

# Neuroimaging Findings in Autism: A Brief Review

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## Abstract

**Objective:** Many structural and functional neuroimaging studies have investigated the neuroanatomical changes and possible pathophysiological pathways in autism. In this review the objective was to assess, with an integrative perspective, recent neuroimaging studies that have contributed to the explanation of the possible pathophysiological pathways in autism.

**Method:** Relevant attainable studies published between 1997 and 2007 were included in this retrospective literature review. The PubMed search engine and the keywords, autism, autistic spectrum disorders, neuroimaging, computerized tomography, magnetic resonance imaging, functional magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, single photon emission computed tomography, and diffusion tensor imaging were used.

**Results:** Structural neuroimaging studies reported an increase in total cerebral volume, both in grey and white matter, mostly in the frontal, temporal and parietal lobes. These global volumetric changes are suggested to indicate a diffuse disturbance in neural networks during early development. In functional neuroimaging studies, activation abnormalities were observed in the temporal lobes and amygdala, which are involved in language and social cognition. An increase in visual activity cortex was also reported.

**Conclusion:** Clinical observations and results from neuroimaging studies were gathered to hypothesize and explain the pathophysiology of autism. Yet, it is still very early to conclude with certainty the neurobiological process responsible for autism.

**Key Words:** Autism, autistic spectrum disorders, neuroimaging, neurobiology

## INTRODUCTION

Autism is a life-long neuropsychiatric disorder that begins early in life and presents with deficits in social relationships and communication, as well as delayed cognitive development. Since autism was described as a disorder caused by family and environment related factors half a century ago, it has been understood that autism is frequently accompanied by mental retardation, epileptic disorders, and EEG abnormalities (Eigisti and Shapiro, 2003). A large number of genetic studies, in addition to anatomical, physiological, histological, and functional studies about the brain have provided impor-

tant data showing that this complicated syndrome is a neurobiological disorder (Lainhart, 2006). Despite the neurobiological findings, it is not yet possible to say that the underlying brain regions or mechanisms have been identified.

During the time since Kanner defined autism many structural and functional brain imaging studies have been conducted to investigate the neuroanatomical abnormalities in autism. These imaging studies have been very important regarding efforts to explain the neuroanatomy and pathophysiology of autism. Nonetheless, while evaluating neuroimaging studies of autism, one

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must consider that the results come from studies of varying design and that the results have been explained by different pathophysiological mechanisms; therefore, an integrative evaluation of their results is necessary. The purpose of the present review was to provide an integrated overview of recent neuroimaging studies. We searched PubMed for relevant studies using the keywords autism, autism spectrum disorders (ASD), neuroimaging, computerized tomography (CT), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), single-photon emission computerized tomography (SPECT), and diffusion tensor imaging (DTI). As the aim was to review studies of the last decade, we searched for studies published between 1997 and 2007 that included a control group or a homogenous and large sample, matched the control and sample groups, and those that were considered pioneering in the field. Furthermore, the Turkish literature was searched using search engines other than PubMed. Those studies' data and the Turkish data were included in the study.

## **STRUCTURAL BRAIN IMAGING IN AUTISM**

The finding that autistic children have larger head circumferences than those of healthy children led to subsequent structural brain imaging studies (Courchesne et al., 2004). In a Turkish sample of 40 children with autism evaluated with EEG, CT, and MRI, 53% were observed to have EEG abnormalities, and cranial pathology was observed in 22% and 24% of the children according to CT and MRI, respectively (Yorbik et al., 2001). Considering the findings on head circumference and post-mortem studies, initial structural neuroimaging studies focused on the total volume of the brain, then individual brain regions were evaluated in order to identify the brain structures that cause increased brain volume. Structural brain imaging studies and their fundamental findings are summarized in Table I.

### **Total Brain Volume**

Ever since Kanner's definition of autism, larger head circumference in autistic children has been observed as a frequent finding in neuroimaging and post-mortem studies (Courchesne et al., 2004). In a case-controlled cohort study by Bolton et al. (2001), male babies with macrocephaly aged between 5 and 12 months were 5 times more likely to be diagnosed with autism after the age of 1 year than babies with normal head circumference. Brain imaging studies show the relationship between

head circumference and brain volume, both in individuals with autism and normal individuals (Bartholomeusz et al., 2002). Therefore, brain volume studies using both head circumference and imaging methods are used as source of information about total brain volume.

In head circumference follow-up studies, while the head circumferences of autistic children were within the normal range at birth, acceleration in the increase of head circumference was observed towards 1 year of age. In 14%-30% of these children an accelerated growth in head circumference occurred through the first year of life and reached the limits of macrocephaly ( $> 97P$ ), while in 20%-95% of these children a head circumference 10% (mean) larger than that of normal controls was observed. These findings might indicate a developmental disorder in brain regions responsible for higher cognitive functions develops later in life, such as the frontal cortex (Fidler et al., 2000; Miles et al., 2000; Courchesne et al., 2001). After infancy the accelerated growth of head circumference gradually slows down, even falls behind head circumference growth in normally developing children. The difference in head circumference and growth rate in autism loses its significance with the onset of childhood. In adolescence and adulthood there are no significant differences in autistic cases and healthy individuals in terms of head circumference and brain volume (Lainhart et al., 1997; Bolton et al., 2001). Although it is not a specific finding, it is striking that the accelerated growth in head circumference begins before the onset of clinical symptoms. Nonetheless, the importance of accelerated head growth in autistic disorder, whether it is a primary cause of the disorder or it develops secondary to the pathology, are questions that remain to be answered. On the other hand, during the evaluation of these results it should be noted that in the early years of life head circumference and brain volume could be influenced by many different genetic and environmental factors.

In the following brain imaging studies, total brain volume, which was normal at birth, was observed to increase in the cortical white and grey matter between 2-4 years of age, and total brain volume was 6%-10% greater than that of normal controls, but in the following years (age 6-16 years) there was a decrease, even halt, in the rate of volume increase, after which white and grey matter volume was similar to that of normal controls (Aylward et al., 2002; Sparks et al., 2002; Courchesne et al., 2004, 2005). Data on brain volume in autism is generally derived from the cross-sectional evaluation of different age groups. The need for brain volume follow-up studies with samples followed from infancy to adulthood is confirmed in the literature.

**Table I.** Structural brain imaging studies.

Study	Autism Group	Control Group	Method	Basic Findings
Filipek et al., 1992	22 autism 15 developmental language disorder 10 MR 6-10 yo	24 HC 6-10 yo	MRI 1.5T 3-4 mm	TBV ranking autism > lang. dis. > control > MR
Courchesne et al., 1994	50 autism 41 male 16.5 yo 27 MR, 23 N-IQ	53 HC 43 male 17 yo N-IQ	MRI 1.5T 5 mm	Sub-types with hypoplasia and hyperplasia in the cerebellar vermis
Hashimoto et al., 1995	102 autism 76 male 6.1 ± 4.7 yo	112 HC 65 male 7.1 ± 5.4 yo	MRI 0.5-1.5T 5-7 mm	Reduced total brain stem volume Reduced volume of the pons, mid-brain, medulla oblongata, and vermis lobules VI and VII
Piven et al., 1997	35 autism 26 male 18.0 ± 4.5 yo N-IQ	36 HC 20 male 20.2 ± 3.8 yo	MRI 1.5T 1.5 mm	No difference in total cerebellar volume and vermis volume
Aylward et al., 1999	14 male autism N-IQ 11-37 yo	22 male HC age-IQ matched	MRI 1.5T 1.5 mm	Reduced bilateral amygdala and hippocampus volume in autism
Chugani et al., 1999	9 autism	5 healthy siblings	MRS 1.5T 3 mm	Reduction in cerebellar NAA levels
Sears et al., 1999	13 autism male 27.7 ± 10.7 yo N-IQ	25 control 18-47 yo IQ matched	MRI 1.5T 3 mm	Increased caudate nucleus volume
Howard et al., 2000	10 male autism N-IQ 15-40 yo	10 male HC age-IQ matched	MRI 1.5T 1.6 mm	Increased bilateral amygdala volume in autism No volumetric differences in the hippocampus and para-hippocampus
Courchesne et al., 2001	60 male ASD 6.2 ± 3.5 yo (2-16 yo)	52 HC male 2-16yo	MRI 1.5T 3-4 mm	Increase in cerebral grey and white matter between ages 2 and 4 years, increased TBV, volumetric reduction in the cerebellar hemispheres and vermis
Rojas et al., 2002	15 autism 13 male N-IQ 29.9 ± 9.0 yo	15 HC 13 male N-IQ 30,4±9,3 yo	MRI 1.5T 1.7 mm	Reduced left planum temporale volume
Aylward et al., 2002	14 male ASD 20.5 ± 1.8 yo	14 HC male 20.3 ± 1.7 yo	MRI 1.5T 1.5 mm	No difference in TBV

There are also studies that compared total brain volume between different developmental disorders or between different types of pervasive developmental disorders (PDD). The results of one structural MRI study of developmental disorders indicated that the descending brain volume ranking was as follows: High functioning autism (HFA), low functioning autism, developmental language disabilities, normal controls, and mental retardation (Filipek et al., 1992). In a study in which the rate of head cir-

cumference growth in birth-2-year-olds with autism and pervasive developmental disorder not otherwise specified (PDD-NOS) was compared, autistic children had a faster rate of head circumference growth between months 6 and 14, which was suggested as being related to a more severe prognosis (Courchesne et al., 2003).

Despite the increased total brain volume the status of brain metabolism has only been studied during the

**Table I.** Continued.

Study	Autism Group	Control Group	Method	Basic Findings
Sparks et al., 2002	45 autism + PDD-NOS 38 male N-IQ 3.9 ± 0.4 yo	26 HC 14 MR 3.9 ± 0.5 yo	MRI 1.5T 1.5-2 mm	Increased TBV, specifically in the frontal and temporal lobes No difference in cerebellar volume in autism Reduced cerebellar volume in MR Amygdala volume autism > PDD-NOS > HC No difference in hippocampal volume
Carper et al., 2002	38 male autism N-IQ + MR 5.7 ± 2.2 yo	39 HC male N-IQ 6.5 ± 2.5 yo	MRI 1.5T 3 mm	Increase in frontal and parietal white matter, and frontal and temporal grey matter volume
Levitt et al., 2003	21 male PDD-NOS N-IQ 10.7 ± 3.1 yo	20 HC 11.3 ± 2.9 yo	MRI 1.5T 1.2 mm Cortical sulcal mapping	Bilateral deviation in the upper frontal sulcus, right Sylvian fissure, upper temporal sulcus, and left lower frontal sulcus
Herbert et al., 2003	17 male ASD 7-11 yo	15 HC male 7-11 yo	MRI 1.5T 3 mm	Increased TBV Increased white matter volume Reduced hippocampus, amygdala volume No differences in thalamus volume
Barnea-Goraly et al., 2004	7 male autism N-IQ 14.2 ± 6.3 yo	9 HC 14.4 ± 6.2 yo	Diffusion MRI 3T 3 mm	Deterioration in white matter pattern in the medial and dorsolateral prefrontal cortex, temporoparietal region, and the frontal region of the corpus callosum
Waiter et al., 2004	16 male Autism + AS 15.4 ± 2.2 yo N-IQ	16 HC male 15.5 ± 1.6 yo N-IQ	MRI 1.5T 1.6 mm	Increased grey matter volume in the right fusiform gyrus, right temporo-occipital region, and left medial frontal cortex
Waiter et al., 2005	15 male Autism + AS 15.2 ± 2.2 yo N-IQ	16 HC male 15.5 ± 1.6 yo N-IQ	MRI 1.5T 1.6 mm	Reduction in corpus callosum and right frontotemporal white matter volume
Keller et al., 2007	34 male autism 18.9 ± 7.3 yo N-IQ	31 HC 18.9 ± 6.2 yo	Diffusion MRI 3T 3 mm	Deterioration in corpus callosum diffusion patterns
Bashat et al., 2007	7 autism male 1.8-3.3 yo	18 HC male 4-23 yo	Diffusion MRI 1.5T 3 mm	Salient deterioration in diffusion pattern in the left frontal lobe
DeVito et al., 2007	26 male autism 9.8 ± 3.2 yo	29 HC male 11.1 ± 2.4 yo	MRS 3T 3 mm	Pervasively low NAA and creatin levels in the cerebral cortex and cerebellum
Tsatsanis et al., 2003	12 autism male 21.0 ± 10.4 yo N-IQ	12 HC 18.1 ± 6.3 age IQ matched	MRI 1.5T 1.2 mm	Reduced thalamus volume in patients with increased TBV

Yo: years old; MRI: magnetic resonance imaging; T: tesla; N-IQ: normal IQ; MR: mental retardation; HC: healthy control; TBV: total brain volume; PDD-NOS: pervasive developmental disorder not otherwise specified; ASD: autistic spectrum disorder; AS: Asperger syndrome; NAA: N-acetyl aspartate.

last decade, following technical developments. In MRS studies of autistic children with increased brain volume, despite the increased volume N-acetyl aspartate (NAA), creatine, and myo-inositol levels were low. Although the

decrease in these metabolites, which are usually found in neuron bodies and axons, and the increase in brain volume appears conflicting, these findings were explained by several different mechanisms. The glial cells, dendrites,

**Table II.** Functional brain imaging studies during rest.

Study	Autism Group	Control group	Method	Basic Findings
Zilbovicius et al., 1995	5 male autism MR follow-up (2-4; 6-7 yo)	5 MR follow-up (2-4; 6-7 yo)	SPECT (xenon)	Temporary frontal hypoperfusion in the autistic group between 2-4 years of age
Chungji et al., 1996	14 male autism 1-5 yo	14 male 1-5 yo	PET	Bi-temporal hypometabolism
Chungji et al., 1996	8 autism 7 male 6.6 yo	Healthy same sex siblings 9.9 yo	PET alpha-[11C] metil-L-tryptophan	Reduction in regional serotonin synthesis in the dentate-thalam-ocortical network in male autistics
Ohnishi et al., 2000	23 male autism 2.4-13 yo	26 MR male 3.4-12 yo	SPECT	Bi-temporal hypoperfusion
Kaya et al., 2002	18 autism 14 male 6.1 yo	11 healthy control 6 male 6.5 yo	SPECT	Frontal, frontotemporal, temporal and temporo-occipital hypoperfusion
Özdemir 2004	6 autism 6-12 yo	None	SPECT	Increase in prefrontal blood flow with risperidone treatment
Gendry Meresse et al., 2005	45 autism male Childhood	None	SPECT	Hypoperfusion in the upper temporal region, correlation between hypoperfusion and autistic symptoms

yo: years old; MR: mental retardation; SPECT: single-photon emission computer tomography; PET: positron emission tomography

and synapses, rather than neurons, could be responsible for the increase in total brain volume, and other mechanisms, such as axodendritic pruning, programmed cell death, and neuro-inflammation (Freidman et al., 2003).

In post-mortem studies large-volume neurons were detected in some areas of the brain in children, while there was a decrease in the volume and number of neurons with progressing age, which were thought to be the results of pathophysiological process underlying brain volume alterations (Courchesne et al., 2004). Findings about volumetric increase have led to different hypotheses related to pathogenesis, such as dendritic branching, increases in new synapse production and axonal myelination, the development of non-targeted and complex networks due to a decrease in dendritic and synaptic pruning, and the existence of numerous, yet smaller and densely settled neurons.

### Alterations in Grey and White Matter

Volumetric enlargement is reported to be 18% in grey matter and 38% in white matter (Courchesne et al., 2001; Herbet et al., 2003). During adolescence, when the growth rate slows down and brain volume re-

duces to that similarly observed in normal controls, a decrease in volumetric growth in both grey and white matter is reported. In comparison to each other the rate of white matter volumetric growth is observed to slow down more than that of grey matter (Lainhart, 2006). When the quantity of white and grey matter in different regions is studied, the results seem contradictory. In adolescents with autism white matter in the right frontotemporal and fronto-occipital regions decreases relatively more, whereas in the frontostriatal and cerebellar regions grey matter decreases relatively more (Waiter et al., 2004, 2005). In a cortical sulcal mapping study of brain surface anatomy, deviation of major sulci in the frontal and temporal regions were reported, and these findings indicate interruption in cortical development (Levitt et al., 2003).

DTG research, which allows the study of white matter integrity, has attracted interest due to such hypotheses as, there is a reduction in the number of connections between distant regions of the brain and an increase in the connections between closer regions of the brain in autism. The findings of DTG studies suggest defects in white matter diffusion patterns in the medial and dorso-lateral prefrontal cortex, temporo-parietal cortex, and in

the frontal region of the corpus callosum (Barnea-Goraly et al., 2004). Moreover, most studies report defects in white matter patterns in the corpus callosum and frontal lobe (Bashat et al., 2007; Keller et al., 2007).

### **Cerebral Cortex**

Findings of increased total brain volume led to structural imaging studies that investigated the core brain regions responsible for the excess growth. The volume of different regions of the brain were adjusted according to total brain volume and then were compared to normal controls. The fundamental finding is that volumetric enlargement is due to an increase in grey and white matter in the cerebral cortex, cerebellum, and limbic structures. When different lobes of the brain were compared excessive volumetric growth was observed in the frontal, temporal, and parietal lobes (Carper and Courchesne, 2000; Carper et al., 2002; Sparks et al., 2002). Detailed studies of the frontal lobe, which was reported to have the greatest volumetric increase, showed that there was an increase in volume, especially in the medial frontal cortex, which includes the dorsolateral prefrontal cortex and frontal cingulate cortex (Carper et al., 2002; Carper and Courchesne, 2005).

MRS studies, despite volumetric increase, reported lower NAA and creatine levels in the cerebral cortex and cerebellum (DeVito et al., 2007).

### **Limbic Structures**

The pathological events that affect the temporal lobes, especially the amygdala and hippocampus, are thought to be related to autistic-like symptoms. In post-mortem studies, densely packed small neurons were repeatedly reported in these regions (Bauman and Kemper, 2005). In structural MRI studies bilateral volumetric increase in the amygdala was frequently observed, especially in HFA patients (Howard et al., 2000); however, there is a remarkable number of studies that report normal or reduced amygdala volume (Eigisti and Shapiro, 2003). Spark et al. (2002) compared patients with PDD-NOS to patients with autism and reported larger amygdala volume in the autism group, suggesting that amygdala enlargement might be related to the disorder's severity. In adult autistic patients hippocampal volume was reported to be reduced (Aylward et al., 1999) or normal (Sparks et al., 2002). The planum temporale, which is located on the upper part of temporal lobe, has been studied because it is the receptive speech region. This region is usually expected to be asymmetrically large in

the hemisphere in which speech is located, yet in autism studies this asymmetry has not been reported (Rojas et al., 2002). This finding is accepted as a sign of early developmental deficits in autism and is thought to be responsible for the pathologies underlying language incapability in autism.

### **Cerebellum**

One of the most repeated findings in post-mortem studies is a reduction in the number of Purkinje's cells in the cerebellum. Imaging studies have reported volumetric reduction (Hashimoto et al., 1995; Courchesne et al., 2001), and volumetric enlargement and no volumetric change (Sparks et al., 2002) in the cerebellar hemispheres and vermis lobules VI and VII (upper vermis, declive, folium and tuber). Regarding these findings, researchers have reported that autistic disorder might have 2 subtypes, in terms of cerebellar pathology, which is related to IQ level (Courchesne et al., 1994), and that autism is related greater volumetric reduction in the cerebellum, that mental retardation is related more to volumetric enlargement in the cerebellum (Piven et al., 1997), and that the cerebellum is one of the most affected regions. Moreover, researchers also posit that volumetric enlargement in the frontal lobe and volumetric reduction in the cerebellum might be related. Insufficient inhibitory signals from the reduced number of Purkinje cells and an increase in excitatory signals from the cerebellum were suggested to be related to volumetric enlargement in the frontal lobe (Courchesne et al., 2004). Allen and Courchesne (2003) emphasized that the ability to learn the predictive relationships between subsequent events, which is governed by the cerebellum, might deteriorate in parallel with volumetric loss in autism. One study in which MRS was used reported that NAA levels in the cerebellum were lower (Chuhani et al., 1999a). The results of studies of the other structures in the posterior fossa usually report a similar volumetric reduction.

### **Basal Ganglia and Thalamus**

The last decade was marked by reports of reductions in the quantity and volume of neurons in the basal ganglia, both in imaging and autopsy studies (Sears et al., 1999); however, recent studies have reported different results based on detailed investigation of different parts of the basal ganglia. Increased caudate nucleus volume and findings that suggest a relationship between this increase and stereotypical symptoms have been reported (Sears et al., 1999). Although a difference in thalamic volume has never been reported (Herbert et al., 2003), a recent study

reported thalamic volume reduction in high-functioning male autistic patients when it was corrected according to total brain volume (Tsatsanis et al., 2003).

## FUNCTIONAL BRAIN IMAGING IN AUTISM

Observations of brain metabolism at rest or during specific sensual, motor, and cognitive tasks using new functional imaging techniques have provided new opportunities for discoveries in the pathophysiology of autism. Nonetheless, the limitations of structural brain imaging studies have continued incrementally in functional studies. Due to differences in study design, such as imaging with different techniques during different tasks and the fact that task-involving studies can only be conducted with adults and adolescents with HFA and Asperger syndrome (AS), studies result in different findings and hypotheses.

### Functional Brain Imaging at Rest

The fact that EEG disturbances are frequently detected in autistic children has led to magnetoencephalography (MEG) studies. Epileptiform activity was reported in 68% of children with autism and PDD-NOS based on EEG, but this percentage increased to 82% with simultaneous MEG, and increased activity was observed, especially in the right frontal lobe (Lewine et al., 1999).

Contrary to other functional brain imaging studies, in SPECT studies mostly low-functioning autistic children have been investigated. The most important repeated finding of independent research groups using high resolution SPECT is reduced blood flow in the bilateral temporal lobes (Ohnishi et al., 2000; Gendry Meresse et al., 2005). In the light of this finding, the hypothesis suggesting that a functional disorder in the temporal lobe is the fundamental deficit in the pathophysiology of autism has gathered support. The temporal lobe is thought to be the fundamental center in the pathophysiology of autism, considering that it contains the receptive speech region and hearing region, that it has numerous connections with the fronto-parietal and limbic structures, and that autistic symptoms are present in temporal lobe pathologies (Eigsti and Shapiro, 2003). A Turkish SPECT study in which 18 autistic and 11 normal aged-matched control children were compared reported reduced blood flow in the frontal, fronto-temporal, temporal, and temporo-occipital regions in the autistic children (Kaya et al., 2002).

In a SPECT study with 5 low-functioning autistic children aged between 2 and 4 years, regional blood flow

in the frontal lobe was decreased, but when these children were investigated again at 6-7 years of age there were no significant differences compared to the control group. This result was interpreted as a delay in the development of the frontal lobe, which is responsible for high cognitive functions such as object constancy, executive functions, and theory of mind functions (Zilbovicius et al., 1995). The findings of a SPECT study in which 11 high- and 11 low-functioning autistic primary school children were compared suggest that there were differences in the asymmetric values of blood flow in the frontal and parietal regions of the brain between the 2 groups (Erman, 1997). A study of 6 autistic children aged between 6 and 12 years reported reduced blood flow in the bilateral medial temporal and prefrontal regions prior to risperidone treatment, and an increase in blood flow in the prefrontal region after the treatment (Ozdemir, 2004).

In PET studies conducted with autistic individuals at rest, findings varied from no difference in metabolism to those suggesting a reduction or an increase (Boddaert and Zilbovicius, 2002). Nonetheless, similarly to results of SPECT studies, 2 studies conducted with high-functioning patients reported decreased metabolism in both temporal lobes (Chungi et al., 1996; Zilbovicius et al., 2000).

Although no single neurotransmitter (NT) system is thought to be responsible for the entire pathology, mostly the serotonergic system in autistic patients was investigated using PET. In normal individuals brain serotonin synthesis is expected to be higher during childhood and to decline with age; however, in studies of autistic individuals in different age groups, the findings suggest otherwise—that serotonin synthesis is low during early childhood, increases with age, and at around age 15 years reaches a level 2 times that of the normal adult level (Chugani et al., 1999). Furthermore, following a marked tryptophan administration in autistic children, a PET study reported an increase in regional serotonin synthesis in the dentate-thalamo-cortical network (Chugani et al., 1997). In the light of these studies, researchers think that abnormalities in serotonin synthesis during the prepartum and early postpartum periods destroy the thalamocortical connections, thus creating a risk for autism (Chugani et al., 1999). Table II displays the fundamental findings of functional brain imaging studies of at rest individuals.

### Functional Brain Imaging During Activity

During the last decade the neural basis of language

and cognitive pathology in autism has been investigated using functional PET and fMRI. These studies focused on determining the regions that become more or less active by comparing regional blood flow and activity alterations in autistic individuals and normal controls while they fulfilled various pre-defined tasks. Functional brain imaging studies during activity have mostly been conducted with individuals that have HFA and AS due to the necessity of the accomplishment of assigned tasks. These studies should be considered as preliminary exploratory studies because of the small sample sizes and the variation in tasks and results.

Studies show that face and object processing have different mechanisms in healthy individuals, and that infants, from the very first moments of life, prefer to look at faces or face-like shapes (Jemel et al., 2006). The results of PET and fMRI studies conducted with healthy individuals show that face processing is performed in the ventral visual cortex, fusiform gyrus (FG), upper temporal sulcus (UTS), amygdala, and insula network. When encountered with familiar faces the FG, and during object processing the lower temporal gyrus (LTG) increase in activity (Haxby et al., 2002). fMRI studies of autistic individuals show that during face processing the FG is less active and that the LTG is more active; thus, autistic individuals process faces similarly to the way they process objects (Shultz et al., 2000). Dalton et al. (2005) conducted a study with HFA adolescents in which they determined what their eyes were focused on, and for how long. Brain activity was measured during tasks like face-emotion pairing, and distinguishing between familiar and unfamiliar faces. They reported that the duration of eye focusing in autistic adolescents was shorter, and FG and UTS activity was lower than in normal controls, and that contrary to controls, looking at familiar faces did not increase FG activity in the autistic adolescents. Another finding was that the duration of eye focusing in the autistic group was in direct proportion to amygdala activity and was inversely proportional to FG activity. The authors argued that in autistic individuals eye-focusing and social stimuli might cause over-activation in the amygdala and the reduction in FG activity might cause a mental blindness toward faces, eyes, and social stimuli, counteracting this over-stimulated state.

PET studies conducted with autistic individuals, in which auditory stimuli were given using the human voice, more activity in the right posterior upper temporal gyrus and less activity in the left posterior upper temporal gyrus, compared to normal controls, was ob-

served (Muller et al., 1999; Zilbovicius et al., 2000). The authors concluded that this reverse lateralization toward verbal auditory stimuli might negatively affect the response to voices and language development, and that this might support the hypotheses of temporal lobe malfunction in autism (Zilbovicius et al., 2000).

Autism manifests itself with clinical symptoms in many different areas; however, based on the literature, deterioration in social abilities is considered the fundamental and specific symptom (Eigisti and Shapiro, 2003). Ever since Baron-Cohen introduced the theory of mind and suggested the hypothesis that the core symptoms in autism stemmed from basic malfunctions in theory of mind, studies in this area have increased. Theory of mind tasks, such as predicting emotions based on photographs of eyes, guessing the emotions of a character in a story by reading the story, and guessing how reliable people are by looking at photographs of them, are commonly used in studies that investigate social cognition in autism. These tasks stimulate the frontal and temporal cortical regions, sub-cortical region, left amygdala, upper temporal gyrus (UTG), left hippocampal gyrus, both insulae, and the left striatum in healthy individuals. The differences between HFA patients and healthy controls during these tasks are that HFA patients have less activity in the orbitofrontal and medial cortexes, and the amygdala, and over-activity in the UTG (Baron-Cohen et al., 1997; Baron-Cohen et al., 1999).

Mimicking is one of the primary methods of learning in early life. It is believed that there is a strong connection between mimicking and social cognition (Dapretto et al., 2006). With the idea that deterioration in mimicking ability might cause the basic symptoms of autism, the mirror neuron system (MNS), which is active during mimicking in both humans and animals, has become a target of investigation. Mimicking in humans was investigated by many different research groups. Findings of these studies suggest that there is an increase in the activity of the posterior part of the lower frontal cortex and lower parietal lobe while observing another person's behavior and guessing its purpose (Iacoboni and Dapretto, 2006). While understanding someone else's emotions and purposes the MNS is thought to be functional in relation to the limbic system. In HFA children, while no activity in the MNS is reported during the task of mimicking face expressions, an increase in activity in the visual cortex, especially in the motor and premotor regions related to the face, and in the amygdala, was observed. In conclusion, it was hypnotized

that due to insufficient MNS functioning, the autistic children tried to mimic faces without attributing any emotional meaning to the faces (Dapretto et al., 2006).

## CONCLUSION

It is well known that autism is a heterogeneous neuropsychiatric disorder that results from the interaction of different environmental, biological, and genetic factors. Many structural and functional brain-imaging studies have been conducted to investigate its possible etiological elements, neuroanatomy, and pathophysiology.

Numerous anatomical alterations have been observed in structural brain imaging studies, indicating a pervasive disorder in neuronal networks during early developmental stages (Bauman and Kemper, 2005). Many confounding variables may account for the differences in the results of these studies: (a) Samples in the structural brain imaging studies were small and heterogeneous; (b) variables such as sex, IQ, age, and accompanying neurological disorders were not controlled for; (c) the lack of studies with large enough samples for normal brain volume for various age groups; (d) total brain volume differences. It is important to note that the reports of brain volumetric increase, decrease, or no change did not report on the functioning of the regions in question. Considering the results of functional imaging studies, it can be expected that future studies will focus on the temporal lobe and amygdala in more homogenous patient groups. Moreover, there is a need for follow-up imaging studies, rather than cross-sectional studies.

In functional studies, while there were differences in the level of activity of the temporal lobe and amygdala, which function in social cognition and language,

increased activity in the posterior cortical regions was reported (Shultz et al., 2000). In language and social cognition, autistic individuals seem unable to activate the required regions of their brains and instead activate different regions to accomplish the same tasks (Baron-Cohen et al., 1999). Although many different and conflicting results cloud our understanding of the neurobiology of autism, it should be remembered that functional imaging studies in autism are quite recent and experimental, and that these differences in results have resulted in many new hypotheses. Among the basic limitations of functional imaging studies are: The disqualification of most autistic individuals due to their failure to complete the assigned tasks; small samples due to this disqualification and also due to samples composed of adolescent or adult high-functioning autistic individuals; the lack of wide healthy sample data. The unknown natural changes in normal brain development make it difficult to interpret the results of autism studies. Brain imaging studies in the field of developmental psychology may shed light on the neurobiology of autism, which is a developmental psychopathology. There is also a need for follow-up functional brain imaging studies with a developmental perspective and that begin early in life. Both in functional and structural brain imaging studies, comparisons not only to normal controls, but also to individuals with mental retardation, language disorders, and other developmental psychopathologies, may reveal new opportunities for identify the neurobiology of autism.

Although there are numerous hypotheses about the pathophysiology of autism that are derived from a combination of clinical observations and imaging studies, it remains too early to definitively know the neurobiology of the disorder.

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