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| Title | Recent Changing Views on Neurobiological Factors and Cortical-Subcortical Theories of Autistic Syndrome |
| Author(s) | Sugawara, Masakazu |
| Citation | 北海道大學教育學部紀要, 67, 61-89 |
| Issue Date | 1995-03 |
| Doc URL | https://hdl.handle.net/2115/29467 |
| Type | departmental bulletin paper |
| File Information | 67_P61-89.pdf |

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# Recent Changing Views on Neurobiological Factors and Cortical-Subcortical Theories of Autistic Syndrome

**Masakazu Sugawara**

**—To Prof. S. Kitajima who encouraged me to wonder and hope—**

## Introduction

Once, infantile autism was considered a primary psychopathological disease of emotional involvement and social communicative deficits in the family environment. It was hypothesized that this disorder with affective contact primarily contributes to the disturbances of social relating and communication in unusual families (Kanner, 1943, 1944; Bettelheim, 1959, 1967). This theory tended to emphasize the emotional environment created by autistic children's parents which was seen as leading to communicative deficit and socially withdrawn isolation (e. g. Tinbergen & Tinbergen, 1983). However, most psychopathological investigation could not provide clear evidence of parental characteristics of abnormal interactions with autistic children. The primacy of the social and emotional dysfunction was usurped by an emphasis on the language disturbance and the assumption that it could be explained by a special cognitive deficit (Rutter, 1978, 1983). However, the concept of cognitive disorder seem to be ambiguous, and cannot explain the disturbances of social relation in autism, because impaired social relation could be understood as consequences of the resistance to novel environment and as a defensive use of stereotypic gestures to reduce arousal evoked either by novel stimuli or from human contact.

About 30 years ago, B. Rimland (1964) and E. M. Ornitz et al. (1965a, 1965b) presented the earliest detailed hypothesis that autism is not primarily a disorder of psychopathological origin, but rather neurophysiological or neurobiological origin in human brain functioning. Since that time, although many neurobiological investigations have tried to find the etiological factors and biological markers in autistic syndrome, we still have little understanding of interaction between the unique behavioral abnormalities and the neurobiological factors.

For the past two decades, new biological evidence has been presented to elucidate the cause of the appearance of characteristic disorders in autistic syndrome. Currently, most investigators might assume that infantile autism is not an etiologically homogeneous syndrome (Ritvo et al., 1982; Stubbs et al., 1985; Mason-Brothers et al., 1987). The multiple conditions (infectious, traumatic, anoxic, metabolic, hormonal, or genetic) can potentially be

activated by the many etiologic possibilities, and cause the autistic behavioral syndrome. Pre-, peri- and postnatal complicated factors (Mason-Brothers et al., 1987), such as the fragile X syndrome (Gillberg, 1983; Goldfine et al., 1985; Colleman and Gillberg, 1985; Rutter, 1985; Gillberg et al., 1985; Fisch et al., 1986; Reiss et al., 1986; Bregman et al., 1988; Ho and Kalousek, 1989; Einfeld et al., 1989; Reiss & Freund, 1990), congenital rubella (Chess et al., 1971, 1977, 1978), phenylketonuria (Lowe et al., 1980), HLA anti-gens (human leukocyte antigens or histocompatibility) (Stubb et al., 1985), genetic (Ritvo et al., 1982) or other neuropathological influences (e.g. Rett syndrome: Gillberg, 1989; Gillberg et al., 1990), might contribute to infantile autism. Mason-Borthers et al. (1987) compared the rate of occurence of pathological pre-, peri-, neo-, and postnatal events in autistic patients from single and multiple incidence families in order to determine if having affected siblings was associated with the presence or absence of specific events. They found that mothers of autistic patients from single incidence families had significantly increased incidences of bleeding and taking medications during pregnancy. Ritvo et al. (1985a, 1985b, 1989) found that mothers of autistic children tend to have an increased incidence of miscarriages or stillbirths.

The various neuroanatomical hypotheses have been considered in terms of either a telencephalic or a brainstem-diencephalic theory of autistic syndrome. The telencephalic theory postulates dysfunction of cortical structures, particularly mesolimbic cortex, including the temporal lobe, and neostriatal structures (Ornitz, 1983, 1987). This theory postulates a cognitive-linguistic disorder at the cortex with caudally directed distortion of attention and arousal level though nonspecific and specific thalamic nuclei (Ornitz, 1992). On the other hand, it is first necessary to clarify that the autistic children suffer from the concomitant cerebral, subcortical and cerebellar impairments (Courchesne et al., 1987, 1988, 1992), and the fault of sensory processing and basic affective human relation at the earliest onset.

More recent work which included study of genetics, neurotransmitter, brain evoked potentials, and the use of positron emission tomography (PET), magnetic resonance imaging (MRI), and magnetoencephalography (MEG) might elucidate this enigmatic syndrome in the not-too-distant future (Campbell and Green, 1985; Courchesne et al., 1987, 1988, 1989, 1992; Rumsey, 1992; Ritvo et al., 1985, 1989, 1990; Hari, 1990; Naruse et al., 1987, 1992; Erwin et al., 1991; Tsai et at., 1992; Makela et al., 1994). This report mainly reviews the recently changing views on neurophysiological evidence, and presents new important findings in recognizing the causes of autistic symptoms.

## 1. Genetic Factors in Autism

In the past decade, some evidence has accumulated indicating that genetic factors might play a contributory role in the appearance of autistic abnormal behavior. Early genetic investigations came to the conclusion that there is no clear evidence indicating that genetic factors play a role in this syndrome (e.g. Hanson & Gottesman, 1976). However, Ritvo et al. (1987) presented an important report of "one family with four autistic siblings and four families with three autistic siblings" in the UCLA Registry for Genetic Studies of

Autism. They hypothesized that genetic factors might be etiologically important in certain cases or subgroups of early infantile autism.

There has been a wide range of autism incidence prevalent in the general population (Table 1), which prior epidemiological surveys estimated to be between 3 and 21 per 10,000. This may be due to statistical problems, relatively varied populations, or the different diagnostic criterias. Recent demographic investigation has presented higher prevalence rates than 15 in 10,000 (Matsuishi et al., 1987; Wing, 1988; Sugiyama et al., 1986, 1992). Although it is generally difficult to unravel the inheritance because of the low incidence of either marriage or parenthood in autistic patients, the UCLA-University of Utah epidemiological survey of autism presented a highly accurate set of genetic data. Utah was selected because the vast majority of people (70% of the population) belong to the Mormon Church which asks members to keep five-generation genealogy records, and they traditionally have large families, a high level of public awareness, education, welfare facilities and cooperation in matters of health. Ritvo and his colleagues reported in their findings that the best estimate for the prevalence of autism is 4/10,000 in the general population, the sex ratio is 4/1 (66% of the autistic patients scored in below 70 in the mentally retarded range, a higher proportion of females with very low IQ, 52% of females and 38% of males scored less than 50, the male-to-female ratio of 6.3/1 for autistic patients with above 70 IQ and 2.7/1 for those with IQs less than 50), and the distribution of autism is not correlated with parental child-rearing, education, personality, occupation and race. These results were consistent with their previous investigations (Ritvo et al.,1989).

There might be a genetically determined subtype of autism, as the data presented in UCLA reports (Ritvo et al., 1985a, 1985b, 1989) (Table 2). Their very important genetic survey revealed the need for counseling of parents of autistic patients, that is, if patents have another child, there is an overrall 8.6 % chance of having other autistic children (7% if they already have an autistic boy, 14.5 % if they already have an autistic girl, and 35% if they already have two autistic children). They suggest that autosomal recessive inheritance may be operative, while a complex polygenic or multifactorial model of inheritance hypothesizes that many genes may affect the expression of autistic abnormalities.

Table 1 Prevalence per 10,000 population

| | | | |
|---|---|---|---|
| Wing et al. (1976) | 8.0 | (25,000) | Camberwell, UK |
| Wing & Gould (1979) | 21.2 | (35,000) | Camberwell, UK |
| Hoshino et al. (1982) | 5.0 | (217,626) | Fukushima, Japan |
| Ishii & Takahashi (1983) | 16.0 | (34,987) | Toyota, Japan |
| Bohman et al. (1983) | 5.6 | (69,000) | Vasterbotten, Sweden |
| McCarthy et al. (1984) | 4.3 | (65,000) | Ireland |
| Gillberg (1984) | 3.9 | (128,584) | Gothenburg, Sweden |
| Sugiyama & Abe (1986) | 21.2 | (12,263) | Nagoya, Japan |
| Steffenburg & Gillberg (1986) | 6.6 | (78,413) | Bohuslan, Sweden |
| Matsuishi et al. (1987) | 15.5 | (32,834) | Kurume, Japan |
| Ritvo et al. (1989) | 4.0 | (602,500) | Utah, USA |
| Sugiyama et al. (1992) | 13.2 | (23,415) | Nagoya, Japan |

## Table 2

Autistic probands and their siblings in the UCLA-University of Utah genetic survey of autism. (A) Diagnosis, sibling, sex, and birth order for 23 pairs of monozygotic twins and 17 pairs of dizygotic twins. (B) Autistic probands and their siblings in 46 families with multiple incidences of autism. (C) Diagnosis, full-half sibling, deceased, and birth order of autistic probands and their siblings in 20 families with multiple incidences of autism in Utah survey. n: normal, a: autism, M: male, F:female, -: dizygotic twins, =: monozygotic twins, d: deceased, miscarriage of stillbirth, 1/2: half sibling. 〔Reproduced from (A) Ritvo et al., (1985a), (B) Ritvo et al., (1985b), and (C) Ritvo et al., (1989)〕.

A

| Dizygotic Twins (17 pairs) | Monozygotic Twins (23 pairs) |
|---|---|
| 1. nM-aM | 1. aM=aM |
| 2. nM-aM | 2. aM=aM |
| 3. ½nM aF-aM | 3. aF=aF d |
| 4. nF-aM aM | 4. ½nF aM=aM |
| 5. nF d nM-aF | 5. nM aM=aM |
| 6. nM nM nF-aF | 6. ½nF aM=aM |
| 7. nF nM nM-aM | 7. nM aM=aM |
| 8. nM nM aM-nM | 8. nF aM=aM |
| 9. aM nM aM-nF | 9. aM=nM nF |
| 10. ½nF ½nM ½nM nM-aM | 10. aM=aM nM |
| 11. ½nF d d aM-aF | 11. nM d aM=aM |
| 12. nM nF nM nM aM-aM | 12. ½nM aM=aM nM |
| 13. d d ½nF ½nM aF-nM | 13. nF d aM=aM |
| 14. nF nF nF nF aM-aM | 14. nM nF aM=aM |
| 15. ½nF ½nM ½nM nF nF aM-nM | 15. nM nF aM=aM |
| 16. aM-nM nM nM nM nM nF nM | 16. nM aM=aM nM |
| 17. nF nF nM nF d nM d nF d nF aF-nM | 17. aM=aM nF nM |
| | 18. aF=aF nM nM nF |
| | 19. nF nF aF=aF dnM |
| | 20. d d aF=aF nF |
| | 21. ½nM ½nM d aF=aF nM |
| | 22. ½nM ½nF ½nM ½nM ½nF ½nF ½nM ½nM aM=aM |
| | 23. nF nM dnF dnF nF nF d nF nM nF aM=aM d nF nM |

B

| | | |
|---|---|---|
| 1. aM aM | 21. nF-aM aM | 41. aM aM aM |
| 2. aM aM | 22. nF aM aM | 42. aM aM aM |
| 3. aM aM | 23. aM aM nF | 43. aF aM aM ½nM ½nM |
| 4. aM aM | 24. nM nF aF aF | 44. nF d nF nM d-d aM aM aF |
| 5. aM aM | 25. nM nM aM aM | 45. nM aF nF aF aF |
| 6. aM aM | 26. aM nF aM nM | 46. nF nF nM nM nM aM nM aM |
| 7. aM aM | 27. aM aM nM nM | |
| 8. aF aF | 28. nF aM aM nF | |
| 9. aM aF | 29. ½nM nM aF aF | |
| 10. aF aM | 30. ½nF aM aM ½nF | |
| 11. aM aF | 31. ½nF ½nM aM nF aM | |
| 12. aF aM | 32. ½nM ½nF nM aF aF | |
| 13. aF aM | 33. ½nM ½nF aM dnM aM | |
| 14. aM d aM | 34. aM nM nM aM-nF | |
| 15. aM aF nM | 35. nF nF nF nF aM-aM | |
| 16. ½nF aM-aF | 36. aM nF aM d d nM | |
| 17. aM nM aM | 37. aM nM d nF d aM | |
| 18. aM nM aM | 38. d nM aM nM aM dnM nM | |
| 19. aM aM nF | 39. nF d nM nF aM nM d aM nF | |
| 20. aF aM nF | 40. nF nM nF nM nM nF aF nF aM nM | |

C

| | |
|---|---|
| 1. nM nF | aF aM aM aF aM nM |
| 2. dnM nF | aM aF nF aF aF |
| 3. nM nF | aF d aM aM |
| 4. nM nF | ½nF nM aF aF |
| 5. nM nF | aM aM |
| 6. nM nF | ½nF aM-aF |
| 7. dnM nF | nF nM aM d d nM d aF |
| 8. nF nF | aM aM |
| 9. nM dnF | aF aF ½nM ½nF ½nF ½nF ½nF |
| 10. nF nF | nF nM nF nF aM aM |
| 11. dnM nF | d aM d nF nF aM nF nM nF nF |
| 12. dnM nF | ½nF ½nF ½nM ½nM d dnM aM aM |
| 13. nF nM | aM nF nF nM aM |
| 14. nM nF | d aM aM nM |
| 15. nM nF | d aM aM nF nM |
| 16. nM nF | nF aM aM nF |
| 17. nM nF | aM d nF nM nM d aM |
| 18. nM nF | aF d aM nM d |
| 19. nM nF | nM aM nF nF aM d ½nF |
| 20. nM nF | aM aM |

## 2. Neurotransmitters in Autism

Particular interest has focused on neurochemical factors around major neurotransmitter systems. This interest derives from the success of phamacological treatments (e.g. R-tetrahydrobiopterin -see Fig. 1A- by Naruse et al., 1987; Nakane et al., 1992) for certain limited aspects of the autistic disorder, and from recent advances in basic neuroscience.

In 1961, Schain and Freedman first found that 6 out of 23 children, ranging in age from 5 to 15 years with a mean of 10.8 years, had consistently elevated blood serotonin (hyperserotonemic) levels (Fig. 1B). Young et al. (1982) mentioned that the cell bodies of serotonergic neurons are located in the hindbrain and project widely. These neuronal systems have modulatory effects on a variety of important physiological and psychological processes involved with depression, and other socially withdrawn psychiatric, sensory, and arousal disorders. Ritvo et al. carried out blood studies including serononin levels (1970), chromosones, gene markers, T & B cell functions, human myelin basic protein, HLA (1985b), and antibody titers for viruses. Their results showed that blood serotonin and platelet counts varied inversely with developmental age in the normal population; compared values of the ratios of serotonin per platelet were not different between age-matched groups of autistic patients and normals (except in subjects under 47-months), but mean serotonin levels and platelet counts significantly increased in autistic subjects. Anderson and Hoshino (1987) estimated that mean serotonin levels in autistics might elevate to be from 17% to 128% higher than in normals, as determined by a variety of assay methods, though the urinary 5-hydroxy-indoleacetic (5-HIAA) excretion rates of the endpoint metabolic pathway and enzyme monoamine oxidase (MAO, both MAO-A and MAO-B) (Minderaa et al., 1987) did not indicate statistical differences in autistic patients compared to normal controls. The 5-HT (5-hydroxytrytryptamine, serotonine) transport and uptake sites have been reported to be reduced in platelets of depressive patients and in brain samples of depressive suicide victims (Blakely et al., 1991). Four major subtypes (nine subtypes) of 5-HT receptors (5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D, 5-HT1E, 5-HT2, 5-HT3, 5-HT4, and 5-HTG) in biogenic amines that mediate a variety of neurophysiological activities have been discovered in the last decade (Marico et al., 1991; Blakely et al., 1991). However, to date there has been little molecular information gathered on the abnormalities of 5-HT receptors or transporters in autistic syndrome.

The catecholamines (dopamine, norepinephrine, epinephrine) in biogenic amines (Fig. 1C) are widely found in the CNS of human brain and peripheral nervous systems as important neurotransmitters (Maas et al., 1980; Young et al., 1980, 1982). Although research studies of certain neuropeptides, catecholamines nor-epinephrine and epinephrine might serve to clarify the fundamental mechanisms underlying perceptual, attentional, arousal disfunction, and autistic self-isolation, these findings remain unclear, and additional research is needed (Coleman & Gillberg, 1985; Anderson & Hoshino, 1987).

The importance of the dopaminergic system in brain function has been emphasized by

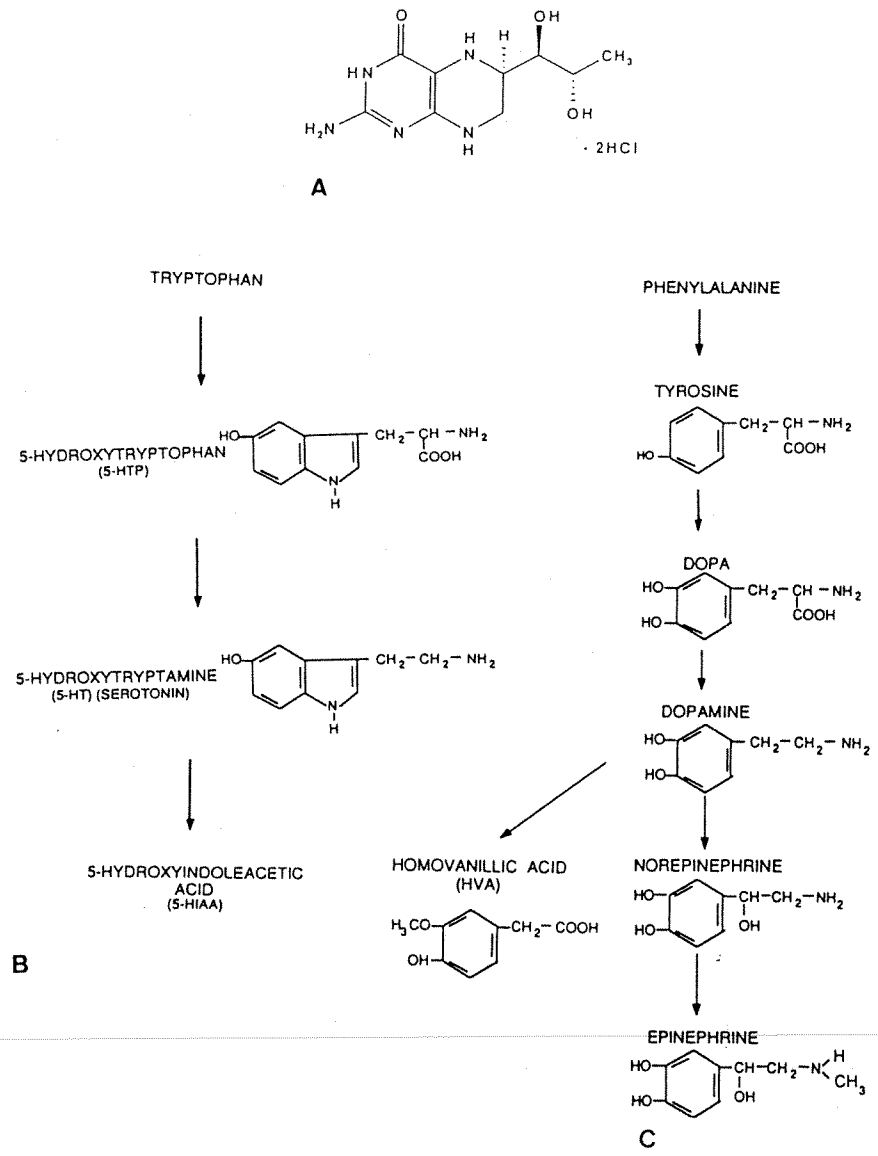


Fig. 1 A: R-tetrahydrobiopterin [reproduced from Naruse et al., 1987] . B,C: 5-HT and catecholamine synthesis and metabolism.

its association with neurological and psychological disorders such as schizophrenia and Parkinson's disease. Stimulant administrations and dopaminergic neuronal dysfunctions in the cell bodies of midbrain pathways have been implicated in stereotyped and rotational behaviors in animal models. These analogies not only to Parkinson disease and other psychiatric neuropathogenesis but also to autistic syndrome facilitated the search for mechanisms of catecholamine metabolism in autism. Dopamine is synthesized from the

amino acids phenylalanine and tyrosine by tyrosine hydroxrase, and is metabolized to HVA (homovanillic acid) and norepinephrine by DBH (dopamine- $\beta$-hydroxylase) (Fig. 1C). The dopamine receptors in the CNS are classified into D1 and D2 subtypes, or into D1 (D1A), D2, D3, D4, and D5 (D1B) (Zhou et al., 1990; Sunahara et al., 1990; Sokoloff et al., 1990; Van Tol et al., 1991, 1992). Dopamine D1 and D2 receptors are targets of drug therapy in schizophrenia, alchoholism, and other psychomotor diseases such as Parkinsonian. The D1 receptors regulate neuron growth and differenciation, mediate some behavioral responses, and modulate activity of D2 dopamine receptors (Zhouet al., 1990; Sunahara et al., 1990, 1991). The D3 receptor is localized in the limbic system such as the hippocampus, septum or mammillary nuclei in the hypothalamus, which are associated with cognitive, emotional, and endocrine functions (Sokoloff et al., 1990). It differs from the previously defined D1 and D2 receptors, because D1 and D2 receptors are widely expressed indiscrete brain areas. Investigations of the dopamine D3 receptor may allow new therapeutic developments for autistic disorders.

The severe perceptual, arousal, attentional, affectional, linguistic, and social communicative disorders in autism may be associated with one expression of genetic influences. As with the clear diagnostic criteria and neurobiological markers for autistic syndrome, much research remains to be done in the relationship between behavioral disturbances and CNS neurobiological systems.

### 3. Telencephalic Theories

The arguments of a pathophysiology of telencephalic structures have been influenced by the concept of a linguistic or cognitive disorder. M. Rutter (1978) postulated that a specifically cognitive disturbance is fundamental to the linguistic and communication disorders in autism. Such a formulation would seem to imply pathophysiological dysfunction in the temporal lobes, or mesolimbic cortex and basal ganglia (neostriatum; caudate nucleus, putamen) (Damasio and Maurer, 1978; Damasio et al., 1980). This hypothesis seems to depend on the pathoneurophysiological model of the newer rostral structures rather than older caudal structures. The assumption of primarity at the brainstem level is directly related to the sensory modulation hypotheses, although M. Rutter, L. Wing and their colleagues had implicated cortical or temporal lobe pathology as a cause of autism. The neurophysiological studies have attempted to identify cortical presumable origin or specific areas of cortical dysfunction involving the left hemisphere or the possibility of a disorder of hemispheric lateralization (Dawson et al., 1986, 1989). The hypotheses of cortical pathophysiology is supported by computed tomography (CT), MRI findings, electroencephalography (EEG) of cerebral lateralization, and brain evoked potential (EP) studies of late components to sensory stimuli.

#### A. CT and MRI Studies

Hauser et al. (1975) examined pneumoencephalograms (PEGs) and reported enlarged left temporal horn lateral clefts in 15 of 18 autistic children, suggesting loss or lack of

development of left temporal lobe tissue. Hier et al. (1979) reported a reversed pattern of asymmetry of the parieto-occipital region in the CT scans of 9 out of 16 autistic patients who failed to understand social nuances and failed to make adequate eye contact, atypical prosody, robot-like intonations and motor output. These findings (the asymmetric reverse or the enlargement of left temporal lateral cleft observed by Hauser et al.) were not replicated in other CT scan studies as evidence of light-hemisphere lesion in autistics. Recent CT studies have attempted to find a correlation between structural abnormalities and functional deficits. Tsai et al. (1982, 1992) could not confirm the reversal of the normal lateral ventricular asymmetry or any significant abnormal findings in CT and MRI scans with comparisons between autistic and neurological patients, because this pattern of asymmetry also occurs in miscellaneous neurological patients and developmentally dyslexic children with low IQs. Thus, the recent CT scan and MRI studies (Hashimoto et al., 1989; Piven et al., 1990; Tsai, 1992) could confirm neither a singular, abnormal pattern such as an enlarged left ventricle (Hauser et al., 1975) nor an abnormal right-left difference in parieto-occipital width (Hier et al., 1979). Such CT or MRI comparison between autistic and control groups demonstrated enlarged ventricles in less than one quarter of autistic cases (Ornitz, 1987), and there were no significant correlations between ventricular measurements and the severity of autistic behavior (Campbell et al., 1982, 1985).

The cerebral lateralization and hemispheric asymmetry studies can not demonstrate significant differences, but they might be able to identify small subgroups of autistics with enlarged ventricles. MRI studies also have shown abnormal structural configurations in only a minorty subgroup of autistic (about one-quarter) subjects, and in those who suffered from a major concomitant organic brain condition (Damasio et al., 1980; Campbell et al., 1982; Gillberg & Svendsen, 1983, 1987; Rosenbloom et al., 1984). Abnormal patterns of cerebral lateralization may represent a maturation delay rather than a neurophysiologic deviancy. PET studies also have failed to demonstrate the precise metabolic reductions or elevations (Rumsey et al., 1985, 1988, 1992).

Table 3 PET (positron emission tomography) findings in autistic syndrome.

| Authors | Subjects | Findings |
|---|---|---|
| Rumsey et al. (1985) | 10 adult auts. | variable metabolic rates |
| DeVoldery et al. (1987) | 18 auts. 2-18 years | no difference, posterior, prefront |
| Horwitz et al. (1988) | 14 adult auts. | variable metabolic elevations |
| Herold et al. (1988) | 8 young adult auts. | no difference, blood flow, oxygen |
| Heh et al. (1989) | 7 adult auts. | no difference, cerebellar vermis |
| Rumsey et al. (1992) | summarized | no difference in resting brain metabolism |

Table 4 CT (computed tomography) findings in autistic syndrome.

| Authors | Subjects | Findings |
|---|---|---|
| Hier et al. (1979) | 16 auts. (13m & 3f), mean age 14 years, 4-27 years | reversed asymmetry in parieto-occipital area in 9/16 autistic subs. left<right |
| Damasio et al. (1980) | 17 auts., 4-31 years | enlarged ventricles in 5/17 auts. |
| Caparulo et al. (1981) | 22 auts., m=14 years | enlarged ventricles in 3/22 auts. |
| Campbell et al. (1982) | 45 auts., 2-7 years | enlarged ventricles in 11 auts. |
| Tsai et al. (1982) | 18 auts., 3-18 years | no significant abnormalities |
| Gillberg et al. (1983) | 27 auts., 2-22 years | porencephaly, enlarged ventricles in 7/27 auts. |
| Rosenbloom et al. (1984) | 13 auts., 3-8 years | no significant differences |
| Prior et al. (1984) | 9 auts., 9-16 years | no significant differences |
| Creasy et al. (1986) | 12 auts., 18-39 years | no significant differences |
| Gillberg et al. (1987) | 18 auts., 3-21 years | abnormalities in 4/18 auts. |
| Jacobson et al. (1988) | 9 auts., 20-34 years | enlarged III ventricles |
| Rumsey et al. (1988) | 15 auts., 18-39 years | no significant differences |

Table 5 MRI (magnetic resonance imaging) findings in autistic syndrome.

| Authors | Subjects | Findings |
|---|---|---|
| Courchesne et al. (1987) | a single case study 21-years-old aut. m | developmental hypoplasia of neocerebellar hemispheres and vermal lobules VI & VII (declive, tuber, folium) |
| Gaffney et al. (1987) | 14 auts., 4-19 years | enlarged IV ventricles, decreased size of cerebellar hemispheres |
| Courchesne et al. (1988) | 18 auts., 6-30 years | significantly smaller size of neocerebellar vermal lobules VI and VII in 14/18 auts. |
| Gaffney et al. (1988) | 13 auts., m=11 years | smaller size of brain-stem (pons) |
| Garber et al. (1989) | 15 auts., m=11 years | no significant differences in neocerebellar vermal lobules VI and VII |
| Gaffney et al. (1989) | 13 auts., 4-19 years | enlarged lateral ventricles |
| Hashimoto et al. (1989) | 18 auts., 2-9 years | left < right hemisphere |
| Murakami et al. (1989) | 10 auts., 14-39 years | significantly smaller size of neocerebellar vermal lobules VI and VII |
| Piven et al. (1990) | 13 auts., 8-53 years | cortical abnormalities in 7 auts. |

### B. Preference for Auditory Stimuli

E. Blackstock (1978) maintained that autistic children usually do not show the normal right-ear advantage, and prefer nonverbal (music) to verbal auditory stimuli in a dichotic listening task. When the experiment was designed to show ear preference for verbal or musical stimuli by placing a child in a room with two speakers, one playing music and one playing various speech stimuli, both at a very low volume to demonstrate asymmetric hemispheric dominance, the subjects put one ear up to the speaker in order to hear it. The

autistic children showed a left-ear preference (right-hemisphere advantage) for both melody and story speech stimuli, whereas normal children showed a slighty left-ear preference for melody and a right-ear preference (left hemisphere superiority) for the speech stimulus. However, Blackstock's data have not at all been confirmed in the recent sophisticated studies that were designed in a dichotic listening task. Autistic children generally exhibit various abnormal patterns of prosodic skills, whereas prosodic disturbances have been related to right-hemisphere functioning. They are also deficient at reading emotional expression (flat, monotonic, emotionless quality of autistic speech is reflected in the faulty use of intonation) which may be specifically depressed, but this deficiency can be attributed to right-hemisphere impairments (Weintraub et al., 1981; Ross, 1981, 1984). Abnormalities in prosodic and pragmatic (social) aspects of language, as well as other emotional behavioral features, suggest analogies to not only left-hemisphere impairment, but also to right-hemisphere disorder patients.

### C. Electrophysiological Studies

The preference for nonverbal (music) or verbal auditory stimuli in a dichotic listening task can provide indirect evidence that autistics have or do not have the same degree of cerebral hemispheric specialization as normal controls. On the other hand, electrophysiological studies (EEG and EPs) provide the direct evidence of brain activities for the lateralized preference of linguistic or non linguistic information processing. It is well known that about 50 per cent of autistic patients have abnormal EEGs characterized by focal or diffuse spike, slow wave, or paroxysmal spike and wave patterns, and unusually low voltage EEGs suggestive of hyperarousal states. The neurophysiological research on cortical studies focused to show the reduced left hemisphere alpha activities specifically during requiring linguistic tasks (Dawson et al., 1986). Tsai et al. (1982) stated that no relationship was found between EEG patterns and handedness. But, a group of children with neurological or CT scan evidence of right-hemisphere lesion frequently fails to understand social nuances and to make adequate eye contact. A EEG study by Dawson et al. (1986) investigated hemispheric specialization of verbal and spatial tasks as measured by alpha blocking (attenuation), which are associated with relatively high functioning of lateral asymmetries, in left versus right hemisphere in autistic and age-matched normal subjects. Differences of hemisphere activation between the two groups on spatial tasks were not significant, but did reach significance on the verbal tasks. Few quantitative EEG studies showed abnormal hemispheric lateralization and reduced left hemisphere alpha attenuation specifically during tasks requiring language, however most recent researchers usually report no statistically significant group differences. Thus, the delayed and reduced cerebral lateralization seen in some autistic children might be related to their maturational rates rather than to specific left hemisphere function.

Some dysfunction in brainstem structures that are vulnerable to birth trauma might result in a very early onset of behavioral abnormalities. The autonomic brainstem auditory

evoked potential (BAEP) measurements are more sensitive to system dysfunctions and structural lesions. It has been used to diagnose hearing deficits of neurologic lesions, including demyeinization, along the auditory pathway between the eighth cranial nerve and the inferior colliculus. A limited subgroup of autistics (from 25% to 33%) show BAEP abnormalities and prolonged brainstem trance mission time (BSTT) values, because the BAEP measures the function of a subset of neurons within the auditory pathway through the brainstem as rostral as the inferior colliculus (Ornitz, 1983, 1987; Sugawara, 1991, 1993).

The impaired information processing has been suggested by reports of small or absent P300 in the late components of brain evoked potentials to oddball stimuli. Novick et al. (1980) reported that autistic patients showed attenuated P300s to signal stimuli than did normal controls. Courchesne and his coworkers also reported that autistic patients showed small or absent late auditory evoked potentials (P3b) to novel target stimuli, and suggested that this electrophysiological evidence of defective auditory information storage might be consistent with some of the components of the cognitive disorder described by Rutter (1978). However, Erwin et al.'s recent work (1991) presented data that are contrary to their hypotheses, where the adult autistics generally showed normal P3b responses to all rare prosodic and phonemic stimuli. Therefore, their lack of lateralized or differentiated evoked potential responses may reflect maturational lag and attentional deficit. Ornitz (1992) indicated that the reduced amplitude of the P300 response in autistics might reflect a generally smaller evoked response, irrespective of the stimulus characteristics, because these evoked potentials to background stimuli were in almost all cases during the task condition smaller in the autistics than in the normal controls. The general reduction of most evoked response components to background stimuli in autistics suggests that the reduced P300 response to specific stimuli must be interpreted in the context of the general response of the autistic subject to the total experimental environmental. The generally smaller amplitudes of late components (N100 or P300) might suggest that, relative to normal controls, the autistics were not directing their attention toward auditory features in the experimental paradigm, whether the sounds were novel, targeted or not targeted, or background. Thus, these results may not indicate specific P300 in autistics, but rather they may demonstrate a nonspecific reduction of event-related potential activity.

Another interpretational question of P300 component was presented by Sugawara et al. (1994), who suggested that P300 might represent a limbic or cortical reflection of the sensory processing taking place in the brainstem. Thus, autistic linguistic deficits could be attributed to dysfunction of both cerebral hemispheres and brainstem mediation affective to linguistic information processing.

### D. Language Disorders in Autism

It is well known that language skills (including inflectional, phonological, syntactic, morphological, grammatical, semantic and vocabulary) are always more severely impaired in autism than perceptual skills. There is now considerable support for the theory that a

severe and global language deficit underlies autism, so that autism is considered to be primarily a disorder of language development. In particular, mean verbal IQ has been reported to be lower than mean performance IQ in most widely used IQ tests. G. Dawson et al. mentioned that the autistic child's relative strength in performing visuo-spatial tasks, identifying complex visual forms and patterns such as Block Design, Form Boards, and Object Assembly, might suggest relative right hemisphere intactness (Dawson et al., 1983, 1986, 1989). On the oter hand, the particular pattern of language developmental disorders in autistic children may constitute the deficits of general abstructive, symbolic thought and cognitive functioning as major symptoms of early infantile autism. M. Rutter et al. have explicitly developed this position (Rutter et al., 1978, 1983), although the latter no longer espouses this hypothesis that autism is considered to be primarily a disorder of language and cognitive development (Hobson, 1986a, 1986b; Ornitz, 1983, 1992). The hypothesis in considering language deficits to be primary in autism should be rejected, because other language-impaired clinical patients, deaf, aphasic, and retarded children all suffer delayed language development, but they do not suffer from the symptoms that autistic children exhibit, and they can use and comprehend gesture in their attempts to communicate, unlike autistic children. Differentiation between primary and secondary etiological causes is important for the focus of treatment. The language deficits in autism are a secondary consequence of their corresponding lack of coordinated reference with other people and difficulty interpreting affective signals (Hobson, 1986a, 1986b).

### E. Handedness in Autism

An increased incidence of left-handedness or mixed-handedness in autistic children has been cited as evidence for the hypothesis of left-hemisphere disorders in autism. Increased left-handedness is taken to indicate that insults to the left hemisphere have caused a switch in manual dominance from the injured left hemisphere (controlling the right hand) to the intact right hemisphere (controlling the left hand).

Normal children usually show inconsistent handedness until age 4, and handedness shows a fluctuation course in early childhood. It has been reported that mixed hand preference might appear to be at a lower developmental level than the children with dominance established, and a lower score on cognitive tasks for these children might result, than children with established hand preference.

We investigated charecteristics of handedness in autistic and age-matched mentally retarded children (Table 6), and analyzed the longitudinal data in evaluation (ten items: such as cutting with a scissors, throwing a ball, forefinger pointing, cutting with a knife, eating with a spoon, shoveling, unscrewing a bottle cap, tracing a circular figure, picking up small objects, and rubbing out with an eraser) concerned with left- or mixed-handedness versus established hand dominance (Table 7). We found that left-handedness or mixed-handedness is found more often in autistic children than in mentally retarded samples (Fig. 3), and autistics with established hand preference were older than autistic children with mixed-

handedness according to the longitudenal data analysis. Although left- or mixed-handedness has an elevated frequency in autistic children compared with mentally retarded subjects, it is revealed only in younger autistic subjects (Fig. 2). There were no significant differences between the older two groups on degree or direction of hand dominance, although the autistic group showed a significantly greater variance in hand preference. This suggests that left- or mixed handedness in these sam-

**Table 6** Test scores of handedness in autistic and mentally retarded children

| Autistic subjects | Age | Vocabulary age * | Handedness quotient ** |
|---|---|---|---|
| 1. T. S. | (m) 6-10 | 2- 0 | R 5 |
| 2. K. Y. | (m) 7- 7 | 2- 0 | R 6 |
| 3. T. K. | (m) 7- 7 | 3- 8 | R 7 |
| 4. #M. F. | (f) 7- 8 | 4- 5 | R10 |
| 5. #T. S. | (m) 8- 5 | 3- 0 | R 7 |
| 6. S. T. | (m) 8- 5 | 5-10 (IQ67) | L10 |
| 7. T. K. | (m) 8- 6 | 4- 0 | R 6 |
| 8. S. S. | (m) 8- 7 | 5- 7 | R 9 |
| 9. #I. S. | (m) 8-11 | 2- 8 | L 3 |
| 10. S. T. | (f) 9- 4 | 6- 0 (IQ68) | L 7 |
| 11. M. I. | (f) 9- 5 | 2- 0 (IQ40) | R 4 |
| 12. #S. T. | (m) 9- 7 | 3-10 | R 8 |
| 13. #H. I. | (m) 9- 8 | 7- 2 (IQ69) | R 7 |
| 14. #H. O. | (m) 9- 9 | 6- 7 | L 6 |
| 15. K. H. | (m) 9-11 | 3-10 (IQ47) | R 5 |
| 16. #H. K. | (m)10- 3 | 3- 4 | R 5 |
| 17. H. Y. | (m)10- 6 | 3- 0 | L 2 |
| 18. Y. A. | (m)10- 6 | 6- 6 (IQ65) | R 6 |
| 19. M. N. | (m)10- 7 | 3-10 (IQ42) | R 6 |
| 20. H. Y. | (m)11- 4 | 2- 0 | L 3 |
| 21. #H. N. | (m)11- 5 | 12- 0 (IQ92) | R 9 |
| Average | 9- 3 | 4- 4 (IQ61.3) | 6.24 |

| Mentally retarded | Age | Vocabulary age | Handedness quotient |
|---|---|---|---|
| 1. #M. C. | (f) 6- 8 | 5- 6 | R 8 |
| 2. M. O. | (f) 7- 8 | 3- 8 (IQ55) | L 6 |
| 3. T. K. | (m) 7-11 | 4- 4 (IQ70) | R10 |
| 4. Y. M. | (f) 8- 3 | 4- 0 (IQ50) | R10 |
| 5. #M. O. | (f) 8- 6 | 4- 0 | L 8 |
| 6. M. Y. | (f) 8- 9 | 4- 2 (IQ40) | R 1 |
| 7. H. I. | (m) 8- 9 | 5- 7 (IQ69) | R 8 |
| 8. #Y. K. | (f) 8-10 | 6- 0 | R 8 |
| 9. #T. K. | (m) 8-10 | 7- 6 | R10 |
| 10. H. O. | (m) 8-11 | 5- 7 | R 9 |
| 11. #Y. M. | (f) 9- 2 | 4- 2 (IQ60) | R10 |
| 12. H. K. | (m) 9- 5 | 3-10 | R 9 |
| 13. #M. Y. | (f) 9- 7 | 3-10 | R 8 |
| 14. K. S. | (m)10- 1 | 12- 0 (IQ72) | R 8 |
| 15. #K. O. | (m)10- 2 | 7- 4 | R 7 |
| 16. A. N. | (f)10- 4 | 3-10 (IQ50) | R10 |
| 17. #C. T. | (m)11- 1 | 9- 8 (IQ73) | R 7 |
| 18. Y. K. | (f)11- 3 | 9- 8 (IQ74) | R 9 |
| 19. Y. K. | (f)12- 0 | 8- 9 | R10 |
| 20. M. A. | (m)12- 3 | 5- 9 | R 9 |
| Average | 9- 3 | 6- 1 (IQ61.3) | 8.25 |

**Table 7** Longitudinal handedness data in autistic and mentally retarded children

| Autistic subjects | Age | Vocabulary age | Handedness quotient |
|---|---|---|---|
| 1. M. F. | (f)12- 8 | 6-10 | R10 |
| 2. T. S. | (m)13- 5 | 3-10 | R10 |
| 3. H. I. | (m)13- 8 | 12- 0 | R 6 |
| 4. H. O. | (m)13- 9 | 7- 4 | R 9 |
| 5. I. S. | (m)13-11 | 6- 1 | R 9 |
| 6. H. K. | (m)14- 3 | 10-10 | R10 |
| 7. S. T. | (m)14- 7 | 3- 8 | R10 |
| 8. H. N. | (m)15- 5 | 12- 0 (IQ91) | R 9 |
| Average | 13- 8 | 7- 8 | 9.13 |

| Mentally retarded | Age | Vocabulary age | Handedness quotient |
|---|---|---|---|
| 1. M. C. | (f)10-10 | 7-10 | R 7 |
| 2. M. O. | (f)12- 8 | 5- 6 (IQ55) | R 8 |
| 3. Y. K. | (f)12-10 | 8- 9 (IQ70) | R 8 |
| 4. T. K. | (m)12-10 | 10- 0 (IQ70) | R10 |
| 5. Y. M. | (f)13- 2 | 5- 6 | R10 |
| 6. M. Y. | (f)13- 7 | 4-11 | R10 |
| 7. K. O. | (m)15-11 | 11-10 (IQ72) | R10 |
| 8. C. T. | (m)16- 1 | 12- 0 | R10 |
| Average | 13- 7 | 8- 2 | 9.13 |

#: Longitudinal subjects

*: PVT (Picture Vocabulary Test by K. Ueno et al. 1979)

**: Evaluation of Preference Handedness (ten items: cutting with a scissors, throwing a ball, fore-finger pointing, cutting with a knife, tracing a circular figure, picking up small objects, and rubbing out with an eraser).

[This work was supported by Nioh Elementary School and Fuzoku Yohgo School in Morioka during 1979-1994. The author wishes to thank R. Iwasaki, Y. Ito, M. Wada, M. Matsuda, K. Sato, K. Nemoto, M. Takeda, R. Sasagawa, N. Sato, and J. Sakamoto]

ples can not be related to incidence of certain left hemisphere damage. It is difficult to draw conclusions based on a comparison of the two groups, because the finding indicates a developmental delay than left-hemispheric impairment.

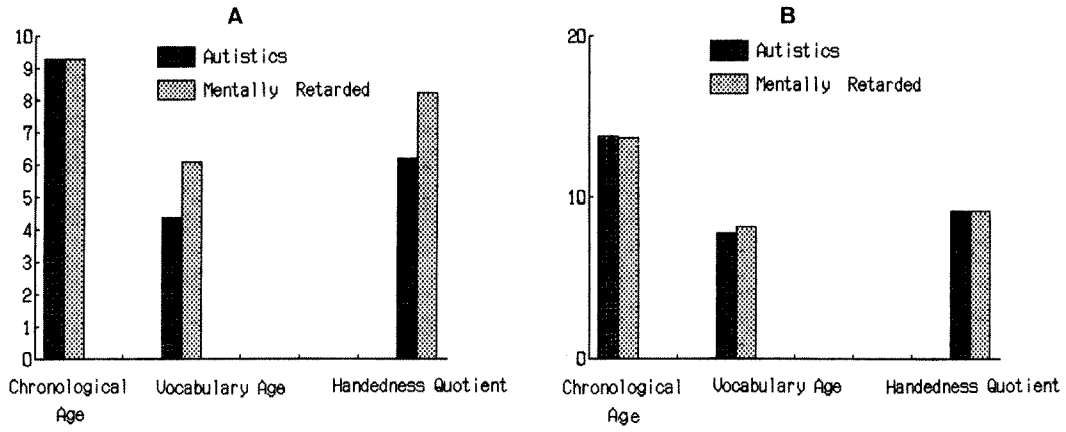


Fig.2 A: Mean handedness quotients and vocabulary ages in autistic (n=21) and mentally retarded (n=20) children. B: Longitudinal handedness quatients in each group.

F. Theories of Left-hemisphere Impairment and Question of Right-Hemisphere Intactness

Various central nervous system loci have been suggested as possible sites of impairment in infantile autism. The possibility of a cognitive defect has stimulated a number of investigations of possible pathology of telencephalic linguistic processing, so that most theorists focus heavily on language impairments as implicating left hemisphere deficit in autism. About twenty years ago, Hauser et al. (1975) initially reported the pathological enlargement of the left temporal horn and general widening of the left lateral ventricle by pneumoencephalographic (PEG) findings in 15 children exhibiting some autistic behavior, which in these cases included dilatation of the third ventricle, cortical atrophy, epilepsy, increased height of the fourth ventricle, neglect of the right visual field, dilatation of the left temporal horn, and distorted frontal lobes. Eight patients were left-handed, and 3 autistics had failed to establish preferred handedness. However, other investigators could not confirm the evidence of the left temporal lateral cleft enlargement presented by Hauser et al. Since that time, it has been hypothesized that left hemisphere impairment underlies the autistic syndrome (e.g. B. S. McCann et al., 1981), because on the surface, the theory of left cerebral hemisphere dysfunction might account for the language deficits and cognitive symptoms of autism. Autistic children apparently are proficent in tasks usually attributed to right hemisphere functioning. Dawson et al. also reported a higher degree of left rather than right hemisphere dysfunction in autistics in a comparison of retardates, autistics, and bilaterally impaired neurological patients. Autistic children showed lower left-hemisphere functioning than the control group, but their right hemisphere performance was equal to

retardates and higher than the performance of neurological patients (Dawson et al., 1983). It is important to note that this pattern is not specific to the autistic children and that most cases exhibit bilateral involvement rather than isolated left-sided damage.

D. Fein et al. (1984)'s critical review suggested that the hypothesis of left-hemisphere impairment overestimates the importance of linguistic abnormalities in autistic patients. They argued that the left hemisphere impairment is not primary, and that attentional, motivational or organizationnal defects of autism are primary for the first several years of life.

There is some evidence suggesting that the right hemisphere is specialized for the directed attention and the perception of negative emotion, whereas the left hemisphere is biased toward positive emotional stimuli (Natale et al., 1983; Rueter-Lorenz et al., 1983). The right hemisphere may be dominant for mediation an attention-arousal response, because patients with right hemisphere disease show emotional indifference and dramatically smaller arousal responses than do patients with left hemisphere disease. Bear (1983) has described patients with right-hemisphere lesions who fail to detect and sustain attention to emotionally significant stimuli, and therefore fail to develop appropriate emotional responses. Intact right hemisphere has the capacity to recognize the components of certain types of emotional facial expression, but autistic patients show a deficiency to direct attention toward emotionally relevant stimuli in their environment. The right hemisphere attends to both contra- and ipsilateral stimuli, whereas the left hemisphere is more limited to contralateral attention. Directed attention can be considered as an element of both sensory processing at lower subcotrical structures and information processing at higher levels. It is a complex neuropsychological construct, but neglect occurs more often after right hemisphere lesions (Toshima et al., 1994). Margulies (1985) has attributed the attentional component of directed attention almost exclusively to the hippocampus and the intentional component to the nucleus accumbens. Thus, these data can not support the theory of right-hemisphere intactness in autism.

### 4. Impairment of Cerebellar Development and Purkinje Cell Reduction

The cerebellum, like brain stem, striatal (nucleus candalis, nucleus lentiformis), and cortico-limbic structures, appears to be involved in the modulation of attentional mechanisms and complex behavior, since stimulation of cerebellar cortex modulates midbrain and forebrain sensory responses, and stimulation of a cerebellar efferent sturucture modulates brain stem behavioral mechanisms. Initial finding of the reduced Purkinje cell counts in the cerebellum of a single autistic subject was reported by Williams and his coworkers (Williams et al., 1980), although they could not find neuronal and glial abnormalities in cortex, hippocampus, thalamus, and striatum of brainstem. They did not mention the specific reduced area within the cerebellum, but their findings suggested that the autistic child's hypothesized inability to relate new stimuli to memory storage results from Purkinje cell's reduction. Bauman and Kemper (1985) found anatomical abnormalities of the neocerebellar cortex, and reduced numbers of Purkinje cells in the cerebellar nuclei. They also observed

Fig.3 A midline sagittal MRI scan of the cerebellum with a autistic patient (4 years old, male). The vermal lobes VI and VII (the superior posterior vermis) show hypoplosia, while the anterior vermis (vermal lobeles I to V) and the inferior posterior vermis (vermal lobele VIII) are similar (supplied by Dr. Courchesne, E. at University of California, San Diego).

hippocampal histopathology and atrophy of the marked loss of granule cells and of cells in nucleus globusus in the deep cerebellar nucleus, but no neuropathological evidence in frontal, parietal, occipital cortex and in thalamus and basal ganglia (Kemper and Bauman, 1992). Coleman et al (1985) found no neuropathological evidence in neuronal and glial cell density in primary auditory cortex, Broca's speech area, and auditory association cortex. Ritvo et al. (1986) presented a detailed autopsy research which suggest pathology may exist in the cerebellar-vestibular axis, for existence of significantly lower counts of Purkinje cells in the cerebellar hemisphere and vermis. They suggested that the link between a cerebellar roof nucleus and the limbic system suggests the possibility of cerebellar involvement in affectual components of abnormal behavior in autisms. The loss of Purkinje cells in the autistic brain could be related to dysfunction of a distributed sensory- and information-processing system. Courchesne et al. (1987) and Murakami et al. (1989) reported that the reduced area of cerebellar pathology is vermal lobules VI and VII seen on magnetic resonance imaging scans (Fig. 3). However, Ritvo et al. have recently failed to find cerebellar vermal differences between autistic patients and normal controls on MRI scans (Garber et al., 1989).

## 5. Brainstem Impairement Hypothesis

The autistic syndrome consists of two major clusters of behavioral disturbances: language, communication and relation to people; and relating to objects and sensory-information processing. The emphasis on the disturbances of social relation, language and communication has attemped to identify the specific areas of cortical dysfunction, notably involving the cognitive left-hemisphere, although the evidence for an abnormality of hemispheric lateralization is inconsistent. There is a controversy concerning neurophysiological evidence for both cortical (cognitive and linguistic) and subcortical (brainstem) pathophysiology in autism.

An older hypothesis of left-hemisphere dysfunction in autism was based on a too-limited clinical picture of autism as a language and cognitive disorder. The view that disturbances of relation, language and communication could be explained as the result of a specific cognitive defect (Rutter, 1978, 1983) may fail to account for the primary components of the

autistic syndrome. M. Sigman et al. (1984a, 1984b) regarded a developmental disorder of emotional information processing and nonverbal communication as one of the first important social-developmental deficits to emerge in early autistic behaviors.

On the other hand, in the subcortical investigations, E. Ornitz (1992) presents the assumption that the cognitive disorder hypothesis (Rutter, 1978, 1983) cannot explain the disturbances of social relation, and the primacy of the social, emotional dysfunction or the special cognitive deficit can be considered consequences of inconstancy of perception due to faulty modulation of sensory input. He assumes that distorted sensoy input, when transmitted to higher centers, rostrally becomes distorted information, and that this in turn becomes the basis of the deviant language and social communication. Autistic dysfunction could be conceptualized as occurring at an interface between information processing and sensory processing involving brainstem and other subcortical mechanisms. Thus distorted sensory processing can induce distorted information processing, while cortical centers and the neostriatum can caudally (inferiorly) modify midbrain and diencephalic function. Again, distortions of information processing at cortical levels might elaborate the emotional disturbance and the distorted sensory input at the diencephalic structures where sensory input is gated.

Autistic children appear to show less selective attention to parents' voices or faces, and spatially oriented response, for the first several years of life. As if they are either receiving too little or too much sensory input with randomly over- or under- amplified or filtered sensory stimuli, the perceptual basis for the development of human relatedness is compromised. Parental reports on infantile autism indicate that the absence of response to sounds and hand flapping, occurs in over 70% of autistic children in early a stage of development, and their occurrence correlates strongly with disturbances of social relating (Ornitz, 1983, 1987). They show a deficiency in autonomic habituation, and a reduction of arousal and motor response to novel or painful stimuli. Increased heart rate variability, failure to habituate respiratory responses, and an incapacity to reduce stimulus novelty are greatest when autistcs ingage in stereotyped behaviors (Dawson et al., 1986, 1989). The increased heart rate variability of autistic children may reflect reticular formation dysfunction involving brainstem cardioregulatory centers which dampen reticular formation responses to insignificant stimuli.

If the primary symptoms of autism are not attributable to dysfunction of the telencephalon or left cerebral hemisphere, it may be suggested that the primary dysfuction is elsewhere in the nervous system. The hypotheses of subcortical (brainstem) pathophysiology is supported by autonomic response studies.

The rostrally directed theory (at midbrain and diencephalic levels) postulated by E. M. Ornitz combines with the role of nonspecific thalamic structures, and it has the basic assumption that sensory input is unavailable to be modulated for normal information processing by higher centers. Dysfunction of these neuronal loops (the faulty modulation of sensory input at the mesencephalic-diencephalic loop) can impinge on thalamic control of the

transmission of sensation to the cortex and on neostriatal functions (Ornitz, 1992). Ornitz and his colleagues assumed that distorted sensory input at the mesencephalic and diencephalic levels can induce distorted information processing at further cortical centers and the neostriatum structures when it is transmitted to higher centers, by drawing on the principle of John Hughlings Jackson that higher levels of the nervous system represent and rerepresent all lower centers. It is implicit in this principle that the functions of lower systems are rerepresented and controlled by, but are not replaced by, phylogenetically newer stuctures. He strongly suggested that brainstem mechanisms can not only integrate complex behavior but also influence the function of more rostral levels for the role of the brainstem in the generation of adaptive behavior. There is evidence that the brainstem may play a fundamental role in the complex adaptive and motivated behavior, the sense of the continuity of self, and social reactivity to the environment, including eye contact, mimetic responses, goal-specific motivated activity, and prosodic aspects of language. Thus, cortical or neostriatal dysfunction can be replicated, or initiated by brainstem or diencephalic dysfunction. Brainstem and diencephalic centers project rostrally to telencephalic structures, and in turn modify caudally brainstem and diencephalic function. Behavior abnormalities (ignoring sudden painful stimuli, hyporeactivity to auditory stimuli, enhancement of vascular responses to visual stimuli, failure to habituate respiratory responses, and indication of an incapacity to reduce stimulus novelty) are related to the brainstem impairment of sensory input to the thalamic reticular nucleus and specific thalamic nuclei via ascending axons from the midbrain reticular formation, rather than to the telencephalic disorders in autistic symptoms.

All sensory input is modulated at both specific and nonspecific thalamic nuclei which could be the primary loci of the system dysfunction in autism. The superior colliculus receives direct projections from cells in area PG of the interior parietal lobule, and is involved with the integration of visual and auditory information. In turn, this becomes the basis of deviant language and social communication. Thus, disturbances of relation, language, and communication can be considered consequences of inconstancy of perception due to faulty modulation of sensory input (Ornitz, 1983, 1987, 1992).

## Conclusion

In very eary life, all mammals can share affective experiences with their parents which is necessary to develop subsequent sharing experiences and learning of social meaning (Klinnert et al., 1983; Hobson, 1986a, 1986b). Zentall and Zentall (1983) noted that all organisms each have biologically determined optimal arousal levels for input stimuli, efficacy of information processing, and sharing affective experiences. However, autistic children "come into the world with innate inability to form the usual, biologically provided affective contact with people" (Kanner, 1943). Why can not the autistic child share affective experiences and social meaning? If these children might be distorted by the abnormalities of perceptual stimulus input and affective experience, they are liable withdraw completely from

any human contact, and show emotional disturbance and a lack of interest in their caretakers from the very first months of life, because of their inability to relate successfully to other person. It has been proven that animals deprived of early experience show reduced dendritic branching in the cortex (Rakic, 1985). There is neurophysiologic evidence for both cortical (cognitive and linguistic) and subcortical (brainstem) pathophysiology in autism.

Recent empirical investigations suggest that the telencephalic theories based on a cognitive hypothesis (left-hemisphere disorder, right-hemisphere disorder, or failure of hemispheric lateralization) could not explain the basic deficiency for the autistic behavioral responses. Nowadays, autism cannot be considered one etiology with a single pathologic mechanism producing a specific set of symptoms, but it is associated with multiple etiologies, since there are numerous pathological conditions, each of which could potentially cause central nervous system (CNS) dysfunction.

The disturbances of language and cognition suggest cortical dysfunction, and the disturbances of sensory and affective information processing (e.g. Donna Williams' autobiography) suggest subcortical dysfunction including the brain stem reticular formation, the substantia nigra, specific and nonspecific thalamic nuclei, and the rostral projections from these structures to cortical and neostriatal structures. The hypothesis of left-hemisphere pathology is an observation about the current focus on cognition and information processing in autism. Failure of lateralized function probably reflects developmental lag or retardation, becouse most autistic children show evidence of bilateral dysfunction. Autism might be explained in terms of dysfuntion of brainstem and related diencephalic behavioral systems which elaborate the system disease of phylogenetically more recent rostral structures (Ornitz, 1992). Ornitz and his colleagues hypothesize that it can be understood as a dysfunction at the interface between sensory processing at the diencephalic level and information processing to the highest levels of association cortex, particularly area PG within the inferior parietal lobule. Future efforts may resolve the complex connection mechanisms that the neocerebellar cortex controls deep cerebellar nuclei which connect to mediation systems for arousal and attention at diencephalon (Courchesne et al., 1987, 1988, 1992), memory and hippocampus (Thompson, 1986), thamamic sensory processing, motor initiation, habituation and coordination (Leaton & Supple, 1986; Supple et al., 1987), eyelid responses (McCormich et al., 1984) and vestibulo-ocular junctioning. They also need to resolve the relation among the Purkinje and granule cell reduction; systems of serotonergic, dopaminergic, noradrenergic activities; and affective, mental skills (Liener et al., 1986).

Thus, autistic behavior should not be understood as a specified cortical impairment but rather as a system disorder of social-affective recognition involving the neurophysiological mechanisms of reticular diencephalic structures between sensory processing and emotional information processing.

## Acknowledgment

The author wishes to express sincere gratitude to Prof. E. R. Ritvo (Neuropsychiatric Institute, School of Medicine, University of California, Los Angeles), Prof. E. M. Ornitz (Brain Research Institute, School of Medicine, University of California, Los Angeles) and their colleagues (Dr. B. J. Freeman, Dr. A. Mason-Brothers, Dr. J. de Traversay, Dr. K. Carr, Dr. H. Hanna, Dr. M. Sadeghpour, Dr. A. R. Kaplan, Dr. H. J. Garber, Mrs. B. Heyert, Mrs. Y. M. Chia, Miss E. Ehteshami) for their important advice and support of my research at the UCLA School of Medicine in the USA. I would like to extend my gratitude to Prof. M. Kanoh, Prof. T. Morotomi, Assoc. Prof. T. Furutuka, and Dr. E. Courchesne.

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