Original article

Regional cerebral blood flow in children with autism spectrum disorders: a quantitative ^{99m}Tc-ECD brain SPECT study with statistical parametric mapping evaluation

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Background Autism spectrum disorders (ASD), which include autism, asperger syndrome (AS) and pervasive developmental disorder-not otherwise specified (PDD-NOS), are devastating neurodevelopmental disorders of childhood resulting in deficits in social interaction, repetitive patterns of behaviors, and restricted interests and activities. Single photon emission computed tomography (SPECT) is a common technique used to measure regional cerebral blood flow (rCBF). Several studies have measured rCBF in children with ASD using SPECT, however, findings are discordant. In addition, the majority of subjects used in these studies were autistic. In this study, we aimed to investigate changes in rCBF in children with ASD using SPECT.

Methods A Technetium-99m-ethyl cysteinate dimmer (^{99m}Tc-ECD) brain SPECT study was performed on an ASD group consisting of 23 children (3 girls and 20 boys; mean age (7.2±3.0) years) who were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria and an age-matched control group with 8 children (1 girl and 7 boys, mean age (5.5±2.4) years). Image data were evaluated with Statistical Parametric Mapping, 5th version (SPM5). A Student's *t* test for unpaired data was used to compare rCBF and asymmetry in the autism and corresponding control group. The covariance analysis, taking age as covariance, was performed between the ASD and control group.

Results There was a significant reduction in rCBF in the bilateral frontal lobe (frontal poles, arcula frontal gyrus) and the bilateral basal ganglia in the autism group, and a reduction in the bilateral frontal, temporal, parietal, legumina nucleus and cerebellum in the AS group compared to the control. In addition, asymmetry of hemispheric hypoperfusion in the ASD group was observed. Inner-group comparison analysis revealed that rCBF decreased significantly in the bilateral frontal lobe (42.7%), basal nucleus (24.9%) and temporal lobe (22.8%) in the autism group, and in the bilateral cerebellum (22.8%), basal nucleus (19.3%) and right thalamencephalon (16.6%) in the AS group (P <0.05).

Conclusions The decrease in rCBF in ASD is a global event, which involves the bilateral frontal, temporal, limbic system and basal ganglias. Asymmetry of hemispheric hypoperfusion was more obvious in the AS group than the autism group, which indicates a different neurobiological mechanism from that of autism.

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Autism spectrum disorders (ASD) are a series of life-long neuropsychiatric disorders that begin in early life. It has been over 60 years since Kanner[1] first used the term "autism" to indicate a condition in a group of children who presented social, communication and behavioral difficulties. Childhood autism is known as an early, severe, developmental disorder of unknown origin with, most likely, multiple aetiologies characterized by qualitative impairment in social relationships, communications and cognitive functioning. In addition, children present an abnormal restricted repertoire of behaviors and interests. These symptoms are defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for an accurate evaluation of the disease. Numerous genetic, histology, anatomy and neuroimaging studies have provided irrefutable evidence that autism is a complicated disorder,[2-5] however, the neurobiological mechanisms remain unclear.

In recent years, single photon emission computed tomography (SPECT), metabolism (^{18}F-FDG) with photon emission tomography (PET) and functional changes with magnetic resonance imaging (MRI) have been widely used to monitor regional cerebral blood flow (rCBF) in individuals with autism and other related disorders. SPECT is a common technique that is used to measure rCBF, which reflects changes in synaptic

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functional activities. In particular, high resolution SPECT and quantitative analysis of images can provide accurate measures of rCBF. Several studies have used SPECT to show abnormalities in focal rCBF in children with ASD.[6-13] However, many of the subjects used were typically autistic, and few had asperger syndrome (AS). The purpose of this study was to clarify which areas of the brain present with abnormalities in rCBF in children with ASD, by investigating changes in rCBF following ^{99m}Tc-ECD brain SPECT in autistic children and non-autistic controls.

METHODS

Participants

The study was performed on an ASD group consisting of 23 children (3 girls and 20 boys; mean age (7.2±3.0) years), which included 14 with autism (11 boys and 3 girls, 10 right-handed and 4 ambidextrous) and 9 with AS (all boys). In addition, an age-matched control group consisting of 8 children (1 girl and 7 boys, mean age (5.5±2.4) years) was used. All patients who had been diagnosed as autistic or with AS according to the DSM-IV underwent a brain SPECT scan. The study was approved by the Ethical Committee of Sun Yat-sen University. Written informed consent was obtained from parents of the patients prior to examination. Because of ethical reasons, the control group consisted of children who had previously been to our department for regular neurological development examination and who had a normal ^{99m}Tc-ECD brain perfusion SPECT and developmental history. Participants with known history of infection, metabolic or chromosomal diseases, persistent seizures, sclerosis tuberose, multiple neuro-fibromatosis, cardiovascular disease and other identifiable neuropsychological psychiatric diseases were excluded.

SPECT scan

A SPECT scan was performed on all participates. Potassium perchlorate ($KClO_4$, 50–100 mg) was taken orally in order to block the choroid plexus and thyroid before scanning. Patients were required to keep resting states for 15 minutes. ^{99m}Tc-ECD (14.8 MBq/kg, Guangdong Xi'ai Nucleus Pharmaceutical Center, China Isotope Company) was administered intravenously in a quiet environment while patients rested in the supine position with eyes closed and without talking. Participates in the ASD group were given chloral hydrate (0.5 ml/kg) before scanning in order to prevent motion artifacts during the acquisition. At least 30 minutes after the radiopharmaceutical injection, the SPECT scan was conducted.

Image data possessing

The image data was acquired with a Discovery VH coincidence detection system (GE, USA) equipped with a low energy high resolution camera. Data were acquired as 128 projections in a 128×128 digital matrix (pixel size 4 mm × 4 mm) with the following parameters: magnification 1.3×, minimum turning radius, continuous scan mode, 4 minutes/round and 8 rotations. The raw data were reconstructed as slices of 1 pixel thickness for the transverse, sagittal and coronal plane. Images were saved and transferred to a Dicom digital format. Data were converted to an Analyze format with MRIcro1.4 software and image data with a matrix size of 79×95×69, pixel size of 2 mm × 2 mm × 2 mm was acquired by spatial normalization and smoothing according to the standard normal brain SPECT images and compared to the template obtained from images of the control group.

Statistical analysis

A two sample independent *t* test for unpaired data was used to compare relative regional cerebral perfusion and asymmetry in the autism group with the corresponding values of the controls. The covariance analysis, taking age as covariance, was performed on the AS and control group. The intensity threshold was set at 80% of the global brain average level, the statistical analysis was performed, and the amount of inference and SPM *t*-statistic (SPM {t}) were determined. A *P* value less than 0.001 was accepted as significant. The significant MNI coordinate value was transferred to the Talairach coordinates to obtain rCBF locations with Statistical Product and Service Solutions, V13.0 (SPSS13.0, USA).

RESULTS

Autism group vs. control group

A significant decrease in rCBF was observed in the autism group in the bilateral frontal lobe (frontal poles, arcula frontal gyrus) and bilateral basal ganglia when compared to the control. Moreover, a significant difference was also observed in terms of the right-to-left asymmetry of hemispheric perfusion between the control group and the autism group, with a greater right rCBF in the autism group, including the inferior and middle frontal gyrus, inferior temporal gyrus, angular gyrus and cuneate lobe. At the same time, hypoperfusion of the left subiculum hippocampi (amygdaloid body cluster) was also observed (Table 1 and Figure 1).

Asperger's syndrome group vs. control group

The covariance analysis, taking age as covariance, was performed on the AS group and control group. Hypoperfusion was observed in the bilateral frontal, temporal, parietal and legumina nucleus and cerebellum. In addition, the left limbic system resulted in a decrease in rCBF located in the caudatum nucleus and parahippocampal gyrus hook, and hypoperfusion of the amygdaloid nucleus was also observed. The asymmetry of hemispheric perfusion appeared more severe in the autism group when compared to the control (Table 2 and Figure 2).

Distribution comparison of rCBF between the autism and AS group

The decreasing pixel cluster values of rCBF in the autism

Table 1. Reduction in rCBF and peak value coordinate in the autism group compared to the control group

Brain region	Talairach coordinates			*t* values	*P* values
	x	y	z		
Right frontal pole	36	50	–14	6.36	<0.001
Right orbital frontal gyrus	18	59	–15	4.33	<0.001
Right orbital frontal gyrus	4	51	–26	3.98	<0.001
Right inferior frontal gyrus	5	22	–25	4.95	<0.001
Right middle frontal gyrus	40	38	5	4.33	<0.001
Left frontal pole	–16	63	–15	6.03	<0.001
Left orbital frontal gyrus	–16	59	–15	4.95	<0.001
Right temporal					
Right superior temporal gyrus	62	–22	–4	4.33	<0.001
Right inferior temporal gyrus	54	–7	–32	5.40	<0.001
Right inferior temporal fusiform gyrus	54	–70	0	4.31	<0.001
Right angular gyrus	50	–54	24	5.06	<0.001
Right cuneate lobe	46	–76	26	4.58	<0.001
Right lenticular nucleus	14	13	–18	6.03	<0.001
Left lenticular nucleus	–32	–3	13	4.94	<0.001
Left Subiculum hippocampi	–20	–3	–13	4.11	<0.001

Talairach coordinates: x: distance from central sagittal plane, "–" : left sides of central sagittal plan. y: distance from front inosculation, "–" : behind of front inosculation. z: distance from front-back inosculation plane, "—" under front-back inoscu lation plane.

Table 2. Reduction in rCBF and peak value coordinate in the AS group compared to the control group

Brain regions	Talairach coordinates			*t* values	*P* values
	x	y	z		
Right orbital frontal gyrus	12	52	–20	4.54	<0.001
Right inferior frontal gyrus	48	46	–14	5.33	<0.001
Left inferior frontal gyrus	–8	–17	51	4.63	<0.001
Right inferior temporal fusiform gyrus	67	–17	–20	6.25	<0.001
Right inferior temporal gyrus	55	–11	–23	5.05	<0.001
Right inferior temporal gyrus	32	–4	–34	4.22	<0.001
Right superior temporal gyrus	63	–25	–2	4.14	<0.001
Left superior temporal gyrus	–55	–13	–28	7.6	<0.001
Right angular gyrus	36	–84	32	4.25	<0.001
Right lingualis gyrus	20	–62	–2	5.84	<0.001
Right cuneate lobe	40	–74	39	3.70	<0.001
Right occipito temporalis lateralis gyrus	52	–72	0	4.84	<0.001
Left lingualis gyrus	–20	–56	–2	4.11	<0.001
Right thalamencephalon	16	–17	0	6.09	<0.001
Left parahippocampal gyrus hook	–22	5	–14	6.29	<0.001
Left amygdaloid nucleus	–24	–3	–14	5.55	<0.001
Right lenticular nucleus	32	14	3	6.25	<0.001
Right lenticular nucleus	20	9	–10	4.30	<0.001
Left lenticular nucleus	–24	–11	10	5.58	<0.001
Left caudatum nucleus	-6	6	–2	4.42	<0.001
Right cerebellum anterior lobe	10	–36	–27	3.88	<0.001
Right cerebellum posterior lobe	42	–72	–39	5.27	<0.001
Left cerebellum anterior lobe	–18	–50	–23	5.43	<0.001
Left cerebellum posterior lobe	–28	–79	–26	4.10	<0.001

and AS groups were extracted to conduct categorical Chi-square analysis in order to compare differences in rCBF between the two groups. A significant decrease in rCBF was identified in the autism group in the bilateral frontal lobe (42.7%), basal nucleus (24.9%) and temporal lobe (22.8%). A significant decrease in rCBF (P <0.05) was identified in the AS group in the bilateral cerebellum (22.8%), basal nucleus (19.3%) and right thalamencephalon (16.6%) (Table 3).

DISCUSSION

Current neurobiological hypothesis assumes that the mechanism of ASD is based on multiple primary clinical deficits in higher order cognitive processing abilities, abnormalities at the neural system level or in multiple structures at several levels of the neuroaxis,[9] which means the involvement of several cerebral cortical regions, including the limbic system and the temporal and parietal lobes. In addition, clinical symptomatology in autism may also be because of the dysfunctional connections between these cortical regions.[5-14]

Several studies on brain metabolism and blood flow with PET and SPECT in patients with ASD have been conducted[6-11,13-16] and the results have been controversial.

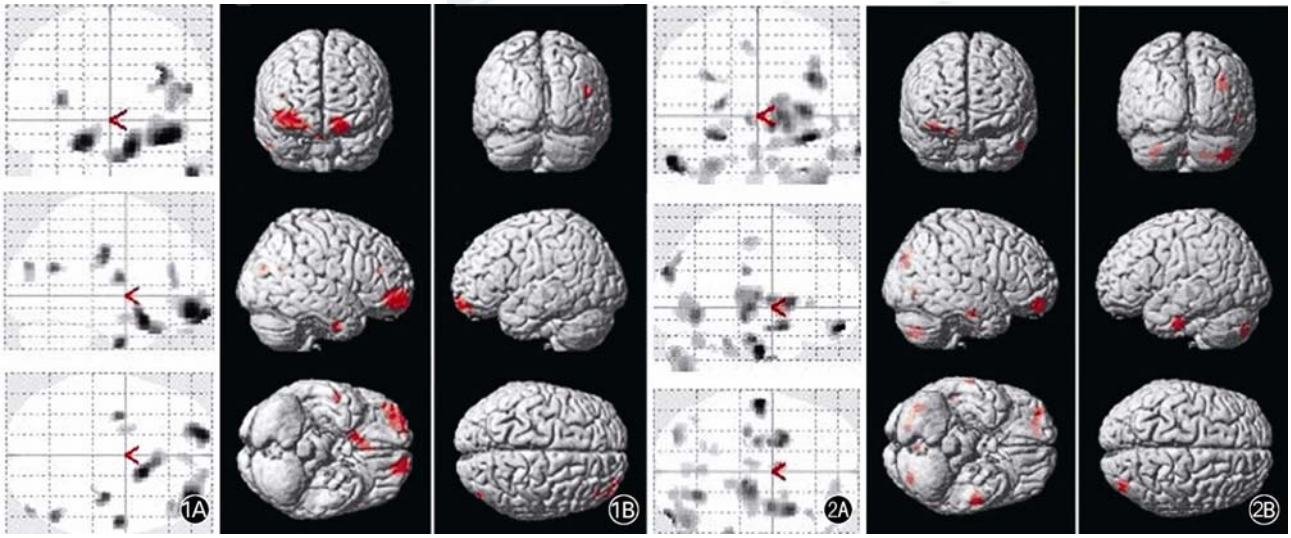

Figure 1. Maximum projective image of the decrease in rCBF in the autism group compared to the control group. **1A:** maximum projective image. **1B:** rendering maximum projective 3D brain structural image.
Figure 2. Maximum projective image of the decrease in rCBF in the AS group compared to the control group. **2A:** maximum projective image. **2B:** rendering maximum projective 3D brain structural image.

Table 3. Distribution comparison of the decrease in rCBF between the autism group and the AS group

Brain regions	Number of pixelcluster (*n* (%))		*P* values
	Autism group	AS group	
RF	928 (41.78)	285 (7.28)	
RT	115 (5.18)	245 (6.22)	
RO	75 (3.38)	396 (10.06)	
RP	90 (4.05)	181 (4.60)	
RB	448 (20.17)	634 (16.10)	
RTh	0	652 (16.56)	<0.001
LF	20 (0.90)	221 (5.61)	
LT	387 (17.42)	67 (1.70)	
LO	0	20 (0.51)	
LB	98 (4.41)	127 (3.22)	
LL	60 (2.70)	214 (5.43)	
LC	–	896 (22.75)	

RF: right frontal, RT: right temporal, RO: right occipital, RB: right basal nucleus, RTh: right thalamencephalon, LF: left frontal, LT: left temporal, LO: left occipital, LB: left basal nucleus, LL: left limbic, LC: left cerebellum.

Most studies show evidence that rCBF is altered in autistic patients, especially asymmetrical brain activity and a reduction in rCBF in the temporal lobes and frontal lobes.[6] However, data from these studies shows a significant decrease in global cerebral perfusion in autistic children compared to normal children. Zilbovicius et al[13] showed hypoperfusion at ages 3–4 years in the bilateral frontal lobes and a study by Kaya et al[9] implied that rCBF in the frontal region in autistic children increases with age. Using SPECT, Baron-Cohen et al[17] found that the mental state recognition task was related to the theory of the mind and concluded that both were impaired in autism. Their SPECT results implicated the orbito-frontal cortex as the basis for this ability. This study compared rCBF distribution between ASD and control patients, taking age as covariance, and the results indicated that the bilateral frontal and temporal lobe in children with ASD corresponded with Zilbovicius et al[13] and Baron-Cohen et al.[17]

A decrease in rCBF was found in the bilateral orbitofrontal cortex in autistic children, however, a decrease in rCBF was observed in the right orbitofrontal and left premotor area of the superior frontal gyrus in AS children. The prefrontal cortex has been regarded as the higher neural center or "social brain" and may involve several high level cognitive processes, such as abstract thinking, executive function,[4] judgment of social information and conjecture.[18-20] Changes in function or morphology of this area may contribute to mis-evaluation of social information, which has been shown in some studies. Autistic children show classic signs of frontal lobe damage, such as repetitive behaviors, an inability to inhibit attention to salient objects, and a deficit in tests for executive function. In this study, the decrease in rCBF in the prefrontal cortex in the autism group was more significant and resulted in greater cognitive impairment than the AS group.

Bilateral temporal hypoperfusion has been reported to be more frequent.[16,21] Contrary to other brain imaging studies, we found that rCBF was reduced in the superior temporal gyrus, inferior temporal gyrus and fusiform gyrus, particularly in the right fusiform gyrus. Interestingly, the fusiform gyrus is known to be involved in face recognition, and the superior temporal sulcus is required for judging eye gaze, emotional expression and lip movement.[22] At the cognitive level, autistic patients present an atypical processing of complex figures, including a deficit in facial perception. In fact, prosopagnosia is a unique syndrome in which the recognition of familiar faces is impaired. In a recent study, prosopagnosia has been related to a lesion of the right fusiform gyrus.[23] The temporal gyrus includes Wernicke's area, which is known to be related to language function. In addition, hypoperfusion of this region may be related to autistic speech and understanding deep lamellar speech.[21] Evidence from genetic studies has proven that language disorders are linked to autism, particularly given the recent finding that genes on chromosome 7q are abnormal both in autism and severe expressive language disorders.[24] The results of this study suggest that under resting states decreases in rCBF are closely associated with communication impairment in children with ASD. Some theories assume that hypoperfusion or functional disorder of the temporal lobe may be the fundamental deficit in the pathology of ASD, considering they contain a receptive speech region and a hearing region.[25] However, we found global changes in rCBF in the right cuneus in ASD brains, and in particular the bilateral lingualis gyrus in AS brains. These alterations in rCBF have been shown to disrupt cortical connections and disturb the integration of information.[9] rCBF changes in the limbic system, including the amygdala and hippocampus, were considered to impair the response to new stimuli in ASD patients.[26]

Whether AS is subordinated to ASD is still controversial. According to the diagnosis criteria, it was classified into a spectrum with other autistic disorders. However, there are opinions insisting that AS is a disorder with a unique neurobiological mechanism, which has not been defined, or denied. Few studies have investigated the neural mechanism between autism and AS. Lotspeich analyzed MRI studies in ASD patients and concluded that AS and autism may track different developmental trends in neurology.[27] Another study on gray matter density reported a decrease in density in the callosal gyrus in the AS group compared to the autism group.[28] A decrease in cerebellum volume in AS but not autism patients was also reported by MaAlonam et al.[29] We found a significant decrease in rCBF in the AS group compared to the autism group. In particular, the asymmetry of hemispheric perfusion in the AS group was more obvious than the autism group, suggesting that AS may possess a special neural base resulting in different impairment.

The results of this study indicate that ^{99m}Tc-ECD brain SPECT is a useful tool to locate perfusion abnormalities, and that a decrease in rCBF in ASD is a global event that corresponds to complex clinical symptoms. Moreover,

these results suggest that AS may have a different neurobiological mechanism from autism, however, further studies are required. This study focused on children ASD and compared their rCFB change in a small sample of childhood participates. More cases enrolled at every age in both groups should conducted for further studies as well.

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