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Structural and Functional Brain Imaging in Autism Spectrum Disorders

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1. Introduction

Damasio and Maurer (1978) proposed that autism occurs due to structural and functional abnormalities at mesolimbic (dopaminergic) brain areas (ventromedial prefrontal cortex, medial temporal lobes, limbic striatum and thalamus), as damage to these brain regions can cause features of autism (impaired social and emotional functioning, stereotyped behaviours, mannerisms and obsessionality) [1]. This hypothesis is supported by studies in animals and human [2]. Areas outside the limbic system, such as the parietal lobes, are associated with autism. The lack of attention about understanding significant social cues in autism is similar to negligence and attention deficiency in the parietal lobe damage [3]. In addition to structural abnormalities in the cerebellum, another aetiological factor associated with autism is functional deterioration in cerebellar-cortical serotonergic pathways due to acquired cerebellar lesions, which can lead to impairment in social and emotional behaviour and impairment in executive functions and obsessions [4]. Brain imaging techniques are used in the investigation of these proposed structural and functional changes within autistic spectrum disorders.

2. Magnetic Resonance Imaging (MRI) studies

2.1. Head circumference and total brain volume

Atypical head circumference growth curve in the first two years of life is a phenotypical risk indicator for autism [5, 6]. In the case of autism, head circumference that is normal or near normal size at birth follows an accelerated growth pattern at about four months [7, 8]. It has been shown that 37% of autistic children between the ages of two and four meet the criteria for developmental macrocephaly [9].

In a follow-up study by Dawson et al. [2007], involving 28 children with autism from birth up to 36 months, has been shown accelerated growth of head circumference and previous studies have indicated that repeatedly [7]. This head circumference growth pattern occurs independently from autistic regression [10]. In autism, head circumference growth rate has been compared to the period from birth to 12 months; after the 12th month, these findings shows that unusually rapid head growth is limited to the 1st year of life [11]. Many studies have shown that the behavioural symptoms of autism become easily understandable during the first eight- to 12 months. [12, 13]. Therefore, the onset of accelerated head circumference growth between four- and 12 months partially leads to significant behavioural symptoms and an overlap between these symptoms. Interestingly, Dawson et al. reported a slowdown in the rate of head circumference growth in the next 12 months to be associated with a loss of or deceleration in the acquisition of new skills. Another study [7] reported that rapid growth in head circumference between birth and the 12-month period, followed by a slowdown in growth after 12 months to be a risk indicator for the development of autism symptoms at 24. months [14].

Magnetic resonance imaging (MRI) is used in order to measure the size and shape of brain structures. The results of research conducted using the MRI method has been consistent with results yielded by head circumference studies in terms of autism. Sparks et al. (2002) reported that children aged three to four with autism had a significantly larger total brain volume compared to normally developing peers or developmental delayed peers [15]. Another study [16] showed that 90% of children with autism spectrum disorders aged between two and four had larger brain volumes than usual. Using the MRI method, the size of the brain among autistic children aged between one-and-a-half and four years old was shown to be abnormally increased (about 5-10%) [8, 15, 16]. Courchesne et al. [16] proposed that an increase in brain volume among children with autism in younger age groups tended to decrease front-to-back (maximum at the frontal lobe, with the occipital lobe growth showing the least). However, it has not been clearly determined whether the growth pattern of young children (four years old) is permanent or not among older children and adolescents [16, 17]. It has been found that brain size in autistic children at birth was 13% smaller than the control group, reached a 10% larger size at the age of one and was at the onset of puberty only 2% larger than the control group; these results were obtained by Redcay and Courchesne [6] following the evaluation of head circumference and brain weight using MRI brain volume and autopsy studies. It has been reported that in a large proportion of individuals with autism in adulthood, the brain volume did not differ from healthy controls [6].

The hypothesis has been put forward that unusual brain growth curves lead to an abnormal pattern of changes in cortico-cortical connections. Changes in the brain during development adversely affect the development and persistence of growth curves among short-and long-haul connections. It has been suggested that the growth rate of brain size is less than the normal rate where developmental disorders are concerned, which leads to an increase in long-haul connections. Moreover, if brain size is larger than normal in developmental disorders such as autism, leads to a reduction in long-distance structural and functional connections [18].

2.2. White and grey matter changes

Abnormal brain growth in autistic children primarily stems from cerebral white and grey matter. However, Herbert and colleagues asserted that this growth originates from the disproportionate increase of white matter, not grey matter [19]. Abnormalities in white matter volume can be linked to differences in axonal density and organization, myelination abnormalities or the abnormal proliferation of glial cells [20]. In two different studies with autistic children (between one-and-a-half and four years old) has been shown to significantly increase white matter rather than grey matter [8, 16]. However, it is not clear whether this increase in older children and adolescents is permanent or not [21, 22]. Even though the growth rate of grey matter has been shown to be smaller than that of white matter in early life, it is reported to be persistent in adulthood [16, 21].

Diffusion tensor imaging (DTI), also called diffusion tensor magnetic resonance imaging (DT-MRI) is a method used to assess the integrity of white brain matter. One of the parameters determined by this method, which identifies the movement of water molecules in the brain, is fractional anisotropy, which reflects asymmetry in fluid movement [23]. High fractional anisotropy values reflect a more intense or more proper structure of the brain. Two separate studies in children and adults with autism have shown a decrease in cerebral white matter using fractional anisotropy. A decrease in the temporal cortex among adults with autism has also been indicated using fractional anisotropy [24], as well as on the ventromedial prefrontal cortex, anterior cingulate, temporal lobe, amygdala and cortical and along subcortical regions containing the corpus callosum in autistic children and adolescents [25]. The most consistent findings concerning decreases in the brain using fractional anisotropy has been found for the corpus callosum [25, 26]. In another study, a 14% reduction in the size of the corpus callosum was shown, which is associated with decreased fractional anisotropy on genu and splenium [27]. In contrast to these findings, Ben-Bashat et al. [28] observed an association between increased fractional anisotropy values and white matter maturity in autistic children at younger ages. These findings have been associated with abnormal increases in brain volume during the early ages of children with autism [28].

A reduction in fractional anisotropy alongside an increase in white matter volume may reflect abnormal connections in the form of increased non-myelinated white matter connectivity. Extremism in the weak links due to the activity of immature myelination may adversely affect information processing. A decrease in white matter integrity reduces the brain's functional integration, a factor that has served as a basis of current theories about abnormal connections [20].

Recently, corpus callosum abnormalities have been associated with the theory of insufficient common functional connectivity (underconnectivity) in adults with autism [29]. Functional brain imaging studies have shown a decrease in the activation of the synchronization of many brain regions concerning different functions like social content interpretation [30], working memory [31], executive functions [29] and visual imagery [32]. These findings have led to the hypothesis that insufficient cortical connections may be associated with autistic disorders [33]. The reduction of white matter structural integrity in the context of autism may cause differences in functional connectivity, while theory of mind deficits [34] within the autism context can potentially be responsible for weak central coherence as well as social and cognitive symptoms [26].

2.3. Cerebral cortex

The largest and most consistent increase has been reported for the frontal lobe, despite a grey and white matter increase having been in the frontal, temporal and parietal lobes in several studies [21, 35, 36]. In autism, there exists an opposite growth rate from the norm following the period of accelerated growth in cerebral and cerebellar regions. For example, it has been shown that frontal lobe grey and white matter volume increase by 19% at two- and four years of age and 46% between the ages of nine and 12 in normal children, while in autistic children, these rates are 1% and 14%, respectively [36, 37].

In autism, abnormal asymmetry patterns in the frontal and temporal regions associated with language have been observed. Herbert et al. has shown that lateral inferior frontal cortex language (Broca's area is associated with pars opercularis) has reverse asymmetry in children with autism. It has also been shown that autistic men have a 27% larger volume in the right side of the frontal language region, compared to controls' 17% larger volume on the left side of the frontal language region. In addition to these findings, planum temporal asymmetry has been reported to be fairly different between the two groups; autistic males showed a 25% left dominance, while this rate was only 5% for the control group. Differences in terms of right-sided symmetry at the supramarginal posterior gyrus have been identified between autistic (39% greater) and control groups (greater than 2%). Another asymmetry region is the posterior superior temporal cortex (greater at the right in controls) associated with Wernicke's area, although this is not statistically significant. Structural abnormalities like abnormal asymmetry observed in autistic males in language regions may be associated with abnormalities in language skills [38].

2.4. Cerebellum

The cerebellum plays a role on coordination between voluntary movements and complex movements. Data obtained from animal and human studies have shown that the cerebellum may play a role in cognitive processes, in language use and emotion [39, 40]. Several MRI studies have determined that when autistic patients in different age groups are compared with a control group, there is a significant increase in cerebellar volume. This increase in cerebellar volume function is usually proportional to the total brain volume [41]. Different from other studies, in a study with autistic children below the age of three (18-35 months), there was no difference in terms of cerebellum size [8]. In contrast to the increase in the total volume of the cerebellum, some autistic children showed a relatively small volume vermis [42, 43]. Specifically cerebellum region is vermian lobules VI-VII that reported about volume reduction in autism [16]. Vermis hypoplasia in autism is associated with deficits in automatically attention directing and research behaviour. [37]. Courchesne et al. [44] suggest that autistic disorders have two subtypes associated with cerebellum pathology: [1] vermis hypoplasia and [2] vermis hyperplasia [44]. However, no differences have been reported concerning IQ levels being affected by vermal volume in different study groups matched for intelligence quotient (IQ) [45]. In addition, it has been suggested that increases in the volume of the frontal lobe is associated with a reduction in cerebellar vermis volume. It has been shown that patients with normal vermis volume have normal frontal cortex volume, while patients with vermis

hypoplasia have greater frontal cortex volume. Abnormal neuronal signals from subcortical structures can affect the development of the cerebral cortex and increased neuronal activity can in this way lead to growth among neuronal elements. Therefore, it has been claimed that abnormal neuronal activity in the cerebelloretinal-thalamocortical projections (possibly associated with a reduction in inhibitor signals as a result of the premature reduction in the number of cerebellar Purkinje cells) can lead to developmental failure in the frontal lobe and in the other input regions [37]. These volume changes are not specific to autism and are also commonly found in various developmental and psychiatric disorders [43, 46]. In autism, hypoplasia at the structure of the brain stem has been identified by Hashimoto et al. [47] in a study that evaluated cerebellum and brain stem structures.

2.5. Amygdala

Amygdala volume shows an increase in proportion to the total cerebral volume in children with autism. Sparks et al. [15] found that autistic children (aged between 36-56 months) had an abnormal amygdala growth rate (13-16%). It has been reported that an increased amygdala volume (without increasing total cerebral volume) at three years of age is associated with severe progress in children aged between three and six years old [48]. An increase in amygdala volume has been associated with more severe anxiety [49] and with poor communication skills and social skills [48]. In a study with autistic males aged between the eight and 18 compared with a healthy control group, , it was found that amygdala volume had grown up to 15% between 8-12 age period, but in the period between the ages of 13-18 were found to be any difference at the amygdale volume. Amygdala volume among men with healthy development increased by about 40% between the ages of eight and 18; however, this was not the same for males with autism. These findings are important for the realization of amygdala volume initially being larger than normal in autistic children, and also important for indicate that autistic children have not age-related increase at amydala volume in the preadolescence period like healthy controls [50]. These findings are supported by some MRI studies, including those pertaining to autistic adolescents and adults where results showed an amygdala volume not significantly different or smaller [51] than those in control groups. It has been suggested that amygdala abnormalities in autism spectrum disorders play a central role in social symptoms [52].

2.6. Hippocampus

In autism, findings are contradictory regarding hippocampal volume. A MRI study by Schumann et al [50] showed that autistic children had an increase of hippocampal volume and this increase persisted during adolescence. A study that included autistic adolescents and young adults reported a decrease in hippocampal volume [51]. Where autism is concerned, various studies have shown no significant differences in hippocampal volume [53, 54].

2.7. Corpus callosum

The corpus callosum is responsible for transferring cortical and subcortical information between homologous regions of the cerebral hemisphere. It is associated with bilateral sensory

and motor integration such as bimanual motor coordination, visual attention scrolling and procedural memory processes. In autism, especially in the posterior region of the corpus callosum, a volume decline was noted in [55]. These findings are associated with interhemispheric weakness in autism [20].

2.8. Caudate nucleus

It has been shown that the caudate nucleus volume is increased in autism. This increase may be associated with observed repetitive and ritualistic behaviour in adolescents and adults with autism [56, 57].

3. MR Spectroscopy (MRS) studies

MRS techniques are used to distinguish between patients with active neurodegenerative process. N-acetyl groups, bearing phospholipids, choline, creatine (Cr), phosphocreatine, lipid and lactate levels can be measured by proton MRS. N-acetyl aspartate (NAA) is a marker of neuronal integrity and lower NAA/Cr ratio is associated with neuronal loss or damage. Choline reflects the integrity of cell membranes and increased levels of choline or choline/Cr ratio indicate increased cell destruction, the destruction of myelin, gliosis or inflammation. Creatine is sometimes used as a standard for relatively fixed elements of cellular energy metabolism in the brain. Creatine signals reflect glial and neuronal cell density. Myo-inositol plays a role in neuronal homeostasis [58].

It has been determined that NAA, creatine and myo-inositol concentration decrease significantly in children with autism spectrum disorders between the ages of three and four [59]. In several studies, it has been shown that NAA concentrations significantly decreased in the amygdaloid-hippocampal region, cerebellum and Brodmann's [41-42] areas (primary auditory area) in children and adults with autism [60, 61]. These findings can be associated with neuronal loss or functional immaturity in these regions, which play an important role in cognitive and emotional processes [60].

Levitt and colleagues [62], in a study involving autistic children, showed that choline and creatine levels increased in the head of the right caudate nucleus, while choline levels decreased in the left inferior anterior cingulate cortex. In the same study, decreased levels of creatine were found in the left body portion of the nucleus caudatus and right occipital cortex. These findings were associated with changes in membrane metabolism and energy metabolism in these regions. In a different study, NAA and glutamate/glutamine (Glx) levels were found to be significantly decreased on the grey matter which involves many cerebral lobes in a common area. at children with autism. These findings have been associated with neuronal integrity and dysfunction, which spreads over a wide area at glutamatergic neurons in autistic children [63]. In some MRS studies, no significant changes have been found in metabolite levels in white matter [63, 64].

Vasconcelos et al. [65] reported that myo-inositol and choline levels were increased in the anterior cingulate cortex and left striatum, in contrast with previous studies that reported no significant changes in NAA levels.

When evaluated, these molecular indicators, amendments and increased white and grey matter volume have been believed to reflect changes in a) the number and size of neurons and glia; b) in the development of axons, dendrites and synapses; c) axodendritic pruning; d) programmed cell death; e) the occurrence of the cortical column; f) changes in myelination [66].

4. PET and SPECT studies

In the context of autism, functional neuroimaging studies were performed at rest or during various activities. Injected or inhaled radiopharmaceuticals were applied in positron emission tomography (PET) methods. Dissolved radioactive isotopes emit positrons that are detected by the PET camera. Some PET methods measure blood flow, while others measure cerebral metabolic rate [67].

In PET studies performed with autistic children at rest it has been determined that a decrease in blood flow occurred in the temporal lobes. Functional dysfunction in the temporal lobe was concentrated within the auditory associative cortex and superior temporal sulcus. Functional impairment in the auditory cortex of autistic children may explain initial diagnoses of going deaf and experiencing serious deterioration in communication. It has been suggested that functional deterioration in the superior temporal sulcus might explain emotional and cognitive components of autistic symptoms indirectly, due to these being closely linked with the frontoparietal and limbic regions of the multimodal association [68].

A PET scan study conducted with autistic adults found a wide increase in glucose utilization in the brain at rest [69]. Despite these findings, different results during the performance of different tasks have also been found. Haznedar et al. [70] reported a decrease in glucose metabolism in the anterior and posterior cingulate gyrus during a verbal learning test for autism and Asperger's syndrome [70]. Similarly, in a different PET study, it a decrease in relative glucose metabolism was determined for frontal lobe medial/cingulate areas during verbal memory operations. The same study showed an increase in relative glucose metabolism for the occipital and parietal regions [71].

Neuronal activation areas associated with auditory cortical processing was also examined using the PET method. In a study by Boddaert et al. [72], activation in the superior temporal gyrus was observed while listening to the complex speech-like sounds of adults with autism, which was similar to the control group [72]. However, while this activation was observed for the right superior temporal gyrus in the autistic group, the opposite pattern was observed in the control group. It has been shown that although there is less activation at the left temporal areas, there is pronounced activation patterns at the right middle frontal gyrus among autistic individuals [73]. In a different study involving children with autism, lower activation patterns in the left superior temporal gyrus (in fields related with auditory) have been identified when

listening to speech-like sounds, similar to what was found for adults. According to these findings, it is suggested that abnormalities in auditory cortical processing are associated with defects in language skills and that they result in a poor response to the voice among those with autism [72].

A PET scan study with high functioning autistic adults which practiced during instruction the tasks of theory of mind identified decreased activity in the medial prefrontal cortex, bilateral superior temporal sulcus and basal temporal area (right temporal tip and left fusiform gyrus adjacent to the amygdala), which are components of the mentalization network [30].

In several PET studies, the association between neurotransmitter systems and autism has been investigated. In a PET study with autistic children, Nakamura et al. [74] showed a reduction in the binding capacity of serotonin transporter protein throughout the entire brain. In autistic individuals, decreased serotonin transporter protein binding capacity in the anterior and posterior cingulate cortex has been associated with deterioration in social cognition, similar to decreased serotonin transporter protein binding capacity in the thalamus being associated with recurrent and obsessive behaviours. It has also been reported that dopamine transporter protein (the dopamine transporter = DAT) binding correlates in the opposite direction with serotonin transporter binding protein in the orbitofrontal cortex. These findings support the relationship between autism and serotonergic/dopaminergic systems.

The single-photon emission tomography (SPECT) method provides information on regional cerebral blood flow and provides a cerebral blood flow map according to the regional cerebral glucose metabolism of the brain. A decrease in regional cerebral blood flow reflects hypome-tabolism and consequently reflects damage in brain functions [75].

In accordance with several PET studies, reduced regional blood flow in the temporal cortex [76, 77, 78], frontal cortex [76], parietal cortex [77], occipital cortex, thalamus, basal ganglia [79] and cerebellar hemisphere [80] has been observed in SPECT studies with autistic children and adults. In a study of children and adolescents with high-functioning autism, evidence has been provided that the presence of abnormal neuronal network lateralization. In this study, it has been found lower blood flow at the right angular region than left angular region and also lower blood flow at left pericallosal, thalamic and hippocampal regions than right pericallosal, thalamic and hippocampal regions [81].

A decrease in regional cerebral blood flow in the bilateral insula, superior temporal gyrus and left prefrontal cortex has been reported by Ohnishi et al. in a SPECT study with autistic children. Autistic symptoms are associated with perfusion patterns at the limbic system and the medial prefrontal cortex. In this SPECT study by Ohnishi et al., support is provided for impairments in communication and social interaction that is thought to be related to the theory of mind deficits associated with perfusion changes in the medial prefrontal cortex and anterior cingulate gyrus, as well as the obsessive desire for sameness, which is associated with the right medial temporal lobe. Regional blood flow patterns are important in terms of indicating the possible location of abnormalities in brain function that underlie abnormal behaviour within the context of autism [82].

A SPECT study that investigated the relationship between neurotransmitter systems and autism showed a reduction of serotonin transporter protein binding capacity in the medial frontal cortex in accordance with PET studies in this area; however, DAT binding capacity did not differ in autistic individuals [83].

5. Functional MRI (fMRI) studies

According to the SPECT and PET methods, the fMRI method has superior spatial and temporal resolution, is not an invasive procedure and does not involve ionizing radiation [67].

Autistic individuals have corrupted cognitive processing, both in a self-referential and other-referential context. Lombardo et al. recently conducted an fMRI study focusing on when autistic disorder adults made reflective "mentalizing" (reflective mentalizing) or physical judgments about themselves or the Queen of England. In another recent study, healthy individuals were compared to autistic patients for self-other reference tasking. The results revealed that autistic patients responded more to other mentalization as opposed to self-referential mentalization at the middle cingulate cortex, while these two operations respond equally at the ventromedial prefrontal cortex [84]. This finding is consistent with earlier study results that reported decreased activity in the middle cingulate cortex while high-functioning autism making their decisions the social condition [85]. These atypical responses only occur in areas that primarily process self-knowledge and do not affect the area that primarily responds to other-referential information. The neural self-other distinction at the ventromedial prefrontal cortex is closely associated with the degree of social impairment in autism in early childhood. It has been shown that individuals whose ventromedial prefrontal cortex can make the obvious distinction between self- and other mentalizing have had the least social disruption during early childhood, while individuals whose ventromedial prefrontal cortex makes little/ any distinction between self- and other mentalizing are more likely to have experienced maximum social disruption during early childhood. These findings are important in terms of showing the atypical organization of neural circuits, primarily in self-information encoding, in the context of autism [84].

Brain regions such as the medial prefrontal cortex, rostral anterior cingulate, posterior cingulate and the precuneus have high metabolic activity during resting states. Internally managed processes (self-trial thought and higher-level social and emotional processes) continuously activate the medial cortical network, which includes the medial prefrontal cortex, rostral anterior cingulate, posterior cingulate and precuneus. This metabolic activity is suppressed during tasks that require cognitive effort. The suppression during activity, which is observed as "deactivations" using the fMRI method, is indicative of interrupted mental activity during rest. Kennedy et al. [86] showed that this deactivation does not appear in autistic individuals. These findings have been associated with the absence or abnormal mental processes in autism. The absence of this deactivation in autism has shown abnormalities in internally managed process and these findings have been suggested to be associated with social and emotional deficits regarding autism.

Individuals with autistic disorders and Asperger's syndrome experience abnormalities in the perception of faces. It has been shown that healthy individuals have increased activation in the fusiform gyrus during face processing and increased activation in the inferior temporal gyrus during processing object activation, while individuals with autistic disorders or Asperger's syndrome have less activation in the right fusiform gyrus and more activation during face discrimination (this is not the case for objects). The autism group tends to use more of the inferior temporal gyrus during face processing when compared to controls. This finding shows that they process faces like objects [87]. The basic zone associated with face processing in healthy individuals is the lateral fusiform gyrus (called as "fusiform face area"). It has been reported to decrease activation in the fusiform gyrus and other areas associated with processing face detection such as the inferior occipital gyrus, superior temporal gyrus and amygdala in individuals with autism during face detection tasks. It has also been reported that autistic individuals use different neuronal systems for seeing faces and have individual-specific, scattered activation patterns when compared to normal individuals [88].

In a fMRI study with high-function autistic adults, detected decreased activation in the fusiform gyrus during the identification of the person who has been seen before, in contrast to previous studies. Social dysfunction in autism has been associated with common abnormalities observed in the social brain network. The severity of impairment in social functioning is associated with a reduction in the connections between fusiform face area and amygdala and also increment in the connections between fusiform face area and right inferior frontal cortex.. This result indicates neuronal abnormalities in the limbic system to be associated with a prevalence of poor social impairment in autism [89].

Neuronal activation fields associated with working memory have been studied using fMRI methods. Luna et al. [90] reported lower activation in the dorsolateral prefrontal cortex and posterior cingulate regions during spatial working memory. Koshino et al. [91] showed that autistic individuals had lower activation in the inferior left prefrontal area (verbal processing and working memory-related) and right posterior temporal area (associated with theory of mind) during a working memory task that used photographic facial stimuli. The same study noted activation in the different division of the fusiform area in autistic individuals. It has also been shown that fusiform activation is in the lower and lateral division and also displaced from the typical region activated during face detection, compared to the region activated during object detection in an autistic group. These findings support the notion that face processing in autism analyse face characteristics as an object in terms of humanitarian significance. Abnormal fusiform activation showing a lower-level link with the frontal area is associated with the presence of the neuronal communication network, which has reduced synchronization [91].

A study conducted by Müller et al. [92] determined activation on opposite sides of the primary sensorimotor (the most powerful) cortex, premotor and/or supplementary motor areas during a simple finger movement task completed by healthy individuals in contrast, autistic groups showed no significant activation. [92]. Autistic individuals showed activation in regions that are not associated with these tasks, e.g., the superior parietal lobe and posterior neuronal precuneus.

Over time, neural outputs decrease in response to recurrent stimuli. This adaptation is believed to be associated with plasticity and learning. In the case of autism, it has been shown that there is no neural adaptation in the amygdala in response to neutral facial stimuli. In the case of autism, abnormal sustained amygdala stimulation in response to social stimuli is believed to be associated with social disruption, as observed in [89] (activation levels in the amygdala never reach the maximum level in healthy individuals).

The mirror neuron system (the pars opercularis in the inferior frontal gyrus) is active during observation, imitation and understanding the actions of others. Therefore, it is considered to provide a neuronal mechanism for a complete understanding of the purpose and actions of others. When on the move, along with the limbic system, it is thought to mediate an understanding of emotions or facilitating sympathy with someone else's feelings. Thus, the feelings of others are perceived as real and not simply at a cognitive level, but understood at an emotional level (empathy). It has been shown that there is no activation of mirror neurons on the pars opercularis during the observation or imitation of emotional expression in children with autism. Activation in this region is inversely proportional to the severity of the symptoms shown. Early functional defects that emerge in the mirror neuron system have been suggested as the primary cause of social and emotional deficits in autistic disorders [93].

In FMRI studies with autistic individuals, a significant reduction has been revealed in the timing of the activation or synchronization between cortical areas associated with memory functioning, language, problem solving and social cognition. These findings support the hypothesis referred to as "insufficient functional connectivity" (underconnectivity) within and between neocortical systems [93].

6. Conclusion

In autism, common neuroanatomical defects in the early stages of brain development such as hypoplasia at specific areas and excessive cerebral growth leads to abnormalities in the development of functional systems. If the developing brain is traumatized by genetic or environmental factors, the functional organization and hence, functional activities, are disrupted. Abnormal functional activity and organization affect different structures in different ways, because autism is associated with neural defects in many types and locations. Many structures that have been shown as affected by autism can in turn affect the different functional areas of cerebral and cerebellar organization, as these structures function as intermediaries for the development of different types of neural defects. Therefore, more obvious abnormalities have been observed in some functions [94].

Functional imaging studies pose various limitations, for example, these studies include patients with autism and Asperger's syndrome together so study groups have heterogeneous diagnostic measurement. It is proposed that in future studies, working groups can be created to be a homogeneous diagnostic measurement comprised of different age groups and different levels of mental development when testing different tasks.

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