Recent Psychophysiological Research of Autistic Syndrome: Cerebellar and Cortical–Subcortical Theories

Masakazu Sugawara
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Introduction

Earlier theories tended to emphasize the emotional environment created by autistic children’s parents which was seen as leading to communicative deficit and socially withdrawn isolation (Kanner, 1943, 1944; Bettelheim, 1959, 1967). 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 seems 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.

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. 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.

1. 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 dysfunc-
tion 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 (Ornitz, 1987, 1989). 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), magnetic resonance imaging (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 14 of 16 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 minority subgroup of autistic (about one-quarter) subjects, and in these who suffered from a major concomitant organic brain condition (Damasio et al., 1980; Campbell et al., 1982; Gillberg and Svendsen, 1983, 1987; Rosenbloom et al., 1984). Abnormal patterns of
Table 1. PET (positron emission tomography) findings in autistic syndrome.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Rumsey et al. (1985)</td>
<td>10 adult auts.</td>
<td>variable metabolic rates</td>
</tr>
<tr>
<td>DeVoldery et al. (1987)</td>
<td>18 auts. 2–18 years</td>
<td>no difference, posterior, prefront</td>
</tr>
<tr>
<td>Horwitz et al. (1988)</td>
<td>14 adult auts.</td>
<td>variable metabolic elevations</td>
</tr>
<tr>
<td>Herold et al. (1988)</td>
<td>8 young adult auts.</td>
<td>no difference, blood flow, oxygen</td>
</tr>
<tr>
<td>Heh et al. (1989)</td>
<td>7 adult auts.</td>
<td>no difference, cerebellar vermis</td>
</tr>
<tr>
<td>Rumsey et al. (1992)</td>
<td>summarized</td>
<td>no difference in resting brain metabolism</td>
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</tbody>
</table>

Table 2. CT (computed tomography) findings in autistic syndrome.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Hier et al. (1979)</td>
<td>16 auts. (13m &amp; 3f), mean age 14 years, 4–27 years</td>
<td>reversed asymmetry in parieto-occipital area in 9/16 autistic subs. left &lt; right</td>
</tr>
<tr>
<td>Damasio et al. (1980)</td>
<td>17 auts., 4–31 years</td>
<td>enlarged ventricles in 5/17 auts.</td>
</tr>
<tr>
<td>Caparulo et al. (1981)</td>
<td>22 auts., m = 14 years</td>
<td>enlarged ventricles in 3/22 auts.</td>
</tr>
<tr>
<td>Cambell et al. (1982)</td>
<td>45 auts., 2–7 years</td>
<td>enlarged ventricles in 11 auts.</td>
</tr>
<tr>
<td>Tsai et al. (1982)</td>
<td>18 auts., 3–18 years</td>
<td>no significant abnormalities</td>
</tr>
<tr>
<td>Gillberg et al. (1983)</td>
<td>27 auts., 2–22 years</td>
<td>porencephaly, enlarged ventricles in 7/27 auts.</td>
</tr>
<tr>
<td>Rosenbloom et al. (1984)</td>
<td>13 auts., 3–8 years</td>
<td>no significant differences</td>
</tr>
<tr>
<td>Prior et al. (1984)</td>
<td>9 auts., 9–16 years</td>
<td>no significant differences</td>
</tr>
<tr>
<td>Creasy et al. (1986)</td>
<td>12 auts., 18–39 years</td>
<td>no significant differences</td>
</tr>
<tr>
<td>Jacobson et al. (1988)</td>
<td>9 auts., 20–34 years</td>
<td>enlarged III ventricles</td>
</tr>
<tr>
<td>Rumsey et al. (1988)</td>
<td>15 auts., 18–39 years</td>
<td>no significant differences</td>
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Table 3. MRI (magnetic resonance imaging) findings in autistic syndrome.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courchesne et al. (1987)</td>
<td>a single case study 21-years-old aut. m</td>
<td>developmental hypoplasia of neocerebellar hemispheres and vermal lobules VI &amp; VII (declive, tuber, folium)</td>
</tr>
<tr>
<td>Gaffney et al. (1987)</td>
<td>14 auts., 4–19 years</td>
<td>enlarged IV ventricles, decreased size of cerebellar hemispheres</td>
</tr>
<tr>
<td>Courchesne et al. (1988)</td>
<td>18 auts., 6–30 years</td>
<td>significantly smaller size of neocerebellar vermal lobules VI and VII in 14/18 auts.</td>
</tr>
<tr>
<td>Gaffney et al. (1988)</td>
<td>13 auts., m = 11 years</td>
<td>smaller size of brain–stem (pons)</td>
</tr>
<tr>
<td>Garber et al. (1989)</td>
<td>15 auts., m = 11 years</td>
<td>no significant differences in neocerebellar vermal lobules VI and VII</td>
</tr>
<tr>
<td>Gaffney et al. (1989)</td>
<td>13 auts., 4–19 years</td>
<td>enlarged lateral ventricles</td>
</tr>
<tr>
<td>Hashimoto et al. (1989)</td>
<td>18 auts., 2–9 years</td>
<td>leaf &lt; right hemisphere</td>
</tr>
<tr>
<td>Murakami et al. (1989)</td>
<td>10 auts., 14–39 years</td>
<td>significantly smaller size of neocerebellar vermal lobules VI and VII</td>
</tr>
<tr>
<td>Piven et al. (1990)</td>
<td>13 auts., 8–53 years</td>
<td>cortical abnormalities in 7 auts.</td>
</tr>
</tbody>
</table>
cerebral lateralization may represent a maturation delay rather than a neurophysiologic deviancy (Sugawara, 1995). PET (positron emission tomography) studies also have failed to demonstrate the precise metabolic reductions or elevations (Rumsy et al., 1985, 1988, 1992).

B. Electrophyiological 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 demyelination, 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).

The impaired information processing has been suggested by reports of small or absent P300 in the late components of brain EPs 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.

2. Impairment of Cerebellar Development and Purkinje Cell Reduction

The cerebellum, like brain stem, striatal (nucleus caudalis, nucleus lentiformis), and cortico-limbic structures, appears to be involved in the modulation of attentional mechanisms and complex behavior, since stimulation of the cerebellar cortex modulates midbrain and forebrain sensory responses, and stimulation of a cerebellar efferent structure 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 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 evidences 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) reported that the reduced area of cerebellar pathology is vermal lobules VI and VII seen on magnetic resonance imaging scans (Fig. 1). 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).

Fig. 1 A midline sagittal MRI scan of the cerebellum with a autistic patient (16 years old, male). The vermal lobes VI and VII (the superior posterior vermis) show hypoplasia, while the anterior vermis (vermal lobes I to V) and the inferior posterior vermis (vermal lobele VIII) are similar (supplied by Dr. Courchesne, E. at University of California, San Diego).
3. Brainstem Impairement Hypothesis

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 (Ornitz, 1983). Parental reports on infantile autism indicate that the absence of response to sounds and hand flapping, occurs in over 70% of autistic children in an early stage of development, and their occurrence correlates strongly with disturbances of social relating (Ornitz, 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 stimulus novelty are greatest when autistics engage in stereotyped behaviors (Dawson et al., 1986, 1989). The increased heart rate variability of autistic children may reflect reticular formation dysfunction involving brainstem cardio regulatory centers which damped reticular formation responses to insignificant stimulus.

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 dysfunction 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 deincephalic 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-deincephalic 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 deincephalic levels where sensory input is gated, 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 structures. They 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 replicat-
ed, 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).

4. Conclusion

The mechanism underlying the autistic behavioral syndrome is likely to involve a system dysfunction rather than a pathological change in a specific group of neurons (Dawson, 1989; Ornitz, 1992). 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 brainstem 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, because most autistic children show evidence of bilateral dysfunction. If these children might be distorted by the abnormalities of perceptual stimulus input and affective experience, they are liable to 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. There is neurophysiologic evidence for both cortical (cognitive and linguistic) and subcortical (brainstem) pathophysiology in autism. Autism might be explained in terms of dysfunction of brainstem and related diencephalic behavioral systems which elaborate the system disease of more recent phylogenetically 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.
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within the inferior parietal lobe. 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 and Supple, 1986), eyelid responses (McCor- 
mich 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).

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