

SPECT Findings in Mentally Retarded Autistic Individuals

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The authors examined specific deficits of cerebral blood perfusion in autistic patients as measured with [^{99m}Tc]HMPAO single-photon emission computed tomography (SPECT). The study, conducted in an outpatient clinic setting, included a consecutive series of 30 patients with autism and 14 patients with mental retardation but no autism comparable in chronological age, mental age, height, weight, and head circumference. All participants were examined with a comprehensive psychiatric and neuropsychological battery and received a [^{99m}Tc]HMPAO SPECT scan. Autistic patients had significantly lower perfusion than the control group in the following brain regions: right temporal lobe (basal and inferior areas), occipital lobes, thalami, and left basal ganglia. The study demonstrated significant perfusion deficits in specific brain areas of moderately to severely mentally retarded autistic patients.

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Autism is a behavioral syndrome defined by the presence of pervasive social deficits, communication abnormalities, and restricted, repetitive, and stereotyped patterns of behaviors.¹ Although autism is etiologically heterogeneous and genetic factors play a primary role,² the biological mechanisms of this disorder remain unknown.

In one of the initial positron emission tomography (PET) studies in autistic individuals, Rumsey et al.³ reported more extreme relative metabolic rates and asymmetries in autistic individuals compared with a group of normal control subjects. A reanalysis of this data⁴ demonstrated reduced correlations of metabolic activity between different brain regions (mainly subcortical structures and frontal-parietal areas) in autistic individuals compared with normal control subjects. The authors suggested this abnormal correlation pattern may produce an imbalance in inhibitory circuits related to attention and inward/outward-directed behaviors.

Single-photon emission tomography (SPECT) had a late development compared with PET, having a lower tomographic resolution and lacking the capacity of PET for direct metabolic measurements. However, in most psychiatric disorders, brain perfusion (as assessed with SPECT) and brain metabolism (as assessed with PET) are tightly coupled.⁵

Zilbovicius et al.⁶ used xenon SPECT to assess 21 autistic children and 14 age-matched nonautistic control subjects with developmental language disorder; they

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did not find significant between-group differences in global or regional cerebral perfusion. Using the same methodology, Chiron *et al.*⁷ examined 18 autistic patients and 10 normal control subjects and found a significantly lower cerebral blood flow in the posterior-inferior prefrontal and posterior temporal lobe regions of both hemispheres in autistic patients compared with control subjects. In a qualitative study, Gillberg *et al.*⁸ found left temporal perfusion deficits in 31 autistic patients, and a similar finding was recently reported by Mountz *et al.*⁹ There are several limitations to these studies, such as small sample size and control subjects not always comparable in mental age. Notably, all of these studies have been of high-functioning autistic individuals. Autism is associated with mental retardation in approximately 70% of cases, and this is very likely an index of etiologic heterogeneity in this disorder. Thus, findings from studies in high-IQ autistic individuals cannot necessarily be generalized to the population of autistic individuals with mental retardation. Given the large proportion of autistic individuals with mental retardation and the possibility that underlying mechanisms may differ in autistic individuals with and without mental retardation, in the present study we examined a series of 30 mentally retarded autistic subjects (most with moderate or severe mental retardation) and a group of 14 nonautistic individuals with comparable mental age, using [^{99m}Tc]HMPAO SPECT.

METHODS

Subjects

A series of 30 subjects who attended the Autism Clinic at the Raúl Carrea Institute of Neurological Research were included in the present study. All subjects had an MRI scan as part of their initial diagnostic evaluation. Subjects with a positive history of medical or neurological disorders (except for seizures in 2 patients) were excluded. A pediatric neurologist carried out a structured neurological evaluation to rule out neurological deficits, dysmorphic features, or neurocutaneous abnormalities. On the basis of this evaluation, 1 patient with tuberous sclerosis and 1 patient with Sturge-Weber disease were excluded from the study. All parents of autistic subjects were interviewed with the Autism Diagnostic Interview (ADI),¹⁰ and all subjects met both the DSM-IV¹¹ and the ADI algorithm¹⁰ criteria for autistic disorder. Only autistic individuals with an IQ lower than 70 were included in the study.

Control subjects were 14 patients with mental retardation who attended the Learning Disorders Clinic at our institute. None of the control subjects had a history

of medical or neurological disorder (except for seizures in 2 patients). Control subjects who had mental ages within the range of the autistic group were selected from a larger pool of 35 individuals with mental retardation who received an MRI scan as part of an ongoing imaging study. All control subjects were assessed with the ADI, and none met the ADI algorithm criteria for either autism or "pervasive developmental disorder not otherwise specified."

Psychiatric Examination

The following psychiatric examinations were administered:

*Autism Diagnostic Interview (ADI):*¹⁰ The ADI is a semistructured diagnostic interview for autism. The ADI has been shown to be reliable, and it adequately discriminates autistic individuals from mental age-matched nonautistic comparison groups.

*Childhood Autism Rating Scale (CARS):*¹² The CARS is a 15-item behavioral rating scale developed to identify children with autism and to distinguish them from developmentally handicapped children without autism syndrome. The CARS has been demonstrated to have high reliability and to be a valid measure of the diagnosis of autism.

*Aberrant Behavior Checklist (ABC):*¹³ The ABC is a 58-item rating scale that measures pathological behaviors in moderately to profoundly mentally retarded individuals with developmental disorders. It is divided into five dimensions: irritability, lethargy, stereotypic behaviors, hyperactivity, and excessive speech.

Neuropsychological Examination

All 30 autistic and 10 of the 14 control subjects were assessed with the Leiter International Performance Scale,¹⁴ a measure of nonverbal IQ. Because of the severity of mental retardation in most of our sample, the Wechsler Intelligence Scale for Children (WISC)¹⁵ was administered successfully in only 4 control subjects and in none of the autistic patients. The Performance IQ of the WISC was used as an estimate of nonverbal IQ in these subjects.

SPECT Examination

This study was approved by the Ethics Review Committee of the Raúl Carrea Institute of Neurological Research. Written consent was obtained from caregivers and, where possible, subjects (5 autistic individuals and 9 control subjects) after a full explanation of the study. A SPECT study was carried out within 1 week after the psychiatric examination. Technetium-99m *d,l*,hexamethylpropyleneamine oxime ([^{99m}Tc]HMPAO; Ceretec [exametazime], Amersham International) 25 mCi was in-

jected intravenously into an antecubital vein. Subjects sat with eyes closed and ears unplugged in a quiet room with dim lights. Fifteen minutes after the injection, subjects were placed in a supine position with the orbitomeatal line positioned vertically, centered in the field of view. Five autistic patients and 3 control subjects were anesthetized before the MRI and SPECT scanning, using inhalatory anesthesia with either halothane or sevoflurane (^{99m}Tc]HMPAO was always injected 1 hour before the anesthesia). The alignment was carried out with vertical and horizontal laser beams, and the subject's head was physically restrained in place. SPECT was carried out on a General Electric 400 AC/T rotating gamma camera attached to a Starcam 3200 computer. The resolution of the system has been measured to be 14 mm full width at half maximum in the plane of reconstructed transverse sections. An MRI scan was carried out in every subject, and slices 5 mm thick were obtained in the axial, coronal, and sagittal planes by use of a fast sequence. To minimize motion during scanning, caregivers were always allowed to stay next to the scanner.

SPECT studies were carried out with a high-resolution collimator and a 64×64 matrix. There were 64 images obtained over 360 degrees, with a 30-second acquisition time and a zoom of 1.6. Processing was carried out with Butterworth filtering, a critical frequency of 0.44, and a slice width of 1 pixel. Reconstructed brain slices were then reoriented in the orbitomeatal line by using the sagittal and axial views, and a set of 30 axial, sagittal, and coronal sections at 6.4-mm increments was obtained. This procedure was carried out by using Starcam software. Square regions of interest (ROIs) consisting of 3×3 pixels (voxel [$3 \times 3 \times 1$ pixels] = 2.35 cm^3) were used to obtain activity ratios in axial slices, taking the cerebellum as a reference. Specific ROIs were identified by using the atlas of Matsui and Hirano¹⁶ and defined for each MRI scan. Measurements (anterior, middle, and posterior) were carried out for each of the following brain areas: frontal orbital, frontal superior (dorsal), temporal basal, temporal inferior, temporal superior, parietal, occipital lobes, thalamus, and basal ganglia. These measurements were averaged for each region in the right and left hemispheres. ROIs were also placed in the cerebellum. To determine the activity ratio (brain region/cerebellum), the counts per ROI of each cortical area were divided by the average counts per ROI found in each cerebellar hemisphere in the region with the highest average count. This ratio was used as a measure of regional cerebral blood flow because none of the previous SPECT studies in autism showed perfusion abnormalities in the cerebellum. All SPECT measurements were carried out by a neuroradiologist blinded to the

clinical data. The intrarater and interrater reliabilities of these measurements have been reported previously.¹⁷

Statistical Analysis

Statistical analysis was carried out with analysis of covariance (ANCOVA) and post hoc Tukey tests. Frequency distributions were calculated by using chi-square tests and a Yates' correction for expected cell sizes smaller than 5. All probability values are two-tailed.

RESULTS

Demographic and Psychiatric Findings (Table 1)

There were no significant differences in gender, chronological age ($t=0.32$, $P=0.74$), mental age ($t=0.66$, $P=0.50$), or performance IQ ($t=1.59$, $P=0.12$) between autistic individuals and control subjects. Height, head circumference, and weight were also comparable. As expected, autistic individuals had significantly higher CARS scores than nonautistic control subjects ($t=5.38$, $df=42$, $P<0.0001$). Autistic individuals also showed significantly higher scores than the control group on all five ABC domains: irritability ($t=6.21$, $df=42$, $P<0.0001$), lethargy ($t=3.27$, $df=42$, $P<0.01$), hyperactivity ($t=5.71$, $df=42$, $P<0.01$), excessive speech (which also assesses repetitive language and stereotypic speech; $t=1.95$, $df=42$, $P=0.05$), and stereotypies ($t=2.51$, $df=42$, $P<0.05$).

MRI and SPECT Findings (Table 2)

All MRI scans were read as normal by a board-certified neuroradiologist. In a recent study that included most

TABLE 1. Demographic and psychiatric findings

Variable	Autism Group	Control Group
Number of patients	30	14
Gender, <i>n</i> (% female)	30 (9)	36 (5)
Chronological age, years	11.1 ± 7.0	11.2 ± 4.3
Mental age, years	2.6 ± 2.5	4.7 ± 3.3
Performance IQ	30.0 ± 18.5	44.9 ± 32.1
Height, cm	135.0 ± 26.7	141.0 ± 18.0
Head circumference, cm	53.2 ± 3.3	52.8 ± 3.1
Weight, kg	39.9 ± 19.3	40.2 ± 18.6
CARS**	43.1 ± 7.9	25.8 ± 13.3
ABC		
Irritability**	17.4 ± 8.1	6.2 ± 8.1
Lethargy**	16.4 ± 10.2	6.5 ± 6.8
Stereotypies*	9.2 ± 5.3	4.5 ± 6.3
Hyperactivity**	19.2 ± 13.8	5.7 ± 10.0
Excessive speech*	3.2 ± 3.8	1.1 ± 1.6

Note: Except for number of patients and gender, values shown are mean ± SD. CARS = Childhood Autism Rating Scale; ABC = Aberrant Behavior Checklist.

* $P<0.05$; ** $P<0.01$.

of the present sample, we demonstrated the autistic group to have significantly smaller corpus callosum measurements compared with the control group,¹⁸ but no significant between-group differences were found in cerebellar vermis measurements.

A three-way ANCOVA with repeated measures for SPECT measurements (group \times region \times side; covariate: mental age) showed a significant group effect ($F=8.13$, $df=1,41$, $P<0.01$, autistic individuals showing significantly lower overall brain perfusion than the control group); a significant group \times region \times side interaction ($F=2.02$, $df=9,378$, $P<0.05$); and a trend for a significant group \times region interaction ($F=1.81$, $df=9,378$, $P=0.06$). Post hoc analyses demonstrated that autistic patients had significantly lower perfusion than the control group in the following brain areas: right basal temporal ($P<0.0001$), right inferior temporal ($P<0.05$), right and left occipital ($P<0.0001$), right and left thalamus ($P<0.0001$), and left basal ganglia ($P<0.0001$). When those individuals who underwent anesthesia or had a history of seizures were excluded from the statistical analysis, there still was a significant group \times region interaction ($F=1.96$, $df=9,270$, $P<0.05$).

To assess the evidence for abnormal connectivity between the above brain areas, we calculated a correlation matrix between these areas for both autistic individuals and control subjects (Table 3). Using a conservative alpha = 0.001 (equivalent to an r of 0.75 for the control group), the control group had 26 of 42 correlations (62%) above this r -value, as compared to only 8 of 42 correlations (19%) for the autistic group ($\chi^2=18.4$, $df=1$, $P<0.0001$).

To explore clinical correlates of the SPECT results, we calculated correlations between the three ADI domains and the relative perfusion in brain areas that differed significantly between autistic and control subjects. We found significant correlations ($P<0.01$) between scores

for ritualistic-repetitive behaviors and both left and right relative thalamic perfusion ($r=-0.39$ and $r=-0.42$, respectively). None of the remaining correlations were significant at the $P<0.01$ level. Within the ritualistic-repetitive behavior domain, relative thalamic perfusion was significantly correlated with the following items: resistance to change in the environment (right thalamus, $r=-0.44$, $P<0.01$); unusual attachments (right and left thalamus, $r=-0.40$, $P<0.01$, and $r=-0.37$, $P<0.05$, respectively); difficulties with minor changes in routine (right and left thalamus, $r=-0.37$, $P<0.05$, and $r=-0.35$, $P<0.05$, respectively); and unusual sensory interests (right thalamus, $r=-0.40$, $P<0.01$).

DISCUSSION

We carried out [^{99m}Tc]HMPAO SPECT studies in a series of autistic individuals and a group of nonautistic control subjects with mental retardation and mental age comparable to those of the autistic group. Autistic subjects showed significantly lower perfusion in the right temporal and both occipital lobes, left and right thalami, and left basal ganglia.

Several limitations of our study should be pointed out. Autistic individuals and several control subjects were assessed with different neuropsychological instruments. However, these assessments are well standardized in autistic samples and provide a valid estimate of mental age. Another limitation is that some of the autistic subjects and control subjects had to be anesthetized before the SPECT and MRI studies. However, anesthesia was always administered no less than one hour after the injection of [^{99m}Tc]HMPAO (i.e., when the radiotracer uptake is in the steady state). Ideally, our study would have also included a normal control group, but there are serious objections to exposing normal children to radio-

TABLE 2. Mean values for regional brain perfusion in autistic and control subjects on SPECT (brain area/cerebellum ratio \times 100)

Region	Autism Group		Control Group	
	Left	Right	Left	Right
Frontal orbital	71.5 \pm 10.9	72.9 \pm 11.4	74.4 \pm 7.4	77.3 \pm 6.9
Frontal inferior	80.5 \pm 8.3	81.1 \pm 9.2	83.3 \pm 6.2	84.2 \pm 5.1
Frontal superior	88.0 \pm 9.3	87.1 \pm 8.2	91.5 \pm 6.1	90.6 \pm 5.7
Temporal basal	78.8 \pm 6.6	78.7 \pm 10.5**	81.6 \pm 8.4	86.8 \pm 8.3
Temporal inferior	85.5 \pm 6.3	85.6 \pm 6.9*	89.4 \pm 6.2	91.4 \pm 6.6
Temporal superior	88.4 \pm 6.1	87.6 \pm 6.3	91.7 \pm 8.4	93.2 \pm 6.2
Parietal	89.2 \pm 7.7	88.0 \pm 7.0	94.2 \pm 7.8	90.8 \pm 7.6
Occipital	94.9 \pm 8.5**	93.0 \pm 9.1**	103.3 \pm 13.8	104.2 \pm 13.5
Thalamus	87.9 \pm 9.5**	89.9 \pm 8.9**	98.2 \pm 16.3	100.1 \pm 14.3
Basal ganglia	87.6 \pm 10.8**	91.7 \pm 10.6	96.3 \pm 16.2	97.1 \pm 13.7

Note: Significant findings are for lower perfusion in autism group vs. control group.
* $P<0.05$; ** $P<0.0001$.

active substances. Our study did not include high-functioning autistic individuals, and whether there are significant differences in regional brain perfusion between high- and low-functioning autistic subjects will have to be examined in future studies.

Our study included primarily autistic patients with moderate to severe mental retardation and a control group comparable in chronological and mental age, Performance IQ, and morphometric variables such as height, weight, and head circumference. Autistic individuals had significant perfusion deficits in ventral brain areas such as the basal and inferior temporal-occipital regions, and in subcortical structures such as the thalami and left basal ganglia. The question that now arises is what relevance these findings have to the brain mechanism underlying autism.

Recent neuroimaging studies demonstrate brain abnormalities in autistic individuals, such as a smaller size of the corpus callosum,^{18,19} enlargement of the cerebellum and the parietal, temporal, and occipital lobes,²⁰ and an increase in basal ganglia volume in high-functioning autistic subjects.²¹ Postmortem studies also showed developmental abnormalities in temporal lobe structures and cerebellum.²² Our finding of significantly lower temporal and occipital perfusion in autistic subjects suggests that the structural abnormalities of these brain areas may result in reduced cortical activity.

Sears et al.²¹ reported significant correlations between lower caudate volumes, as measured with MRI, and higher scores in the ritualistic-repetitive domain of the ADI. In the present study, we found a significant negative correlation between left and right thalamic perfusion and ritualistic-repetitive behaviors, suggesting that subcortical dysfunction may be related to the production of stereotyped and ritualistic behavior in low-functioning autistic individuals.

We calculated correlation matrices for relative perfusion in the brain areas found to be significantly different between autistic and control subjects. We found these cor-

relations to be more robust in the control group than in the autistic group, supporting Rumsey and co-workers^{3,4} finding of reduced correlations of metabolic activity between different brain regions in autistic individuals compared with normal control subjects. It is important to note, however, that our results were generated after a post hoc analysis that included a large set of correlations, and they should be considered in the light of this methodological limitation.

It is still unclear how the above brain abnormalities may account for the social and communication deficits and stereotyped-repetitive behaviors that define autism. Our present SPECT findings may help to explain several behavioral features of autism, such as impulsive and aggressive behaviors (to self and others), motor disinhibition (such as stereotypic and manneristic movements and echophenomena), and deficits in planning, sequencing, and attention. In recent years, Starkstein and Robinson²³ examined the neuroanatomical correlates of disinhibition syndromes (e.g., euphoria, hyperactivity, irritability, aggressive outbursts, and impulsive behaviors) in adult individuals with focal brain lesions. They found significant involvement of paleocortical brain areas such as the inferior temporal and orbitofrontal brain regions. Pandya and Yeterian²⁴ recently suggested that ventral temporal and middle prefrontal areas as well as paleocortically derived regions of the thalamus and basal ganglia may provide response modulation, planning and sequencing, means of holding events "online," and attentional resources. Thus, dysfunction of these brain areas, as demonstrated in the present study, could produce some of the emotional and behavioral disorders usually described in autistic subjects.

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TABLE 3. Correlation matrix for relative perfusion in brain regions with significantly lower perfusion in autistic individuals compared with mental age-comparable control subjects

Region	Right Temporal-Basal	Left Basal Ganglia	Left Thalamus	Right Thalamus	Left Occipital	Right Occipital	Right Temporal-Inferior
Right temporal-basal	—	0.79 / 0.44	0.69 / 0.60	0.76 / 0.46	0.53 / 0.36	0.54 / 0.53	0.67 / 0.46
Left basal ganglia	0.79 / 0.44	—	0.91 / 0.81	0.96 / 0.82	0.84 / 0.28	0.85 / 0.37	0.75 / 0.34
Left thalamus	0.69 / 0.60	0.91 / 0.81	—	0.92 / 0.88	0.88 / 0.37	0.89 / 0.54	0.72 / 0.27
Right thalamus	0.76 / 0.58	0.96 / 0.73	0.92 / 0.77	—	0.87 / 0.40	0.89 / 0.56	0.75 / 0.12
Left occipital	0.53 / 0.36	0.84 / 0.28	0.88 / 0.37	0.87 / 0.58	—	0.95 / 0.90	0.61 / 0.27
Right occipital	0.54 / 0.53	0.85 / 0.37	0.89 / 0.54	0.89 / 0.65	0.95 / 0.90	—	0.69 / 0.44
Right temporal inferior	0.67 / 0.46	0.75 / 0.34	0.72 / 0.27	0.75 / 0.37	0.61 / 0.27	0.69 / 0.44	—

Note: Correlations for autistic individuals are shown in **bold** and correlations for the control group in medium type.

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