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# Abnormal regional cerebral blood flow in childhood autism

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## Summary

**Neuroimaging studies of autism have shown abnormalities in the limbic system and cerebellar circuits and additional sites. These findings are not, however, specific or consistent enough to build up a coherent theory of the origin and nature of the brain abnormality in autistic patients. Twenty-three children with infantile autism and 26 non-autistic controls matched for IQ and age were examined using brain-perfusion single photon emission computed tomography with technetium-99m ethyl cysteinate dimer. In autistic subjects, we assessed the relationship between regional cerebral blood flow (rCBF) and symptom profiles. Images were anatomically normalized, and voxel-by-voxel analyses were performed. Decreases in rCBF in autistic patients compared with the control group were identified in the bilateral insula, superior temporal gyri and left prefrontal cortices. Analysis of the correlations between syndrome scores and rCBF revealed that each syndrome was associated with a specific pattern of perfusion in the limbic system and the medial prefrontal cortex. The results confirmed the associations of (i) impairments in communication and social interaction that are thought to be related to deficits in the theory of mind (ToM) with altered perfusion in the medial prefrontal cortex and anterior cingulate gyrus, and (ii) the obsessive desire for sameness with altered perfusion in the right medial temporal lobe. The perfusion abnormalities seem to be related to the cognitive dysfunction observed in autism, such as deficits in ToM, abnormal responses to sensory stimuli, and the obsessive desire for sameness. The perfusion patterns suggest possible locations of abnormalities of brain function underlying abnormal behaviour patterns in autistic individuals.**

**Keywords**: autism; theory of mind; regional cerebral blood flow (rCBF); single photon emission computed tomography (SPECT)

**Abbreviations**: BA = Brodmann area; DQ = developmental quotient; fMRI = functional MRI; rCBF = regional cerebral blood flow; SPECT = single photon emission computed tomography; SPM = statistical parametric mapping; 99 Tc-99m ECD = technetium-99m ethyl cysteinate dimer; ToM = theory of mind

## Introduction

Autism, defined as a psychiatric disorder of early onset with qualitative impairments in social interaction and verbal and non-verbal communication and an abnormal repertoire of behaviours, is a severe developmental disorder. Autism holds a peculiar fascination for neuroscientists, because most of the core deficits of autism lie in the domain of social relations with others, which is essential to one's humanity. Autism research has also stimulated philosophical debate on self-consciousness, since it provides an example of failure to reflect on mental states (Frith, 1997).

Over the past two decades, many studies of autism have shattered the classical image of the autistic child, the child in the glass shell. Despite general agreement that autism has a biological basis rather than being a psychological disorder, the biological study of the underlying brain abnormalities and of putative genetic mechanisms has received little attention (Bauman *et al*., 1994). Neuropathological studies have revealed abnormalities in the limbic system and cerebellar circuits (Bauman *et al*., 1994). *In vivo* neuroimaging studies have also demonstrated a number of abnormal patterns of the structure and function in these and additional sites (George *et al*., 1992; Hashimoto *et al*., 1995; Mountz *et al*., 1995; Saito *et al*., 1995; Haznedar *et al*., 1997; Filipek, 1999). These findings are not, however, specific or consistent enough to build up a coherent theory of the origin and nature of the brain abnormality in autistic patients.

In the present study, we used single photon emission tomography (SPECT) with technetium-99m ethyl cysteinate dimer (Tc-99m ECD) to measure regional cerebral blood flow (rCBF) in patients with infantile autism and a control group of non-autistic children matched for age, gender and IQ. To clarify which regions of the brain abnormality contribute to autistic behaviours, we also studied the relationship between rCBF changes and the symptom profile in the autistic patients.

## Methods

Twenty-three children (19 boys and 4 girls) with infantile autism and 26 children (21 boys and 5 girls) with non-autistic mental retardation participated in this study. Infantile autism was diagnosed according to the criteria of DSM-IV (American Psychiatric Association, 1994). We excluded subjects with the following criteria: (i) abnormal MRI; (ii) persistent seizure; and (iii) known infectious, metabolic or chromosomal disease. Patients with non-autistic mental retardation did not have a diagnosis and the cause of their condition was unknown. The mean ages of autistic children and non-autistic controls were 6.5 years (SD = 2.4, range 2.6–13) and 8.7 years (SD = 3.2, range 3.4–12), respectively. The mean IQ (measured by the Stanford–Binet test) or development quotient (DQ) was 48 (SD = 19.5) in the autistic group and 57 (SD = 17.52) in the control group. The mean age and IQ or DQ of the control group tended to be higher than in the autistic group. However, a two-sample *t*-test revealed no significant group difference ($P = 0.01$). Written informed consent was obtained from all parents or guardians of the subjects according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the National Center of Neurology and Psychiatry, Tokyo, Japan.

Before the SPECT scanning, all subjects had an intravenous line established while they were lying down. Each subject received an intravenous injection of Tc-99m ECD, which crosses the blood–brain barrier on first pass, is rapidly taken up by neural cells, and is distributed in proportion to regional cerebral perfusion. Because it remains fixed in the cells after uptake, its distribution provides a picture of the pattern of brain perfusion immediately after administration. Therefore, the effect of sedation on measured rCBF should be negligible. The dose of Tc-99m ECD was calculated with the formula [(age in years + 1)/(age in years + 7)] × 740 MBq. However, the maximum dose was regulated so as not to exceed 11 MBq/kg body weight or 555 MBq. Five minutes after the administration of Tc-99m ECD, sedation was given (~3 mg/kg of pentobarbital) to avoid motion during scanning. Ten minutes after injection of Tc-99m ECD, SPECT scanning was done with a three-head SPECT system (Multispect3, Siemens) equipped with high-resolution fan-beam collimators (full width at half maximum, 7.6 mm). For data projection, we used a 128 × 128 format for 24 angles of 120° for each camera with 50 s per angle. A Shepp and Logan Hamming filter was used for SPECT image reconstruction at 0.75 cycles/cm. Attenuation correction was performed using Chang's method.

Symptom scores of autistic patients were obtained by factor analysis of behavioural scores. The behavioural scores were obtained from informants (mainly the patient's mother) in a standardized interview and by clinical observation. The rating system we used for behavioural score was similar to that of the Childhood Autism Rating Scale (Schopler *et al*., 1980). Two paediatric neurologists assessed the patient's behaviour, and inter-rater reliability was good (Cohen's κ value 0.86). Because of the small number of subjects, it was necessary to limit the number of behavioural scores entered in the factor analysis to nine. The nine items selected were: echolalia; abnormal prosody; abnormal grammatical construction; treat people as interchangeable; no symbolic play; no use of finger-pointing; fascination with certain objects; insistence on sameness; and stereotyped behaviour. We eliminated items that are related to odd sensory exploration and motor clumsiness, because current nosologies (DSM-IV) suggest that symptoms of social impairment are critical in the definition of the autistic disorder (Charman *et al*., 1997). Scores were as follows: 1 = severe abnormality; 2 = moderate abnormality; 3 = mild abnormality; 4 = within normal limits. The factor analysis was done using the SPSS (Statistical Package for the Social Sciences). The method of principal factors was used to extract initial factors, a varimax rotation was performed, and factor scores were calculated.

Images were analysed with the statistical parametric mapping software SPM99 and SPM96 (Wellcome Department of Cognitive Neurology, UK). The SPECT data were transformed into a standard stereotaxic space (Talairach and Tournoux, 1988). Because the distribution of Tc-99m ECD in the brain is different from that of $H_2O^{15}$, which is used as the PET template in the SPM program, we made a Tc-99m ECD template for spatial normalization. The ECD template was made by averaging 14 young normal volunteers' Tc-99m ECD images that were spatially normalized using parameters from co-registered $T_1$ volume MRIs. Co-registration of SPECT images and $T_1$-MRIs and spatial normalization of the ECD template were also performed with SPM99. The default spatial normalization of SPM99 used linear and non-linear transformation. A Gaussian filter (12 mm full width at half maximum) was used to smooth each image to accommodate intersubject differences in morphological and functional anatomy and to suppress high-frequency noise in the images. The effect of global differences in CBF between scans was removed by proportional scaling. The subject and covariate effects were estimated with the general linear model at each voxel. To test hypotheses about regional population effects, the estimates were compared using linear compounds or contrasts. The resulting sets of *t* values constituted statistical parametric maps (SPM{*t*}). The SPM{*t*} were transformed to the unit normal distribution (SPM{*Z*}) and thresholded at $P < 0.001$. To correct for the multiple non-independent comparisons that were inherent in this

**Table 1** *Factor analysis of behavioural scores*

| Behaviour | Factor 1: impairments in communication and social interaction | Factor 2: obsessive desire for sameness | Mean score | Standard deviation |
|---|---|---|---|---|
| Eigenvalue | 5.9 | 1.9 | | |
| Variance explained (%) | 53.80 | 17.30 | | |
| Echolalia | 0.802 | 0.138 | 1.91 | 1.74 |
| Abnormal prosody | 0.857 | 0.012 | 2.95 | 1.17 |
| Abnormal grammatical construction | 0.876 | –0.116 | 1.45 | 1.51 |
| Treat people as interchangeable | 0.928 | 0.033 | 1.83 | 0.66 |
| Expressionless face | 0.766 | 0.428 | 2.95 | 0.95 |
| Withdrawal | 0.704 | 0.47 | 3 | 0.87 |
| No symbolic play | 0.794 | –0.103 | 1.68 | 0.99 |
| No finger-pointing | 0.928 | 0.033 | 2.31 | 1.08 |
| Fascination with certain subjects | 0.001 | 0.892 | 2.77 | 1.07 |
| Insistence on sameness | 0.17 | 0.818 | 3.13 | 0.83 |
| Stereotyped behaviour | –0.054 | 0.928 | 1.98 | 0.73 |

analysis, the resulting foci were then characterized in terms of their spatial extent ($k$). This characterization was in terms of the probability that a region of the observed number or of bigger voxels could have occurred by chance over the entire volume analysed (Bonferroni correction, $P < 0.05$). Correlation analyses were performed to study the relationship between rCBF changes and symptom profiles. In order to identify region-dependent correlations across the subjects, a pixel-by-pixel linear regression of regional out of global CBF was performed to remove the confounding effect of differences in global CBF. The correlations between factor scores and CBF were then computed on a pixel-by-pixel basis by covariance analysis. Gender and age were treated as nuisance variables.

## Results

### *Symptom profiles in autistic patients*

The factor analysis of behavioural scores generated two factors with eigenvalues greater than unity, accounting for 88.3% of the variance in behavioural scores (Table 1). The first factor loaded heavily onto the following items: treating people as interchangeable; no use of finger-pointing; abnormal grammatical construction; abnormal prosody; echolalia; and no symbolic play. This group of behaviours was designated 'impairments in communication and social interaction'.

The second factor loaded heavily onto stereotyped behaviour, insistence on sameness, and fascination for certain objects. This group of symptoms was designated 'obsessive desire for sameness'. For each factor, low scores mean severely abnormal behaviours. The same factor structure was obtained when age was a covariate. There was no significant evidence of correlation between factor scores and age, IQ or DQ (Table 2).

**Table 2** *Correlation between each factor score and age, gender and IQ*

| | Factor scores | |
|---|---|---|
| | Factor 1 | Factor 2 |
| Age | 0.06 (n.s.) | 0.11 (n.s.) |
| IQ or DQ | 0.15 (n.s.) | 0.18 (n.s.) |

DQ = development quotient; n.s. = not significant.

### *Changes in rCBF in autistic patients*

Table 3 lists the peaks of significant changes in rCBF obtained in this study, with their anatomical location, Brodmann area (BA), Talairach and Tournoux coordinates (Talairach and Tournoux, 1988) and the corresponding $Z$ scores. Figure 1 shows the SPM in a standard format as a maximum-intensity projection viewed from the right, the back and the top of the brain. The anatomical space corresponds to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988).

Decreases in rCBF in autistic patients compared with the control group were identified in the bilateral insula, superior temporal gyri (BA 22), left inferior frontal gyrus (BA 45) and left middle frontal gyrus (BA 9) (Table 3 and top row of Fig. 1). There was no region of increased rCBF in the autistic group.

In the correlational analysis, positive correlation was observed between scores for factor 1 and rCBF in the left medial prefrontal cortex (BA 9/10) and the anterior cingulate gyrus in autistic patients (Table 3 and middle row of Fig. 1). There was a positive correlation between scores for factor 2 and rCBF in the right hippocampus and the amygdala (Table 3 and bottom row of Fig. 1). A negative correlation between rCBF and scores for factors 1 or 2 was not seen in any region.

## Discussion

Autism is known to have a biological origin, and understanding the brain mechanisms underlying such a severe disorder is a major challenge for research in functional neuroimaging. Nevertheless, as mentioned earlier, SPECT

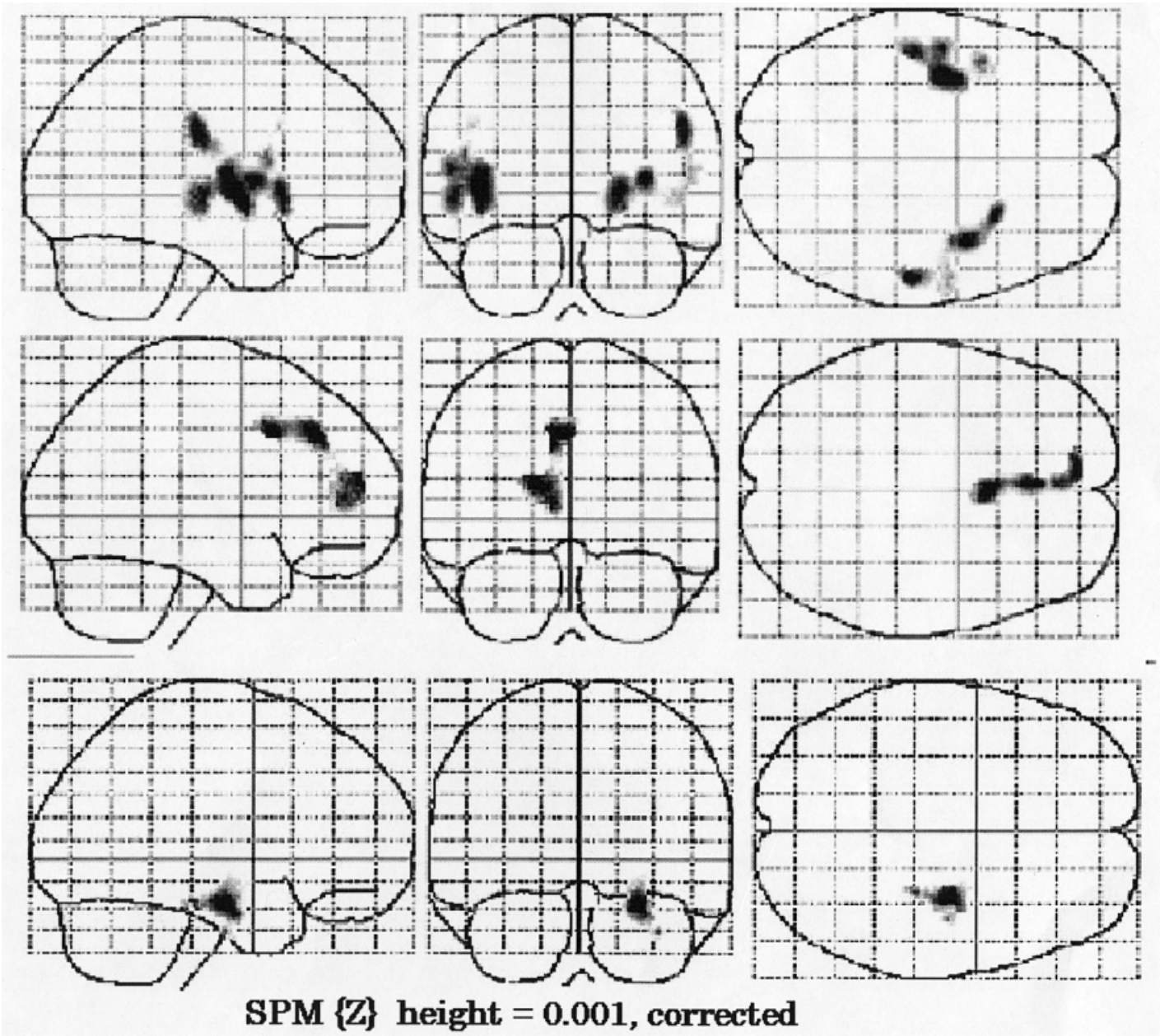


**Fig. 1** *Top*: statistical parametric map of the $t$ statistic after transformation to a SPM$\{Z\}$ for this contrast. The SPM is displayed in a standard format as a maximum-intensity projection viewed from the right, the back and the top of the brain. The anatomical space corresponds to the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988). Representation in stereotaxic space of cerebral regions with significantly decreased rCBF in autistic group compared with the control group ($P = 0.001$; with Bonferroni correction $P = 0.05$). *Middle*: representation in stereotaxic space of cerebral regions positively correlated with scores for factor 1 ($P = 0.001$; with Bonferroni correction $P = 0.05$). *Bottom*: representation in stereotaxic space of cerebral regions positively correlated with scores for factor 2 ($P = 0.001$; with Bonferroni correction $P = 0.05$).

and PET studies with small numbers of subjects have produced the most inconsistent results of all the neuroimaging methods that have been used in autism (George *et al*., 1992; Bauman *et al*., 1994; Mountz *et al*., 1995; Frith, 1997; Haznedar *et al*., 1997; Filipek, 1999). There are several reasons for this inconsistency. First, autism is defined only behaviourally, which often contributes to the heterogeneity of cohort studies. Secondly, factors such as age, gender, IQ and behavioural traits often diverge considerably, with non-uniform matching of controls. The problems of which subjects should be studied and what the criteria for comparison should be confound the interpretation of the results of neuroimaging studies (Filipek, 1999). Therefore, we used IQ- or DQ-matched retarded children as the control not only for ethical reasons but also to avoid this issue.

In the present study, the autistic children had abnormal rCBF in the bilateral insula, superior temporal gyri and left prefrontal cortices (BA 9/45) compared with the non-autistic

**Table 3** *Location and peak of abnormal rCBF areas in autism*

| Region | Talairach coordinates (mm) | | | *Z* score | Corrected value |
|---|---|---|---|---|---|
| | *x* | *y* | *z* | | |
| Decreased rCBF areas in autism | | | | | |
| Left insula | –38 | –2 | 2 | 3.98 | <0.001 |
| Left superior temporal gyrus (BA 22) | –50 | –16 | 0 | 3.75 | <0.001 |
| Left inferior frontal gyrus (BA 45) | –46 | 12 | 18 | 3.34 | <0.001 |
| Left middle frontal gyrus (BA 9) | –42 | 18 | 30 | 3.34 | <0.001 |
| Right insula | 36 | 6 | 4 | 3.85 | <0.001 |
| Right superior temporal gyrus (BA 22) | 52 | 0 | –2 | 3.42 | <0.001 |
| Correlation between rCBF and factor 1 score | | | | | |
| Left anterior cingulate gyrus (BA 32) | –14 | 58 | 14 | 3.89 | <0.001 |
| Left medial prefrontal gyrus (BA 9/10) | –2 | 14 | 36 | 3.98 | <0.001 |
| Correlation between rCBF and factor 2 score | | | | | |
| Right hippocampus | 28 | 12 | –20 | 3.93 | <0.001 |
| Right amygdala | 26 | –4 | –12 | 3.28 | <0.001 |

controls. We suggest that these abnormal areas are related to the cognitive impairments observed in autistic children, such as deficits in language, impaired executive function and abnormal responses to sensory stimuli. Disturbance in the perception and modulation of sensory information is often observed in autistic patients (Ornitz, 1983). Several studies suggest that the insular cortex should be connected to a variety of paralimbic systems and heteromodal association areas that are important in processing complex sensory information (Mesulam *et al*., 1984; Augustine, 1996). Dysfunction in this area could cause abnormal responses to sensory stimuli because of abnormal integration of sensory stimuli. The frontal and temporal abnormalities in autism have also been demonstrated in EEG studies and other SPECT studies (George *et al*., 1992; Dawson *et al*., 1995; Mountz *et al*., 1995). Dawson and colleagues reported that autistic subjects had reduced EEG power in the frontal and temporal regions (Dawson *et al*., 1995). Some SPECT studies using Tc-99m HM-PAO (hexamethyl propylene amine oxime) also revealed abnormal perfusion in the frontal and temporal cortices (George *et al*., 1992; Mountz *et al*., 1995). As for Tc-99m HM-PAO SPECT, SPECT with Tc-99m ECD can be carried out under anaesthesia or sedation without affecting the results.

The relationship between rCBF and symptom profiles in autistic children provides a new insight into autistic behaviour patterns. Factor analysis revealed that the patients' behaviours could be classified into two syndromes: (i) impairments in communication and social interaction; and (ii) an obsessive desire for sameness. Factor 1 (impairments in communication and social interaction) was associated with altered rCBF in the left medial prefrontal regions, including the anterior cingulate gyrus (BA 9/10, BA 32). Activation studies using theory of mind (ToM) tasks have revealed that the left medial prefrontal cortex is a crucial component of the brain system that underlies the understanding of other minds (Fletcher *et al*., 1995; Goel *et al*., 1995; Happe *et al*., 1996; Gallagher *et al*., 2000). The present result, showing altered rCBF in the left medial prefrontal cortex associated with impairments in communication and social interaction, is concordant with the findings of these PET and functional MRI (fMRI) studies.

A deficit in the ToM is one of the most widely accepted explanations of cognitive disorder, such as verbal and non-verbal communication and the socialization and imagination handicaps of autistic individuals (Baron-Cohen *et al*., 1985; Happe, 1993; Frith and Happe, 1994; Fletcher *et al*., 1995; Goel *et al*., 1995; Happe *et al*., 1996; Frith *et al*., 1997). The ToM refers to our ability to explain and predict the behaviour of others in terms of their mental states, such as beliefs, prides and desires. The task most often used to study ToM abilities is the so-called false-belief task (Wimmer and Perner, 1983). Baron-Cohen and Frith and their collaborators have shown in a series of studies that most autistic subjects fail such a ToM task, and they concluded that a deficit in ToM is a central cognitive deficit in autism (Baron-Cohen *et al*., 1985; Happe, 1993; Frith and Happe, 1994; Fletcher *et al*., 1995; Goel *et al*., 1995; Happe *et al*., 1996; Frith, 1997). As we mentioned above, neuroimaging studies have revealed that the ability to attribute mental states is mediated by the medial prefrontal cortex (Fletcher *et al*., 1995; Goel *et al*., 1995; Happe *et al*., 1996; Gallagher *et al.*, 2000). Furthermore, a recent fMRI study suggested that such functional neuroanatomy should be independent of modality (verbal and non-verbal domains) (Gallagher *et al*., 2000). In this context, the present study would support the hypothesis that a deficit in ToM is a central cognitive deficit in autism, and provides some functional relevance for PET and fMRI activation studies using the ToM task.

The altered left anterior cingulate gyrus was also associated with impairments in communication and social interaction. We assume that left anterior cingulate (BA 32) could also be a crucial component of the brain system that underlies ToM. The area BA 32, which receives afferents from BA 9, the temporal pole and the orbitofrontal cortex, has been implicated in higher cognitive function and in the expression and recognition of affect, functions that are compromised in

autism (Pandya and Yeterian, 1985). The anterior cingulate gyrus is the only part of the cerebral cortex that demonstrates cytoarchitectonic abnormalities (Bauman *et al*., 1994). Haznedar and colleagues reported that glucose metabolism and gyrus volume in the right anterior cingulate gyrus (BA 24) were reduced in adult autistic disorder (Haznedar *et al*., 1997). We assume that the discrepancies between Haznedar's study and ours can be explained by the differences in the patient population and in the methods used for data analysis (Haznedar and colleagues used a small sample size, adult patients and the region of interest method).

Another possible brain region associated with the ToM is the orbitofrontal cortex and amygdala (Baron-Cohen *et al*., 1994, 1999). In the studies of Baron-Cohen and colleagues, which used a word task and the 'eye' task, there was no involvement in the medial prefrontal area, but instead an indication that the orbitofrontal cortex and the amygdala are sites of the ability to attribute mental states. It is plausible that the amygdala is closely associated with socialization, because patients with an amygdala lesion show impairments in social judgement and the only animal model of autism involves the amygdala (Bachevalier, 1991; Young *et al*., 1996). However, we could not find any association between rCBF changes in the amygdala and factor 1. Further study is needed to clarify whether abnormal perfusion in the amygdala is associated with impairments in social interaction.

A specific deficit in the ToM cannot account for the whole of the clinical picture of autism (Frith and Happe, 1994; Frith, 1997). This is particularly true for the features of autism that are encompassed by an obsessive desire for sameness. In the present study, the obsessive desire for sameness (factor 2) was segregated from deficit in the ToM (factor 1) by factor analysis. We hypothesized that the obsessive desire for sameness is a kind of perseveration. Therefore, it could be associated with altered rCBF in the prefrontal cortex. Poor performance in many executive function tasks, such as planning, impulse control, working memory, and the initiation and monitoring of action has been documented in autism (Ozonoff *et al*., 1991; Pennington and Ozonoff, 1996). Poor performance in these tasks is often observed in patients with frontal damage and is directly related to stereotyped and rigid behaviours in everyday life. However, we found an unexpected correlation between the score for factor 2 and altered rCBF in the right medial temporal lobe without any prefrontal abnormality. One possible explanation is that the obsessive desire for sameness in autism is related to deficits in orienting to novelty rather than perseveration. Individuals with autism do not seem to orient to novel information in a normal way (Courchesne *et al*., 1984; Bauman *et al*., 1994). Electrophysiological evidence supports this notion (Courchesne *et al*., 1984; Bauman *et al*., 1994). The ability to respond to unexpected stimuli (the orienting response) is a fundamental characteristic of mammalian behaviour and is critical for both survival and normal memory function. Knight reported that the hippocampal region, in addition to its known role in memory formation, is an essential component of the distributed limbic–cortical network that detects and responds to novel stimuli (Knight, 1996). However, we cannot deny the possibility that the obsessive desire for sameness in autistic subjects is caused by prefrontal dysfunction. Further study will clarify this issue.

In conclusion, we found perfusion impairments involving the insula, temporal cortex, medial prefrontal cortex, anterior cingulate gyrus and hippocampus in patients having infantile autism. These abnormalities seem to be related to the cognitive dysfunction observed in autism, such as deficits in the ToM, abnormal responses to sensory stimuli, and the obsessive desire for sameness. The perfusion patterns suggest possible locations for the abnormalities of brain function underlying abnormal behaviour patterns in autistic individuals.

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### References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. DSM-IV 4th ed. Washington (DC): American Psychiatric Association; 1994.

Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. [Review]. Brain Res Rev Brain Res 1996; 22: 229–44.

Bachevalier J. An animal model for childhood autism: memory loss and socioemotional disturbances following neonatal damage to the limbic system in monkeys. Advances in neuropsychiatry and psychopharmacology, Vol. 1. Schizophrenia research. New York: Raven Press; 1991.

Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a 'theory of mind'? Cognition 1985; 21: 37–46.

Baron-Cohen S, Ring H, Moriarty J, Schmitz B, Costa D, Ell P. Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. Br J Psychiatry 1994; 165: 640–9.

Baron-Cohen S, Ring HA, Wheelwright S, et al. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci 1999; 11: 1891–8.

Bauman ML, Kemper TL. The neurobiology of autism. Baltimore: Johns Hopkins University Press; 1994.

Charman T, Swettenham J, Baron-Cohen S, Cox A, et al. Infants with autism: an investigation of empathy, pretend play, joint attention and imitation. Dev Psychol 1997; 33: 781–9.

Courchesne E, Kilman BA, Galambos R, Lincoln AJ. Autism: processing of novel auditory information assessed by event-related brain potentials. Electroencephalogr Clin Neurophysiol 1984; 59: 238–48.

Dawson G, Klinger LG, Panagiotides H, Lewy A, Castelloe P. Subgroups of autistic children based on social behavior display distinct patterns of brain activity. J Abnorm Child Psychol 1995; 23: 569–83.

Filipek PA. Neuroimaging in the developmental disorders: The state of the science. [Review]. J Child Psychol Psychiatry 1999; 40: 113–28.

Fletcher PC, Happe F, Frith U, Baker SC, Dolan RJ, Frackowiak RS, et al. Other minds in the brain: a functional imaging study of 'theory of mind' in story comprehension. Cognition 1995; 57: 109–28.

Frith U. The neurocognitive basis of autism. Trends Cogn Neurosci 1997; 2: 73–7.

Frith U, Happe F. Autism: beyond 'theory of mind'. [Review]. Cognition 1994; 50: 115–32.

Gallagher HL, Happe F, Brunswick N, et al. Reading the mind in cartoons and stories: an fMRI study of 'theory of mind' in verbal and nonverbal tasks. Neuropsychologia 2000; 38: 11–21.

George MS, Costa DC, Kouris K, Ring HA, Ell PJ. Cerebral blood flow abnormalities in adults with infantile autism. J Nerv Ment Dis 1992; 180: 413–7.

Goel V, Grafman J, Sadato N, Hallett M. Modeling other minds. Neuroreport 1995; 6: 1741–6.

Happe FG. Communicative competence and theory of mind in autism: a test of relevance theory. Cognition 1993; 48: 101–19.

Happe F, Ehlers S, Fletcher P, Frith U, Johansson M, Gillberg C, et al. 'Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. Neuroreport 1996; 8: 197–201.

Hashimoto T, Tayama M, Murakawa K, Yoshimoto T, Miyazaki M, Harada M, et al. Development of the brainstem and cerebellum in autistic patients. J Autism Dev Disord 1995; 25: 1–18.

Haznedar MM, Buchsbaum MS, Metzger MM, Solimando A, Spiegel-Cohen J, Hollander E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am J Psychiatry 1997; 154: 1047–50.

Knight R. Contribution of human hippocampal region to novelty detection. Nature 1996; 383: 256–9.

Mesulam MM, Mufson EJ. Neural inputs into the nucleus basalis of the substantia innominata (Ch4) in the rhesus monkey. Brain 1984; 107: 253–74.

Mountz JM, Tolbert LC, Lill DW, Katholi CR, Liu HG. Functional deficits in autistic disorder: characterization by technetium-99m-HMPAO and SPECT. J Nucl Med 1995; 36: 1156–62.

Ornitz EM. The functional neuroanatomy of infantile autism. Int J Neurosci 1983; 19: 85–124.

Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. J Child Psychol Psychiatry 1991; 32: 1081–105.

Pandya DN, Yeterian EH. Architecture and connections of cortical association areas. In: Peters A, Jones E, editors. Cerebral cortex, Vol. 4. New York: Plenum Press; 1985. p. 3–61.

Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. [Review]. J Child Psychol Psychiatry 1996; 37: 51–87.

Saito O, Courchesne E, Egaas B, Lincoln AJ, Schreibman L. Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. Neurology 1995; 45: 317–24.

Schopler E, Reichlet RJ, DeVellis RF, et al. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). J Autism Dev Disord 1980; 10: 91–103.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Wimmer H, Perner J. Beliefs about beliefs: representation and constraining function of wrong beliefs in young children's understanding of deception. Cognition 1983; 13: 103–28.

Young A, Hallawell D, De Wal C, et al. Facial expression processing after amygdalectomy. Neuropsychologia 1996; 34: 31–9.

Zilbovicius M, Garreau B, Tzourio N, Mazoyer B, Bruck B, Martinot JL. et al. Regional cerebral blood flow in childhood autism: a SPECT study. Am J Psychiatry 1992;149:924–30.

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