Study of Brain Single Photon Emission Computed Tomography in a Sample of Egyptian Children with Autism

Omar M, AbdelHady M, El-Missiry A, Faris L, El-Mahallawy N, and Mansour M.

Abstract:

Autistic Spectrum Disorder (ASD) is a disorder characterised by impaired communication, reciprocal social interaction, language deficits and behavioural maladaptation. The aim of this research is to study the functional neuroanatomical correlates of ASD in a sample of Egyptian autistic versus non-autistic children using brain SPECT, and to investigate the relationship between SPECT findings and scores of adaptive and maladaptive behaviour measured by the Adaptive Behaviour Scale (ABS). *Subjects and Method:* Thirty autistic children and thirteen non autistic controls were examined using Technetium-99m HIMPAO brain SPECT. The cortical regions of interests (ROIs) were the superior and inferior frontal, parietal, temporal, occipital, cerebellum, and basal ganglia. *Results:* findings indicate that the frontal lobe was the commonest site of hypoperfusion, followed by the cerebellum and other brain areas. Cerebral hypoperfusion was more on the left in comparison to the right hemisphere. Hypoperfusion of the right superior frontal and bilateral cerebellar regions correlated statistically with the low profile of milstones of development and social independence. Language development correlated statistically with bilateral cerebellar hypoperfusion. Social isolation had a significant statistical correlation with right parietal and bilateral basal gangla hypoperfusion. Left occipital perfusion abnormality was detected with stereotyped behaviour, whilst self mutilation, hyperactivity and odd social behaviour related to hypoperfusion in different brain regions. *Conclusion:* this study postulates the complex dysfunction in some brain regions involved in the development of the autistic symptoms. SPECT is one of the investigation techniques that can give reliable information about the brain function in the autistic children and their relation to the pattern of adaptation.

Introduction:

Autism is a severe pervasive disorder of childhood development. Since its first description by Kanner in 1943, it has attracted the attention of researchers from numerous disciplines. The disorder is characterized by restricted, repetitive behaviours and impairment in socialization ***(Sokol and Brown, 2004)***. The core clinical features also include, verbal and non-verbal communication deficiencies, limited activities and interests and stereotypical patterns of behaviour ***(Boddaert and Zilbovicius, 2002)***.

Symptoms are usually evident by the age of three years, with children often showing regression in previously learned behaviour, deficits in cognitive processing, verbal sequencing, abstraction, rote memory and reciprocal verbal exchange ***(Kaya et al., 2002)***. Research indicates that a spectrum of neurological abnormalities involving the brain stem, frontal, temporal, parietal cortices, limbic system and possibly other brain regions may play a role in autism ***(Palmen and Van England, 2004)***.

Morphological neuro-imaging studies revealed various brain abnormalities in patients with autism. The structural abnormalities of the brain observed in some children with autism initially reported using

computed tomography (CT) had illustrated cerebral asymmetry ***(Palmen and Van England, 2004)*** and enlargement of lateral and third ventricles**.** Additionally, Magnetic resonance imaging (MRI) studies found hypoplasia of the cerebellar vermis, enlargement of fourth ventricles and reduced size of corpus callosum ***(Piven et al., 1997)***.

The majority of structural brain studies indicated a variety of diffuse anatomical, differences, reflective of an early developmental change in the growth or pruning of neural tissue, rather than localized lesions. Similarly, neurochemical studies suggest early, neuromodulatory discrepancies rather than gross or localized abnormalities ***(Eigsti and Shapiro, 2003)***.

Functional neuro-imaging added significantly to our understanding of brain dysfunction in Autism. Positron Emission Tomography (PET) measured the regional metabolic rate of glucose utilization in the brains of autistic subjects, and revealed decreased glucose metabolism in frontal, parietal and anterior cingulate cortices ***(Haznedar et al., 1997).***

Single Photon Emission Tomography (SPECT) studies examining regional cerebral blood flow showed hypoperfusion, in bilateral frontal, fronto-temporal and tempro-occipital regions ***(Kaya et al., 2002).***

SPECT is currently considered as a research tool in the evaluation of autism and has no role in clinical diagnosis of autism. However, some researchers claimed that it may be considered as a favourable index and reliable predictor tool for the outcome and prognosis of autism ***(Rapin, 2000).***

Aim:

The purpose of this research was to study the functional neuro-anatomical correlates of the Autistic Spectrum Disorder (ASD) in a sample of Egyptian children by using Tc99m Hexamethyl Propylene Amine Oxime (HIMPAO) Brain SPECT; compare changes in SPECT in autistic and non autistic children; and finally to investigate the relationship between SPECT findings and some clinical variables estimated by the Adaptive Behaviour Scale (ABS).

Subjects and Methods:

The study was approved by the Ethical Committee of the Institute of Psychiatry and informed consent was obtained from all parents of the subjects included.

Thirty (30) children with autism spectrum disorder (10 girls and 20 boys) with a mean age 7.36±2.5 year, range from 3 to 12 years were recruited from the outpatient psychiatric clinic of the Institute of Psychiatry, Ain Shams University. All the autistic children satisfied the criteria for autistic disorder according to the ICD-10 diagnostic criteria for research (DCR).

25 subjects (83%) were having "typical autism", 3 subjects (10%) labelled the diagnosis of "atypical autism" and two (6%) were diagnosed as Rett's syndrome. The majority of the children included were left handed (73%), the rest (27%) showed ambivalent handiness. An experienced pediatrician examined the children thoroughly to exclude those with history of neurological diseases, significant medical diseases, known infections, metabolic, or chromosomal diseases.

As other case-control studies in this field e.g. ***(Wilcox et al., 2002; Degirrmenci, 2008)***, we included normal children as a control group. The National Institute of Health (NIH) encouraged the inclusion of children in research after optimizing the

non exposure to any risk ***(Arnold et al., 2000)***. Hence, thirteen (13) left handed non autistic controls (9 boys and 4 girls), with a mean age 7.48 ± 2.26 year were selected from relatives of admitted children in the Paediatrics Ain Shams Hospital, who came to visit them, they were matched, as much as possible with the study group as regards age and socio-economic level. They were medically examined by the same paediatrician to ensure their physical health. They were also interviewed carefully by a psychiatrist to exclude those with any psychiatric morbidity.

We used the Adaptive Behaviour Scale (ABS) constructed by Nehira et al., (1974) and translated into Arabic and validated by Farag and Ramzy, (1995). The scale is used to assess the adaptive skills of emotionally disturbed children.

The brain metabolism was assessed through brain imaging using Tc-99m (HMPAO), a sophy gamma camera DSX rectangular was used with a computed system for controlling the acquisition parameters and performing data processing functions. Parallel whole low energy super high resolution collimator was used. The data were acquired using "step and shot technique" two methods were applied for SPECT reading which was performed by senior specialized radiologists.

The analysis was done by:

***The visual technique*:** The number of affected areas which represent the extent of cerebral hypo perfusion and the predominantly affected area.

The quantitative analysis technique: Three trans-axial slices were summated at three levels to represent frontal level, basal ganglia level and cerebellar level. Regions of Interests (ROIs) were drawn on each summated frame to calculate counts in superior, inferior frontal parietal, temporal, occipital, basal ganglia, and cerebral regions on both right and left sides.

Data obtained were tabulated processed in a personal computer and analyzed using the Statistical Package for Social Science "SPSS" version 13. Independent student's t-test was used to evaluate the statistical differences in regional cerebral blood flow (%rCBF) between autistic and non autistic subjects. We used the Pearson's correlation coefficient for the bivariate correlation procedure.

Results:

The comparison between the qualitative SPECT findings of autistic and non autistic control subjects is shown in table (1). The control group showed normal perfusion, while the autistic group showed qualitative hypoperfusion in different regions. The frontal lobe was the commonest site for hypoperfusion in (76.6%), followed by the cerebellum (30%), parietal lobe (23.3%), basal ganglia (16.6%). The least affected sites were the temporal region (10%) and the occipital area (6.6%). The left hemisphere showed more hypoperfusion in the frontal, parietal, temporal, basal ganglia and cerebellar region, in comparison to the right hemisphere. The right occipital area showed hypoperfusion while there was normal perfusion in the left side (table 1).

The quantitative SPECT was used to compare cases and controls as regard % rCBR (mean brain count /pixel) in different brain regions. Results displayed in (table 2) showed that there was a significant hypoperfusion in the bilateral superior frontal, bilateral basal ganglia, bilateral parietal, left inferior frontal, left occipital, right temporal, and right cerebellar regions.

No statistical significant difference elicited when we compared cases with controls as regard perfusion in the right inferior frontal, left temporal and left cerebellar regions.

Brain SPECT and its relation to scores of Adaptive Behaviour Scale (ABS):

The Adaptive Behaviour Scale was used to assess the adaptive and maladaptive behaviour of the autistic patients. The first three subscales (milestones of development, social independence, language development) covered the development of the expected adaptive behaviours according to age, i.e. the lower the scores of the percentile, the more impairment of the normal adaptation of the child behaviour.

Autistic children in this research had very low profile in milestones of development (48.3%), followed by social independence (36.6%) and language development (32.3%) in comparison to the expected adaptive behaviour in normal children population for the age range which is above (90%). The other five subscales (social isolation, stereotyped behaviour, self mutilation, hyperactivity, and odd social behaviour) scored the maladaptive behaviour of the child, i.e. the higher the percentile of the child on these subscales, the more the maladaptation and impairment.

Children with autistic disorder in our research showed very high profile of social isolation (81.6%) followed by stereotyped behaviour (78%), odd social behaviour (72.3%), then hyperactivity (53.3%) and self-mutilation (21.6%) in comparison to the expected maladaptive behaviour in normal children which should be below (10%).

We correlated items of Adaptive Behaviour Scale (ABS) with brain SPECT regions of interests. Results shown in table (3) illustrate significant hypoperfusion in the right superior frontal, bilatral cerebellar regions with social independence and delayed milestones of development. When we correlated %rCBF with language development; we found significant hypoperfusion in the right and left cerebellar region. Social isolation shows significant correlation with hypoperfusion in the right parietal, and bilateral basal ganglia regions.

The stereotyped behaviour significantly correlated with left occipital hypoperfusion. Self-mutilation significantly correlated with hypoperfusion mainly in the right and left superior frontal regions, temporal and basal ganglia regions. The hyperactivity showed significant correlation with hypoperfusion in the right superior frontal, left basal ganglia and both cerebellar regions. The odd social behaviour showed significant correlation with the left occipital and left cerebellar regions.

Table (1): Comparison between brain regions showing qualitative hypoperfusion in both hemispheres in patients with autistic spectrum disorder (ASD)

	Right Number	**Left** Number	**Bilateral** Number	**Total Number& (%)**
Frontal lobe	6	10	7	**23 (76.6%)**
Cerebellum	2	4	3	**9 (30%)**
Parietal lobe	1	4	2	**7 (23.3%)**
Basal Ganglia	0	3	2	**5 (16.%)**
Temporal lobe	0	3	0	**3 (10 %)**
Occipital lobe	2	0	0	**2 (6.6%)**

The total percentage is more than 100% because of the multiple brain regions affected.

Table (2): Comparison between quantitative perfusion (%rCBF) in autistic and non-autistic children (brain count /pixel)

Brain Region	Patients N = 30	Control N = 13	t	P
Right superior frontal	0.85 ± 0.14	1.15 ± 0.13	-6.8	< **0.001**
Left superior frontal	0.87 ± 0.15	1.02 ±0.03	-5.1	< **0.001**
Right inferior frontal	0.95 ±0.14	1.0 ±0.1	1.53	> **0.05**
Left inferior frontal	0.96 ± 1.13	1.19 ± 0.16	-3.08	< **0.01**
Right parietal	0.94 ±0.16	1.03 ±0.02	-3.16	< **0.01**
Left parietal	0.95 ±0.15	1.06 ±0.03	-3.78	< **0.01**
Right temporal	1.06 ± 0.19	0.97 ±0.03	2.24	< **0.05**
Left temporal	1.05 ± 0.24	0.99 ± 0.07	1.2	> **0.05**
Right occipital	1.17 ±0.17	1.14 ± 0.03	0.69	> **0.05**
Left occipital	1.15 ± 0.21	1.04 ± 0.05	2.55	< **0.01**
Right basal ganglia	0.74 ± 0.23	0.90 ± 0 12	- 2.81.	< **0.01**
Left basal ganglia	0.78 ± 0.13	092 ± 0.110	-3.97	< **0.001**
Right cerebellum	0.90 ± 0.24	1.24 ± 0.07	- 6.83	< **0.001**
Left cerebellum	1.19 ± 1.57	1.23 ± 0.08	-0.12	> **0.05**

Table (3): Brain SPECT regions of interests (mean brain count /pixel) correlated with items of Adaptive Behaviour Scale (ABS)

Adaptive Behaviour Sub-scale / Brain Region	Social Independence	Milestones of development	Language development	Social isolation	Stereotype behaviour	Self mutilation	Hyperactivity	Odd behaviour
Right superior frontal	0.61*	0.46*	0.43	0.12	-0.28	-0.55*	-0.53*	-0.31
Left superior frontal	0.18	0.39	0.34	0.15	-0.00	-0.49*	0.37	-0.02
Right parietal	-0.14	-0.81	0.34	0.61*	-0.21	-0.20	0.44	-0.3
Left parietal	0.09	0.31	0.16	0.39	0.11	-0.50*	-0.04	-0.24
Right inferior frontal	-0.15	0.14	0.26	0.51	-0.30	-0.47*	0.55	-0.31
Left inferior frontal	0.25	-0.13	-0.32	-0.31	-0.38	-0.10	0.13	-0.98
Right temporal	0.17	0.13	-0.40	-0.32	0.21	-0.49*	0.29	-0.17
Left temporal	0.14	0.01	- -0.23	0.26	0.30	-0.51*	-0.19	0.12
Right occipital	-0.027	-0.24	-0.26	-0.07	0.18	-0.18	-0.38	-0.14
Left occipital	0.000.	0.34	0.39	0.01	0.64*	-0.43	0.12	0.55*
Right basal ganglia	0.30	0.004	-0.14	0.46*	-0.08	-0.60*	-0.22	-0.23
Left basal ganglia	0.06	-0.25	-0.40	0.67*	-0.17	0.50*	-052*	-0.24
Right cerebellum	0.45*	0.49*	0.53*	-0.11	-0.37	-0.29	0.64*	-0.36
Left cerebellum	0.75*	0.38	0.45*	-0.21	0.41	0.22	0.63*	-0.53*

Test used= Pearson's correlation coefficient. - *= significant correlation

Discussion:

Various studies on brain blood flow in autistic children have been performed ***(Hashimoto et al., 2000).*** The results were inconsistent due to the differences of subjects, methods or technical ground of SPECT data analysis.

Few studies have examined the relationship between %rCBF alternation and clinical symptomatology. In the present study we found a decrease in %rCBF in different brain regions which was found to be correlated with items of adaptive behaviour scale (ABS). In an attempt to compare %rCBF in autistic versus non- autistic children, we examined the following regions of interests (ROIs).

Frontal Lobes:

The "*theory of mind skills*" implicates a role for the frontal lobes which have long been considered to play a special role in executive function ***(Ozonoff et al., 1996).*** In autism, affected children show classic signs of frontal damage, such as repetitive behaviours, inability to inhibit attention to salient objects, and deficit in tests of executive functions.

Frontal lobe dysfunction in autism, mirrored by perfusion abnormalities, have been demonstrated within a growing number of studies ***(Gillberg and Coleman, 2000; Hashimato et al., 2000; Luna et al., 2002)***. In the present study, frontal lobe was the most common brain area that showed hypoperfusion, and in agreement with Kaya et al. (2002), our results showed hypoperfusion in the bilateral frontal region in autistic children as compared to non autistic controls. The bilateral frontal hypoperfusion can interpret some of the autistic symptoms of aloofness impaired communication and, socialization, inability to generalize and adapt to change, and other maladaptive behaviour. Hence, when we correlated the adaptive and maladaptive behaviour of the patients group using the ABS we found that the frontal lobe hypoperfusion had a significant correlation with the lower profiles of social independence and milestones of development subscales, also significant correlation was detected with the worse profiles of social isolation, self-mutilation, hyperactivity and odd social behaviour subscales.

Examining the frontal ROI, our results demonstrated hypofunction in the left inferior frontal area in subjects with autistic spectrum disorders, while, in a recent study, **Degirrmenci et al. (2008)** detected hypoperfusion in right inferior frontal cortex. Together, these findings provide a putative functional explanation for the previous reports of decreased volume of the inferior frontal gyri in autistic children by structural neuro-imaging study ***(Abell et al., 1999)***.

Temporal Lobe:

Some high resolution functional imaging reported marked bilateral hypoperfusion in temporal lobes ***(Zilbovicius et al., 2000)***. In the current study showed that only 10% of patients had temporal lobe hypoperfusion which was significantly correlated with self mutilation. This finding is in agreement with previous reports by ***Ito et al. (2005)***.

It has been suggested that the temporal lobe hypoperfusion is related to the presumed pathophysiology of autism and that it may be caused by an underlying pathology that is also responsible for the autistic

symptoms ***(Boddaert and Zilbovicius, 2002)***.

This temporal region dysfunction has been implicated in almost all of the clinical symptoms (perception, emotion and cognitive deficits) observed in autism ***(Ohnishi et al., 2000)***, possibly, because of the anatomical connectivity between the superior temporal cortex, and the frontal, parietal, auditory, and visual cortices. Thus the impairment of neural circuits between these connected regions may be related to the symptoms of autism ***(Boddaert and Zilbovicius, 2002)***.

Basal Ganglia:

Because the stereotyped ritualistic behaviours seen in autism, the basal ganglia have been extensively studied in autistic children, most of these studies showed hypoperfusion ***(Otsuka et al., 1999)***.

As many studies in this field, we reported 16.6% of autistic children having basal ganglia hypo perfusion. However, we did not find correlation between the stereotyped subscale of the adaptive behaviour scale and the basal ganglia hypoperfusion.

Interestingly, our results showed significant correlation with self-mutilation and hyperactivity subscales of ABS. The later subscale abnormality may be related to a dysfunction in the fronto-straital pathway. However, we have no viable explanation of the correlation of self mutilation with basal ganglia hypoperfusion. **Sokol and Brown, (2004)** stated that there was increase in the volume of caudate; but not of the putamen and globus pallidus in autistic children and this increase is positively correlated with complex motor movement but negatively correlated with compulsions and rituals.

Parietal Lobe:

Results of our study showed that (23.3%) of patients group showed hypoperfusion of the %rCBF of the parietal lobe, more to the left side. These findings agreed with many SPECT techniques, where focal areas of hypoperfusion in parietal lobe were found in autistic children ***(Ryu et al., 1999)***.

In this study, hypoperfusion of the parietal lobe showed significant correlation with the lower profile of social isolation and self mutilation subscale of ABS.

Occipital lobe:

Our study results showed that only (6.6%) of the patients group had occipital lobe hypoperfusion which is the least area affected. Previous studies reach the same findings ***(Jambaque et al., 1998)***.

When we correlated the ABS subscales with the occipital hypoperfusion, we found significant positive correlation seen with the odd social and stereotyped behaviour subscales. Many studies argued the importance or the relevance of occipital lobe in ASD ***(Ozbayark et al., 1991)***. However, few studies considered occipital lobe as an important region of interest in autism.

Several electrophysiological studies highlighted a subgroup of children with autism who have significantly smaller visual -event- related potential P300 waves which indicate occipital lobe dysfunction ***(Gillberg and Coleman, 2000)***. Hence, it has been suggested that there is under stimulation of the occipital lobe by visual stimuli in autistic children ***(Mottron et al., 1997)***.

We recorded significant correlation between the highest scores of stereotyped behaviour with the degree of hypoperfusion

in the occipital lobe, this could be explained by the fact that proprioceptive input as: repetitive flickering of fingers, rolling objects, spinning, touching, and holding hard objects, dominate over visual input in children with autism, as an alternative strategy to compensate for a lack of visual control over fine motor performance ***(Gillberg and Colmen, 2000)***.

Cerebellum:

30% of the patients group in our study showed cerebellar hypoperfusion this result was coinciding with many other studies ***(Courchesene et al., 2001)***. Some PET studies results described impaired cerebellar metabolism among autistic children ***(Gillberg and Coleman, 2000)***. Moreover, functional MRI studies and MR spectroscopy studies showed significantly lower function of cerebellum in autistic patients, and smallness of cerebellar vermal lobules.

Our results displayed in table (3) showed that cerebellar hypoperfusion had significant correlation with the worse profile of social independence, milestones of developmental, language development, odd behaviour, social isolation, and hyperactivity subscales. The negative correlation between %rCBF in the cerebellum and developmental level was also reported by **Hashimoto et al. (2000)**.

SPECT and PET studies correlating cerebral dysfunction with language impairment in autistic patients demonstrated that metabolic activation of regions within the right neocerebellum increased in normal subjects while performing certain language tasks. Contrary to the hypofunction reported in autistic individuals ***(Courchesene et al., 2001)***.

The disturbed language function in autism was explained by **Eliez and Reiss, (2000)** by the presence of abnormality in the dentato-thalamic pathway (frontal cortex, thalamus and dentate nucleus) a circuit known to constitute to language functions.

The cerebellum is associated with motor integration and may be seen an unlikely candidate to account for the profound effects of autism ***(Sokal and Brown, 2000)***.

Which side of the brain is involved in autism?

Qualitative SPECT results in this study proved that the left hemisphere showed hypoperfusion in all regions of interests in the brains of the autistic children compared to the non autistic children. Previous investigators reached the same findings ***(Bailey et al., 1999)***. In a study done by **Chiron et al. (1995)** using 133 X e-SPECT in children with autism, results showed that there was a reverse asymmetry due to a qualitative hypofunction of the left hemisphere in the brain of autistic children. Moreover, another study on serotonin synthesis using PET-scan evidenced low serotonin synthesis in the left hemisphere in the brain of the autistic subjects ***(Makkonen et al., 2008)***.

Lastly, autistic children showed limitation in variety of spontaneous activity, their movements were characterized by ritualistic and stereotyped quality, the stereotyped movements were consistent with a general movement controller in the left hemisphere acting out without restraining influence of the right hemisphere to ensure that movement were appropriate to the situation, so the execution of skilled hand movement requires left hemisphere involvement, under the right hemisphere control ***(Gillberg and Coleman, 2000).***

The modern neurological model of autism

postulates the involvement of several cortical regions as contributors to the pathophysiology of autism ***(Degirrmenci et al., 2008)***.

The disconnection from the frontal lobes to the other cortical regions may be crucial in the development of autistic disorder by disorganizing the integration of cognitive functions ***(Palmen and Van England, 2004)***.

The involvement of several cerebral cortical regions and the disruption of communication between these cortical regions may lead to the clinical symptomatology in autism. Hence, the brain changes in autism appear not to be limited to a single brain area; but rather involve different structures within a globally affected neuronal network ***(Degirrmenci et al., 2008)***.

Conclusion:

There are strong evidences to conclude that the psychopathology of Autistic Spectrum Disorders symptoms is related to an underlying deranged brain function across several neuro-anatomical areas and reflects a pervasive dysfunctional neuronal networking. Although the aetiology of Autism remains unknown, functional brain studies can still provide a non-invasive and reliable gateway to the understanding of the complex nature of this pervasive developmental disorder. This, along with other SPECT studies that correlate symptoms with brain perfusion, can enhance our knowledge about the complex perfusion abnormality in different brain regions implicated in the development of autistic disorders. Further functional case-control studies are still required to unleash the secrets of brain functioning in Autism.

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Authors

Omar M.
Lecturer in Psychiatry,
High Institute of Childhood Studies
Ain shams University.

Abdelhady M.
Assistant Professor of Pediatric
Faculty of Medicine
Ain shams University.

El-Missiry A.
Lecturer in Psychiatry
Faculty of Medicine
Ain shams University.

Faris L,
Professor of Radio-diagnosis
Faculty of Medicine
Ain shams University.

El Mahallawy N.
Professor of Psychiatry,
Faculty of Medicine
Ain shams University.

Mansour M.

Professor of Psychiatry
Faculty of Medicine
Ain shams University.

Address of Correspondence,

El-Missiry A.
Lecturer in Psychiatry
Faculty of Medicine
Ain shams University.
e-mail: missiry@yahoo.com