in a community-based sample of autistic children and adults. The evidence showed that fourteen percent of the autistic subjects experienced macrocephaly (11% of males and 24% of females). Furthermore, the examination demonstrated that macrocephaly was not present at birth in most cases, but rather developed in early and middle childhood as a result of accelerated rate of cortical growth. Lainhart noted that cortical macrocephaly was associated with core features of ASD, though there was no evident correlation with nonverbal IQ, verbal status, seizure disorder, neurological signs and minor physical

abnormalities in autistic subjects. This explains the variability of these traits in autistic patients, as the nonverbal IQ in 2/10 of the subjects assessed is average, compared to 7/10 of individuals assessed in neurotypical patients. Therefore, nonverbal IQ in autistic individuals is more probable to be either below the average or higher than the average range (85-115) .

Regarding the potential volume composition of individuals with ASD and macrocephaly, scholars identified that diencephalon, cerebral white matter, cerebellum and globus-pallidus putamen were significantly larger in autistic individuals . Since the diencephalon is involved in numerous crucial functions in the endocrine system, as for example hormones secretion, an enlargement in this area might signify that hormone release is impaired in individuals with ASD . Recent evidence indicates in fact that plasma levels of Growth Hormone (GH) and ghrelin are altered in autistic patients . The ghrelin hormone, in particular, is involved in neuroinflammatory and apoptotic processes (the processes that lead to cell death) that both have an impact on the pathogenesis of autism . In fact, ghrelin, a 28 amino acid peptide hormone, is mainly secreted in the stomach, promoting the release of growth hormone . Intriguingly, several studies indicate that ghrelin has anti-inflammatory effects against T cells and macrophages in vitro . In addition, studies of the rodent hippocampus have shown that ghrelin is related with higher brain functions, including learning and memory .

Therefore, an altered secretion of ghrelin might be associated with learning impairments and memory. As previously investigated, hypermyelination and hypermetabolism in the temporal lobe are also involved in an alteration of memory stimuli processing. Therefore, these physiological abnormalities (hypermetabolism, hypermyelination, altered secretion of ghrelin) suggest that ASD is an extremely complex disorder, and that its features are a result of multiple irregularities in chemical/neuronal processes. So, this perspective contributes to the idea that the view of ASD as a dysfunction in the social brain is overly simplistic.

To further investigate the role of memory processing in ASD in social situations, researchers particularly note the relevance of working memory in processing complex cognitive information, social cognition, and interpersonal interactions . Koziol (2014) further reported an interrelation between the functioning of working memory in ASD and recognition of language, one of the main traits associated with ASD. In fact, in experimental studies infants with ASD revealed a lack of responsiveness regardless of whether researchers spoke stimulus words during presentation, or whether they instructed the child to execute an action with named objects . Then, researchers conducted standardized tests to capture individual variation, and they typically do not include complete grammatical and morphological constructions . As a result, several contemporary studies showed that autistic language development is delayed compared to typical development . However, studies found that the amount of language development in the subjects was phenotypically and genetically unrelated to autistic traits . In fact, there is a significant heterogeneity in language phenotypes, ranging from nonverbal to superior linguistic abilities.

Scholars hypothesize that the variability in language development in ASD is associated with abnormalities in parietal lobes

development. In fact, findings demonstrated cortical volume loss in the parietal lobes in seven of the 21 autistic patients examined. In contrast, scholars observed cortical volume expansion into the adjacent superior frontal and occipital lobe . Additional abnormalities detected with MRI in the patients included white matter volume destruction in the parietal lobes (3 autistic patients out of 21) and thinning of the corpus callosum along the posterior area observed in 2 patients out of 21.

The researchers further employed the diffusor tensor imaging (DTI) scanning technique to examine the microscopic structure of the corpus callosum in 100 individuals with ASD and 56 controls, in order to provide an estimate of whether the white matter was intact or compromised. Aoki, Osamu and Yasumasa in 2013 found that typically developing infants possess lower white matter integrity in the corpus callosum than the autistic individuals . The role of the corpus callosum in infants with ASD is associated with linguistic abilities as it transfers and integrates information between the hemispheres .

Therefore, cortical enlargement in ASD can also be the origin of altered social behavior, as the areas involved (frontal and occipital lobes, corpus callosum) are responsible for a great variety of functions, such as sensorial information processing, reasoning, motor control and language . Therefore, an alteration in the structures responsible for these functions might lead to impaired social features (as an example, altered reasoning might interfere with social conversations). So, enlarged cortical areas and their implications are further evidence that ASD features originate from complex physiological abnormalities, and support the idea that the view of ASD as a dysfunction in the social brain is over-simplistic.

2.4 Enlarged amygdala

However, impairments in imitation abilities and empathic deficits are also connected to other physiological abnormalities. The researcher Herbert has in fact employed neuroanatomic segmentation of the subject's neuroanatomy using semi-automated algorithms based upon intensity contour mapping (that represent the difference in elevation between successive contour lines) and differential intensity contour algorithms. Neuroanatomic segmentation is a process of extraction of a description of particular neuroanatomical structures of interest that reflect the morphometry (shape measurements) of the subject's neuroanatomy, and is in this case particularly relevant as it permitted Herbert to perform segmentation on coronal images, and manually separate and delineate the brain into white and gray matter regions. Examiners used a univariate general linear model (a model used to map between patterns of brain activity and a measure X, that could be a feature of the stimulus) to assess differences in total brain volume between autistic and control (typically-developing) children .

The results of the coronary sections indicated that the amygdala in autistic children increases in size proceeding rostrally, and it is bordered dorsally by the substantia innominata and fibers of the anterior commissure . Regarding the expectations in terms of behavioral processes in individuals with ASD, scholars acknowledge that the amygdala is primarily involved in the mediation of social interrelations and other cognitive processes in humans. These include face processing , recognition of emotions , enhancement of memory for emotionally significant events and predicting reward values . This evidence therefore suggests that the amygdala might be the primary structure to influence the social impairments in autism spectrum disorder . To further explain how the functions of the amygdala are related to the experiences of people with autism, a study in 2005 showed that when evaluating facial expressions, autistic people show less activation in their amygdala than controls do. This means that autistic individuals do not perceive others' emotional and physical states as typically-developing individuals, and are therefore less able to imitate their features. This finding therefore demonstrates that an abnormality in the amygdala is related to a decreased ability to imitate other people's physical states, and this therefore supports the idea that ASD symptoms are not exclusively related to the social brain.

Moreover, current research on ASD indicates that the malformation of the amygdala is

associated with the emergence of anxiety states. A first study discovered enlarged right amygdala volume to be associated with increased scores on the CBCL anxious/depressed scale in autistic children. However, a second study indicated no correlation between the abnormal amygdala and CBCL measures in patients with ASD . These findings further indicate that features of ASD are complex and variable. In the case of the amygdala and the prevalence of anxiety, the differences in individuals may occur due to environmental factors during the set of the two studies (potential stress factors in the setting of the second experiment that altered the data). Furthermore, experimental data indicates that autistic children that experience an autism-specific form of anxiety (a sensation of uneasiness present in autistic patients) tend to have an unusually reduced amygdala .

Therefore, this physiological difference might have accounted for the differences in results in the first and second studies. The presence of anxiety states in autistic patients might be relevant, as it could impact their behavior within social contexts. Therefore, the disruption of the amygdala and the relation to anxiety states further indicates that ASD symptoms do not exclusively arise from an impairment in the social brain, but rather from physiological abnormalities. These findings therefore further subvert the initial idea that ASD is an impairment in social abilities, and indicate that the focus of ASD research should rather be on the brain areas' morphology.

Other findings that indicated an interrelation between the amygdala and autistic features were in vivo electrophysiology recordings. In Neuroscience, electrophysiology is the measure of the electrical activity of neurons, and in particular the action potential activity . These data revealed modifications in neuronal activity in autistic patients in the basolateral amygdala (BLA) during social interaction behaviors, as increased firing in the BLA is related to alteration in social behavior . Therefore, increased amygdala activity might relate to altered emotional states, excessive responses, joint attention ability and imitation impairments . These alterations all contribute to the development of distinctive features of ASD (Sharp, 2017). In particular, the role of the BLA is to communicate with brain regions involved in cognition, motivation and stress responses including the prefrontal cortex, hippocampus, and nucleus accumbens . Increased activity in the BLA (as the study indicated) could therefore be related to increased stress responses, that might lead to altered responses within social situations.

3. Conclusion

To summarize, this paper investigated the neurodevelopmental impairments in infants with ASD, and analyzed their relevance and influence in social behavior. In fact, the paper incorporated the discussion of the variable nature of symptoms of this disorder, and indicated that since the progression and neurodevelopmental patterns in ASD involve the interconnection of perceptual and social impairments, the view of ASD in terms of an impairment in the social brain is over simplistic. Then, the study provided evidence to address that social impairments in ASD arise due to physiological abnormalities that involve implications in information processing. Therefore, altered social behavior in ASD should be evaluated by research in terms of a secondary consequence due to neurodevelopmental impairments, and not as the primary significance of ASD. The paper clearly addressed this intention and developed this point by considering physiological abnormalities and the specific manner they would interfere with social interrelations.

Initially, the paper considered the role of the Mirror Neuron System (MNS), premotor neurons that respond equally as humans perform an action and as they witness another individual perform the same action . The relevance of the Mirror Neuron System in the progression of ASD is that, since the MNS incorporates internal representations of actions common to a single organism, it leads to an impairment to empathize. In infants with ASD, a dysfunction in the MNS might in fact lead to an absence of recognition of sensations within a social context and therefore to abnormal emotional processing, that might lead to altered social behavior.

Moreover, the paper investigated the role of hypermyelination in the development of ASD features. In particular, the study addressed positron emission tomography (PET) studies

that denoted the presence of hypermetabolism (an abnormal increase in metabolic rates) within the internal capsule, corpus callosum, frontal and temporal lobes of adult subjects with ASD . The significance of hypermetabolism in these brain areas is that it leads to an increased number of connections between neurons in specific regions . This can supposedly lead to altered interrelations between cognitive functions, that could alter behavior in social situations (the paper proposed the example of an excessive logical reasoning that could impede social relations).

Furthermore, the study investigated the consequences of cortical enlargement and macrocephaly on ASD symptoms. These abnormalities are connected to hypermyelination, as increased white matter levels in ASD could potentially have led to an enlarged prefrontal cortex. In particular, the diencephalon, cerebral white matter, cerebellum and globus-pallidus putamen were significantly larger in autistic individuals . Since the diencephalon is mainly responsible for the secretion of hormones, the paper specifically investigated the altered secretion of ghrelin, a hormone related with higher brain functions, as learning and memory . The role of working memory in social interrelations is fundamental, as it permits individuals to recognize previous experiences, memories and therefore create an emotional connection.

In order to provide further evidence for emotional impairments in individuals with ASD, the paper addressed the altered development of the amygdala. The amygdala is primarily involved in the mediation of social relations and other cognitive processes in humans, such as face processing, recognition of emotions and enhancement of memory for emotionally significant events . Therefore, an increase in volume of this structure might contribute to the attainment of positive and negative symptoms in ASD. Since the amygdala mediates the cognitive patterns for face processing and recognition of emotions, the study also noted that social impairments, communication difficulties and auditory disturbances might also be associated with a dysfunction in working memory, a temporary storage system related to attentional control.

In conclusion, this paper incorporated the perspective that neurodevelopmental impairments in infants with ASD involve an indissoluble interrelation and influence of perceptual, social and linguistic disturbances that contribute to a peculiar and individualized progression of the condition, as supported by experimental data. The objective of this paper was therefore to address these neurodevelopmental abnormalities, in order to explain their relevance in the case of social impairments. Therefore, the paper's intention was to provide evidence and reasoning that the perception that ASD features as a result of an impairment in the social brain is overly simplistic and ineffective in addressing the complexity of ASD. In particular, the paper achieved this by providing specific evidence of how the MNS, hypermyelination, cortical enlargement and enlarged amygdala volume led to altered social behaviors. Moreover, this study was efficient to the research field in ASD in terms that it introduced the readers to understand the origins of the essential features of autism spectrum disorder and associate the symptoms to impairments in specific cerebral areas.

3.1 Available research, limitations and potential improvement:

Furthermore, since available research often considers ASD in terms of an impairment in the social brain, it ignores the fundamental interrelation between perceptual systems and core features of ASD. As a consequence of this over simplistic consideration of ASD, current research frequently does not address individualized neurodevelopment in autistic patients or the association of autistic features with specific cerebral areas. In fact, a simplification of the impairments in ASD leads to an absence of focus in details that determine the development of individual features in patients, and this is a fundamental aspect in order to understand the disease and identify the causes of individual variability. However, methodological issues in available research might be remediated by conducting specific experiments that differentiate within a single group of autistic patients, in order to clarify that ASD is not a uniform disorder, and that because of its complexity and prevalence among the population (16.8/1000 autistic children in the US) it should be addressed meticulously.

Furthermore, as the paper indicated, researchers usually consider physiological impairments as separated and distinct, instead of analyzing the interrelation with other dysfunctions (as language developmental impairment and hyper acute hearing). In fact, since the paper concludes that numerous features in ASD are not determined by cognitive impairment, a more accurate and precise method to address this disease might prevent the divulgation of false information and prejudices in this disease (as the perception that ASD patients have a lower IQ). In particular, this paper is therefore beneficial to society as it introduces the readers to the perspective that the vision of ASD primarily as a cognitive and social disease is not accurate and over-simplistic, and so this perception addresses the complexity of ASD and the necessity to understand its origins and complexity.

The paper then proposes a new, more accurate perspective of ASD, and incorporates a more effective definition of this disorder, that includes the evidence investigated. ASD is therefore, more accurately, "A developmental disability, that is caused by alterations in neurodevelopmental patterns. Brain differences such as the functioning of MNS, hypermyelination, enlarged cortical area and enlarged amygdala volume can lead to complex and individualized symptoms that range from language impairments to altered social behavior".

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