The Special Case of Down Syndrome*

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Introduction

Down syndrome is one of the main causes of mental retardation. Given its high incidence (1.6 cases per 1000 live births) and the social importance of reeducation and of enabling those affected to enter a working environment, the syndrome has become an object of research with regard to retardation and learning failure.

Macroscopic neuropathological findings appear indicative of the peculiarity of Down syndrome compared with other forms of mental retardation: there is a slight weight loss and brain size reduction; the fronto-occipital diameter is shorter, and the frontal lobes, brain stem, and cerebellum are smaller. The cortical structure appears to be simplified: the main sulci are less deep, while the secondary ones are fewer; the gyri are wider and the cortex is thinner (Colon 1972).

These macroscopic characteristics are due to a structural organization at the microscopic level consisting in (a) poor myelinization or demyelinization of nervous fibers, particularly of arcuate fibers, which connect primary sensory cortex with association areas (Benda 1969), (b) a severe cellular neuronal loss, including cholinergic neurons of Meynert's nucleus, and (c) abnormalities in the dendritic formation process (Ball and Nuttal 1980; Colon 1972; Balazs and Brooksbank 1985; Ohara 1972). The formation of dendritic spines seems to be normal throughout gestation but then drastically decreases during the postnatal period. This process, which can be attributed to an early growth standstill (Takashima et al. 1981), explains the reduced numbers of dendritic spines in adults (Balazs and Brooksbank 1985).

However, most histopathological microscope investigations deal with the relation between early onset of mental deficiency in Down syndrome and dementia in Alzheimer's disease. These two conditions present similar histopathological patterns that are characterized by cerebral atrophy and by the occurrence of senile plaques, neurofibrillar bodies, and granulovacuolar degeneration (Crapper et al. 1975; Ball and Nuttal 1980; Balazs and Brooksbank 1985). In subjects with a normal karyotype the occurrence of senile plaques and

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neurofibrillar bodies has been found to increase with age and to correlate positively with the degree of intellectual decay. In contrast, it is not at all certain that in Down syndrome the early occurrence of and the rapid increase in such changes are associated with early mental deterioration (Ropper and Williams 1980), although it is acknowledged that it is difficult in Down syndrome to detect clinical signs of a demential process given that mental retardation is in any case a clinical characteristic. In fact, it has been shown that the most significant age-related clinical signs in Down syndrome are much subtler and more selective and concern the short-term memorization of visual stimuli and the occurrence of frontal inhibitory release reflexes (Crapper et al. 1975; Ropper and Williams 1980). So it seems that dementia and neuropathological alterations in Down syndrome dissociate: the high incidence of such abnormalities in itself is not sufficient to explain the sporadic appearance of a demential pattern in elderly Down syndrome subjects.

Investigations aiming to show in Down syndrome the early occurrence of biochemical, cerebral, and noncerebral reactions typical of the normal aging process have been carried out. In the process, abnormalities in the metabolism of nucleic acids and particularly of free oxygen radicals have been detected. A basic enzyme in the metabolism of free oxygen radicals is superoxide dismutase, which is codified by chromosome 21 and the activity of which is increased by 50% in the red blood cells of Down syndrome subjects (Balazs and Brooksbank 1985). An increased production of peroxides with consequent lipoperoxidation of biological membrane lipids would alter the fluidity of the double lipidic layer, causing a biochemical and functional disorganization in biological membranes. It seems likely that in Down syndrome the formation of both biochemically and functionally anomalous cellular membranes takes place at an early ontogenic stage. However, neither the increased production of intracellular free radicals nor the loss of membrane fluidity are peculiar to Down syndrome. In fact both events occur in the normal aging process (Hansford 1983), but in subjects affected by Down syndrome they occur earlier and more clearly, being present even during the initial postnatal period (Balazs and Brooksbank 1985).

Biochemical investigations also provide information about the involvement of various receptor systems, at both central and peripheral level. In particular, in Down syndrome as well as in Alzheimer's disease the cholinergic system is certainly involved, as shown both by the decrease in cortical choline acetyltransferase (CAT) activity and by the neuronal reduction of Meynert's nucleus, which is considered to be the origin of most cholinergic projections towards the neurocortex. However, since the CAT activity decrease exceeds by far the neuronal loss of the basal Meynert's nucleus, the subcortical damage is likely to be secondary to primary cortical damage (Perry et al. 1985). Histochemical investigations carried out on subjects affected by Alzheimer's disease show it to be probable that just the senile plaques might be the site of damage of cholinergic nerve endings (Kitt et al. 1984; Price et al. 1982).

The remarkable sensitivity of subjects affected by Down syndrome to the peripheral effects of atropine, a selective blocker of the muscarine receptor, points to a generalized anomaly of the cholinergic transmitter system (Harris and Goodman 1968).

The dopaminergic neurons of the substantia nigra projecting towards the basal ganglia and of the ventral tegmentum area projecting towards the frontal and limbic cortex also appear to be seriously affected, probably by secondary reverse degeneration from primitive cortical damage (Mann et al. 1987). The low blood concentration of serotonin in patients with Down syndrome and the reduced plasmatic activity of dopamine-β-hydroxylase may be peripheral signs of a change in the catecholaminergic metabolism (Wetterberg et al. 1972).

In addition to neuroanatomical and biochemical studies, investigations have been carried out by recording the cerebral electrical activity. It has been shown that the diffuse neuronal loss, the senile plaques, and the neurofibrillar degeneration may bring about a change in synaptic transmission: in fact, the involved neurons would lose the ability to produce postsynaptic potentials (Crapper et al. 1975).

Despite the neuropathological findings, electroencephalography in Down syndrome has proved to be only moderately helpful in describing cerebral development. Ellingson and Peters (1980) found significant retardation in the maturation of brain electrical activity in trisomy 21 infants which was correlated with delayed early behavioral development but not with the presence of conventional signs of EEG abnormality. Electroencephalography is also of little use for the description of cerebral aging in Down syndrome subjects (Callner et al. 1978), since from the fourth to the sixth decades of life 75% of these subjects have a normal EEG, while the rest show a diffuse but nonspecific slowing of the cortical electrical activity (Ellingson et al. 1973). Moreover, there are few EEG characteristics that specifically correlate with any form of mental retardation (Bigum et al. 1970).

More recently, investigations have been carried out by recording the sensory evoked potentials (EPs) and cognitive potentials (event-related potentials = ERPs), allowing cognitive components of mental deficiency to be distinguished from the merely perceptive ones. Despite the absence of specific EEG patterns characterizing the brain in Down syndrome, studies of the early and late components of EPs and ERPs have yielded consistently abnormal findings which confirms at the neurofunctional level that such patients are unique in that they differ substantially in this respect from both normal subjects and subjects affected by other forms of mental retardation.

Brainstem auditory evoked potentials (BAEPS) reflect the brainstem function at the pontomesencephalic level. Comparing Down syndrome and normal subjects, waves II and III and the IV–V complex show shorter latencies in the former in response to monaural (Ferri et al. 1986; Gigli et al. 1984; Gliddon et al. 1975) and binaural stimulation (Squires et al. 1980). Only the latency of wave I is prolonged in correspondence with the auditory deficit that is particularly frequent in Down syndrome, and is often serious and bilateral (Balkany et al. 1979). The central conduction time measured from the interpeak latency (IPL) I–V is

shorter than in normal subjects. It should be pointed out that the IPL I–V is prolonged in subjects affected by "idiopathic" mental retardation and in subjects with cerebral malformations (Chiarenza and Radelli, in preparation).

The reduction in the brain stem conduction time has been related by some authors to the shorter brain stem length, measured as the inion–C7 distance, and to its perpendicular insertion in the brain (Squires et al. 1980), identified in anatomopathological studies (Benda 1969; Burger and Vogel 1973); others, in contrast, have related the reduction to the degree of mental retardation (Ferri et al. 1986) or to a generalized abnormality of the nerve conduction speed also present at a peripheral level (Scott et al. 1982).

But the most constant and significant finding concerning EPs in Down syndrome is the greater amplitude and the longer latency of late components as compared with findings in both normal subjects and subjects affected by other forms of mental retardation. This particular aspect emerges with all types of evoked potential (Gliddon et al. 1975; Galbraith et al. 1970; Straumanis et al. 1973; Dustman and Callner 1979), irrespective of age and with reduced intra- and interindividual variability (Bigum et al. 1970).

On this basis it has been assumed that the increase in the amplitude of EPs in Down syndrome is due to a failure of cerebral inhibitory processes. This inhibitory deficit, which lowers the neuronal threshold of discharge, might cause an increase in amplitude of cortical evoked responses through a neurophysiological disinhibition mechanism. The inhibitory failure is probably due to the reduced activity of the reticulothalamic sensory gating system, which would result in absent or abnormal inhibition of the sensory stimuli afferent to the cortex. In fact, experimental block of the nonspecific thalamocortical system produces an increase in the amplitude of visual and auditory EPs (Skinner and Lindsley 1971). In support of the assumption that reduced activity of the reticulothalamic sensory gating system occurs, there are some investigations showing that subjects affected by Down syndrome do not present the phenomenon of "habituation" in cerebral EPs (Schafer and Peeke 1982). Habituation, defined as the decreasing response to repeated stimuli, acts as a fundamental adaptive mechanism of central origin allowing the organism not to react to insignificant external stimuli in an environmental situation characterized by continuous sensory stimulation. The inability of Down's syndrome subjects to display this elementary form of "learning" could be an important neurobiological substrate of mental deficiency. According to Luria (1963, 1973), subjects affected by mental retardation have a reduced "plasticity" because of a failure of central inhibitory processes that does not allow them to adopt mental states adequate to the continuously evolving requirements of the external environment.

The amplitude decreases in subjects not affected by mental retardation could indicate that they perceive the relative lack of significance in a series of identical stimuli more promptly than do Down syndrome subjects. Therefore the latter are thought to have no ability to inhibit selectively the meaningless-stimulus-related information (Dustman and Callner 1979).

Furthermore, in Down syndrome there is not the typical decrease in amplitude of cerebral potentials evoked by self-induced stimuli, whose time span is therefore known (Schafer and Peeke 1982): these subjects can be considered unable to perceive the sequential order in a succession of external events, and for that reason to reduce the response not only to insignificant stimuli but also to foreseeable ones. Such habituation requires an unimpaired short-term memory function and the correct utilization of the fundamental time parameters, similarity and timing of sequential events, that control voluntary actions.

The lack of age-related changes in evoked responses in Down syndrome suggests furthermore that the development of central inhibitory processes stops very early. This harmonizes with the hypothesis that the rate of cortical development in Down syndrome quickly decreases after the first months of life (Barnet and Lodge 1967).

The ERPs in Down syndrome have shown that the main differences with regard to the control groups do not concern the components N1–P1, but rather the components N2–P3, which have a longer latency and a lower amplitude in Down syndrome (Karrer and Ivins 1976b; Squires et al. 1979; Lincoln et al. 1986). Therefore differences in ERPs between Down syndrome subjects and control subjects cannot be attributed to a different sensory perception, because latencies and amplitudes of the component N1 do not differ in the two groups. The appearance of P3 is usually related to the recognition of an external event. The increase in P3 latency would represent a greater slowness, in Down syndrome subjects, of the processes of stimulus recognition for decisional purposes. In contrast the P3 amplitude is influenced by dimensions such as subjective probability, stimulus meaning, and the proportion of information lost during transmission owing to equivocation or inattention (Johnson 1986). The lower amplitude of P3 in Down syndrome could reflect a failure in one of these dimensions and in the processes of memory and formation of expectancy patterns (Squires et al. 1979). This assumption is confirmed by studies carried out on contingent negative variation (CNV) in subjects affected by mental retardation and in a control group; there were no significant differences between the groups as regards amplitudes, but such differences were seen in respect of latency and CNV rise time recorded at Cz, both of which were prolonged in the mentally retarded subjects (Karrer and Ivins 1976a,b). Down syndrome subjects take more time to develop the CNV, which then tends to increase during the test. As the CNV is considered an "expectancy" potential that can reflect both an orientation process following a warning stimulus and the expectancy and/or preparation for the motor response after an imperative stimulus, this behavior could indicate the inability to evaluate and utilize correctly the time succession of external events in programming a motor-perceptual act. From a behavioral point of view this results in an increase in reaction times, which are steadily and markedly longer than those of control subjects.

Until now there have been few controlled investigations of the electrical cerebral activity of subjects with severe mental deficiency in relation to complex tasks consisting in programming a temporal sequence of self-paced and goal-

directed actions. It occurred to me and my co-workers that in Down syndrome subjects we might employ the same method used in respect of learning-disabled children, which consists in the study of motor performances, electromyographic activity, and movement-related macropotentials in order to evaluate motor-perceptual skills and cognitive processes related to the selection and evaluation of operative strategies.

Material and Method

Down syndrome subjects aged from 18 to 25 (average 23.10), with a mean IQ of 63 on the Wechsler Intelligence Scale (WISC), a mean mental age of 10.6 years on the Termann Merril Scale, and a mean age of 10.2 years on the Psychosocial Development Scale were examined. In addition two control groups were tested. The first control group, matched to the retardates' mental age, consisted of nine normal children (group C), with a mean age of 10 years and a mean IQ of 123.3 on the WISC. The second control group, matched to the retardates' chronological age, consisted of nine young adults (group A) of normal intelligence, with a mean age of 25.9 years. None of the examined subjects had visual or auditory deficiencies or severe neurological abnormalities.

The employed method is reported on pp. 131–146.

Results

The Down syndrome subjects required a longer training period than the control groups to learn the correct bimanual sequence of movements.

Performance

The mean performance time was 178.50 ms in the Down syndrome subjects, 62.93 ms in group C, and 57.79 ms in group A. The target performance rate was 13.82% in the Down syndrome subjects, 26.00% in group C, and 32% in group A. The Down syndrome subjects were also less accurate, their performance shift being 134.15 ms, whereas that of the children was 19.27 ms and that of the normal adults, 14.00 ms. All these differences were significant by Student's t-test ($P < 0.01$). Group A showed a higher target performance rate than group C ($P < 0.05$) and was also more accurate ($P < 0.01$) (Table 1). Moreover the Down syndrome subjects showed a higher rate of performance above 60 ms (58.1%) than either group C (47.5%) ($P < 0.01$) or group A (39.8%) ($P < 0.01$). The difference was also significant between the two control groups ($P < 0.05$). In the Down syndrome group 32.30% of performances were above 200 ms, against 0.25% in the adults and 0.22% in the children (Fig. 1).

Table 1. Means and SD of the performance of the Down syndrome subjects and of the two control groups. In this and in Table 2, a superscript a or b indicates a significant correlation between the Down syndrome subjects and the control group in question. The asterisks indicate a significant difference between the two control groups

		Performance time (ms)		Performance shift (ms)		Target performance (%)	
Block		$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
I	A	70.30^{b}	45.90	22.01^{b}	38.86	31.11^{b}	46.39
	C	67.54^{b}	37.87	22.31^{b}	26.59	22.22^{a}	41.66
	D	260.76	278.98	214.14	268.30	12.00	32.58
II	A	56.21^{b}	27.67	12.93^{b}_{*}	17.13	32.44^{b}	46.92
	C	64.32^{b}	53.35	21.28^{b}	45.67	23.11^{a}	42.24
	D	161.41	224.54	117.48	215.79	13.71	34.49
III	A	51.20^{b}	22.64	9.84^{b}_{*}	11.81	34.22^{a}	47.55
	C	59.40^{b}	45.35	16.40^{b}	38.24	31.55^{a}	46.57
	D	119.47	110.63	76.26	98.04	17.24	37.93
IV	A	53.45^{b}	25.19	11.20^{b}_{*}	14.67	30.22^{a}	46.02
	C	60.47^{b}	33.20	17.07^{b}	22.20	27.11^{a}	44.55
	D	128.42	122.59	86.15	109.12	13.18	34.02
Total	A	57.79^{b}_{*}	32.51	14.00^{b}_{**}	23.67	32.00^{b}_{*}	46.67
	C	62.93^{b}	43.18	19.27^{b}	34.49	26.00^{b}	43.88
	D	178.50	220.13	134.15	210.22	13.82	34.54

A, adults; C, children; D, Down syndrome subjects
a/*, $p < 0.05$; b/**, $p < 0.01$

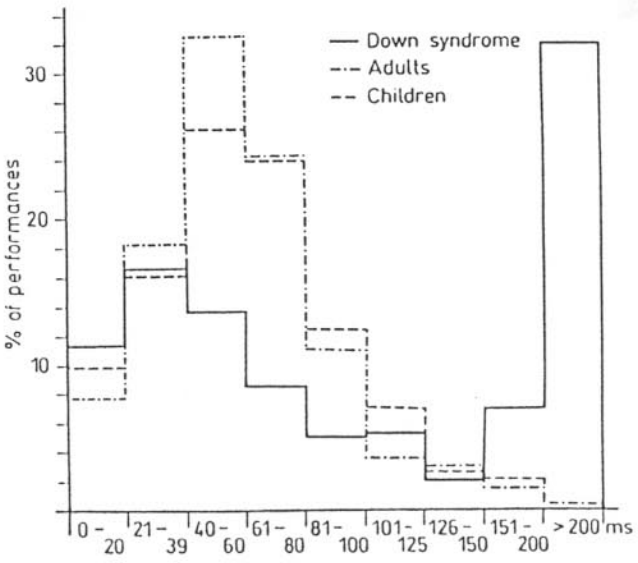

Fig. 1. Performance times of Down syndrome subjects, adults, and children in the nine time intervals

In the Down syndrome subjects practice produced only a partial improvement in the performance time, which remained steadily higher in all four blocks in comparison with the two control groups ($P < 0.01$). In fact, their performance time decreased from 260.7 ms in the first block to 128.4 ms in the fourth, whereas it dropped from 70.3 ms to 53.4 ms in group A and from 67.5 ms to 60.4 ms in group C.

The performance accuracy in the Down syndrome subjects showed the same course: the performance shift decreased from 214.1 ms in the first block to 86.1 ms in the fourth. In group A it fell from 22.0 ms to 11.2 ms and in group C from 22.3 ms to 17.0 ms. Comparison of the performance shift in the Down syndrome subjects in the four blocks with that of the two control groups was steadily significant ($P < 0.01$). Moreover, in comparing the two control groups, the adults were found to improve their accuracy with practice more than did the children: their performance shift did not differ from that of children in the first block, whereas it considerably diminished in the second one ($P < 0.05$) and retained this advantage in the following blocks. The target performance rate in Down syndrome subjects was steadily lower than that of the other two groups: 12% in the first block and 13% in the fourth, against 31% ($P < 0.01$) and 30% ($P < 0.05$), respectively, in group A and 22% ($P < 0.05$) and 27% ($P < 0.05$), respectively, in group C. No significant differences were found in the target performance rate between the two control groups in any of the four blocks, although the adults had a significantly higher total target performance rate than the children ($P < 0.05$) (Table 1).

Electromyography

The EMG of the left forearm muscles group did not show any significant difference in the three groups as regards the amplitude before and during the movement and the rise time. In the Down syndrome subjects the EMG of the right arm related to the arrest of the sweep was not different in amplitude before and during the movement in comparison with the other two groups. In contrast, the rise time was slower in comparison with both control groups, with a significant difference ($P < 0.05$) between the Down syndrome subjects and group C.

Movement-Related Brain Macropotentials

Remarkable differences were found in movement-related brain macropotentials (MRBMs) during all four motor periods (Fig. 2).

In the premotor period the Bereitschaftspotential (BP) was present as a negative deflection in the frontal, central, and precentral regions in both control groups; the amplitude and the area of BP did not differ in a statistically significant way, except for Pz ($P < 0.01$), where the amplitude value was higher in adults. In the Down syndrome subjects it was absent or showed a reduced amplitude

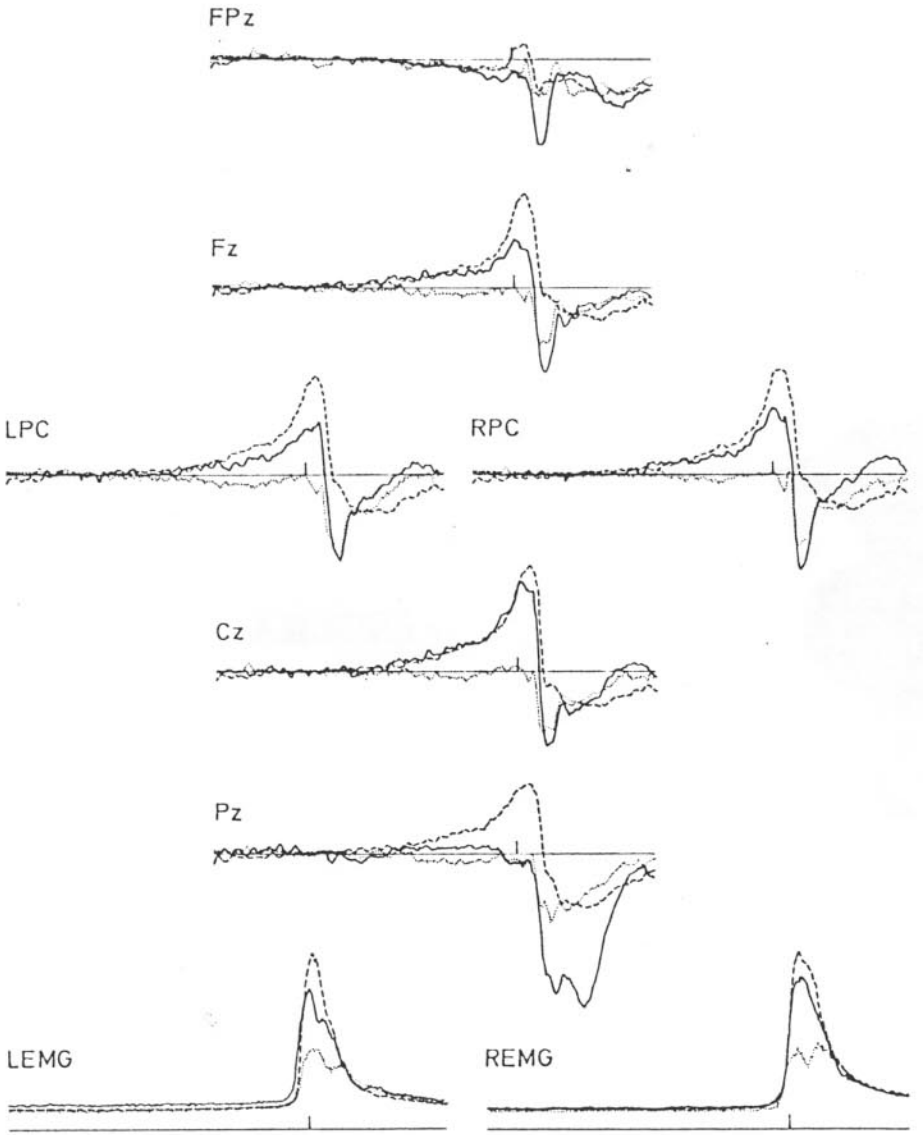

Fig. 2. Grand averages of rectified EMGs and MRBMs of Down syndrome children (..... *traces*), adults (----- *traces*), and normal children (—— *traces*). In this and in Fig. 3 the *vertical bar* in each trace indicates the instance of the computer trigger and a calibration signal of 5 μV. Negativity is upwards. The time scale is 3200 ms

at all recording sites. So there were statistically significant differences in BP between the Down syndrome subjects and the control groups at all recorded cerebral areas, except for FPz in the comparison between Down syndrome subjects and group A, and for FPz and Pz in the comparison between Down syndrome subjects and group C. The results of the BP area comparison in Down syndrome subjects and in adults were the same as those for the amplitude (Pz: $P < 0.01$; Fz, Cz, RPC, and LPC: $P < 0.05$). In Down syndrome subjects and in children, too, results of the BP area comparison proved statistically similar to those regarding the BP amplitude, except for Fz and LPC (Table 2).

The BP onset did not differ between the two control groups, whereas it could not be recorded and measured in the Down syndrome subjects because of the poor or insignificant amplitude of the potential.

In the sensory-motor period the motor cortex potential (MCP) was markedly present in control subjects in the central and precentral regions. In the Down syndrome subjects the MCP was absent or showed a significantly reduced amplitude in all cerebral areas compared with group A (Fz, Cz, Pz, RPC, and LPC: $P < 0.01$; FPz: $P < 0.05$) and in the frontal, central, and precentral areas compared with group C (Fz: $P < 0.05$; Cz, RPC, LPC: $P < 0.01$). The two groups of normal subjects were also different from each other: the MCP amplitude was larger in group A in all cerebral regions (Fz, Pz, RPC, and LPC: $P < 0.01$; FPz, Cz: $P < 0.05$). The latency of the MCP with respect to the EMG onset did not differ in adults and control children, whereas in the Down syndrome subjects it was impossible, because of the reduced MCP amplitude, to find a peak whose latency could be measured with respect to the EMG onset. The absence or reduction in MCP, as well as in other potentials dealt with later, should not be attributed to a jitter effect related to the performance variability, since, as shown in Fig. 3, the grand average of rectified EMGs and MRBMs related to the target performance of all the three groups confirms the absence of MCP in the Down syndrome subjects.

The latency of N100 was always shorter in the Down syndrome subjects at all recording sites, in comparison with both group C and group A. The difference was significant only for FPz and Pz ($P < 0.05$) between the Down syndrome subjects and group C; the two control groups did not differ from each other. Since the measurement of the N100 amplitude depends on the amplitude of BP, it was impossible to carry out a statistical comparison.

In the motor completion period the latency of P200 was not significantly different in the Down syndrome subjects and the adults. The children presented a P200 latency significantly higher than that of the Down syndrome subjects in the frontal (Fz: $P < 0.01$) and in the central and left precentral regions ($P < 0.05$). In the children, P200 had a larger amplitude in all cerebral regions; the differences, with respect to both the adults and the Down syndrome subjects, were statistically significant for all recording sites ($P < 0.01$). The lowest amplitude values were found in the Down syndrome subjects.

In the postmotor period, skilled performance positivity (SPP) was present as a positive deflection in all cerebral regions in all three groups, but with a

Table 2. Means and SD of the MRBMs of the Down syndrome subjects and the two control groups.

			FP_z		F_z		C_z		P_z		RPC		LPC	
			$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
BP	Amp.	A	1.65	4.34	−6.55[b]	5.01	−8.33[b]	6.22	−7.10[b]**	4.74	−8.96[b]	4.73	−8.36[b]	4.88
		C	3.15	4.89	−4.41[a]	6.99	−9.25[b]	7.59	−0.68	7.66	−6.51[b]	6.56	−5.02[a]	6.50
		D	1.67	6.22	0.58	5.05	−0.16	4.89	1.13	4.18	0.06	4.39	0.89	5.18
	Area	A	370.95	1332.94	−1090.41[a]	1073.42	−1657.03[a]	1421.66	−1641.59[b]	1241.66	−1468.81[a]	1086.28	−1319.90[a]	1227.94
		C	941.39	1261.16	−1054.68	1661.59	−1771.81[a]	1641.04	−568.91	1872.87	−1342.44[a]	1333.52	−954.48	1345.34
		D	1061.77	2152.90	508.00	1567.65	318.55	1865.01	1063.66	1261.20	436.25	1541.84	1158.62	2303.43
MCP	Amp.	A	0.36*	5.22	−13.95[b]**	6.50	−15.07[b]	7.78	−10.94[b]**	4.70	−15.49[b]**	5.75	−14.57[b]**	6.06
		C	3.64	5.94	−6.09[a]	8.50	−11.45[b]	10.98	3.19	8.32	−7.33[b]	9.45	−6.27[b]	10.40
		D	2.09	9.59	1.27	8.40	0.53	6.81	1.81	4.87	0.88	6.34	1.98	7.47
N100	Lat.	A	113.70	20.12	120.27	19.53	118.34	21.61	123.02	25.25	116.83	22.33	119.72	20.45
		C	121.70[a]	20.21	119.48	19.66	118.47	17.89	127.61[a]	25.18	117.57	18.81	116.91	16.95
		D	104.16	8.50	109.30	14.16	109.05	7.92	112.71	5.06	108.33	10.80	111.22	11.29
P200	Amp.	A	7.77**	3.22	15.86**	5.89	17.82**	10.38	14.53**	5.30	17.17**	7.10	15.91**	7.10
		C	12.62	4.64	22.19[b]	6.98	26.04[b]	7.60	22.03[b]	10.57	25.34[b]	7.29	23.32[b]	6.46
		D	7.59	6.30	11.12	7.16	13.60	7.53	11.64	5.42	13.36	6.99	12.55	8.01
	Lat.	A	192.81*	15.48	210.61	21.88	211.16*	15.91	219.00	18.91	211.50	19.25	213.83	18.95
		C	210.44	23.50	223.05[b]	18.80	266.55[a]	26.76	232.51	27.38	219.27	27.05	227.00[a]	28.37
		D	201.06	23.50	195.73	25.87	201.73	31.19	210.34	33.41	210.56	23.21	201.82	27.20
SPP	Amp.	A	7.70	5.54	8.08	6.21	8.18	7.96	10.24**	5.25	7.50	5.68	7.30	5.53
		C	6.97	7.42	5.84	9.56	7.65	12.90	25.24[b]	10.86	5.08	9.71	6.09	9.92
		D	6.97	13.25	4.05	11.24	5.60	11.38	9.28	8.31	4.91	9.58	5.15	11.02
	Lat.	A	525.80	126.32	507.33	102.18	501.88	98.90	497.82	79.89	516.05	99.34	509.72	97.08
		C	537.09	99.23	539.41	99.84	501.74	65.34	495.27	45.70	516.75	81.92	510.70	79.83
		D	532.55	88.71	521.10	72.88	532.38	77.31	508.85	66.15	515.70	48.99	507.82	62.05

Adults; C, children. D, Down syndrome subjects
*, $P < 0.05$; b **, $P < 0.01$

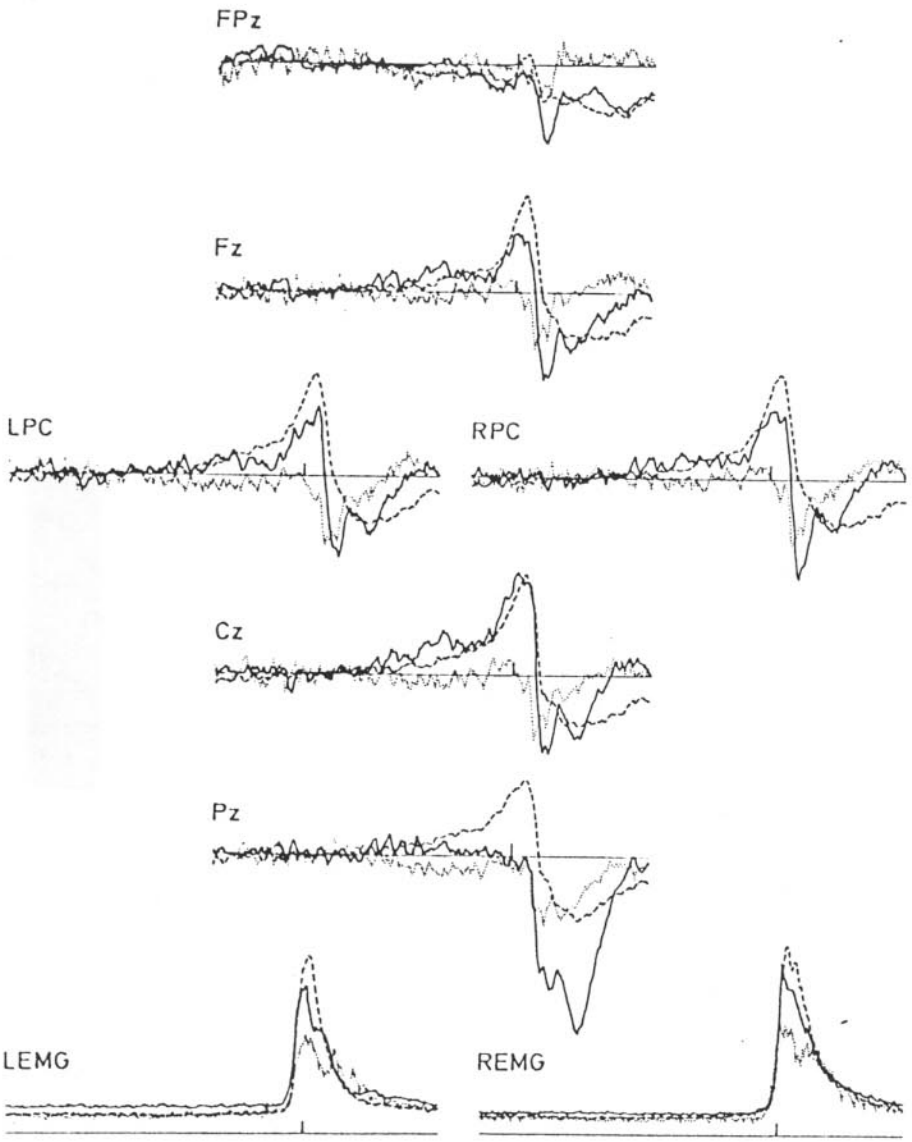

Fig. 3. Grand average of rectified EMGs and MRBMs related to target performances of Down syndrome subjects (..... *trace*), adults (---- *trace*), and children (—— *trace*)

lower amplitude in the Down syndrome subjects. The latencies of this potential were not significantly different in the three groups. The amplitude of SPP measured from the baseline was not significantly different in the three groups, except for Pz in the comparison between Down syndrome subjects and children (Table 2). When comparison was made with SPP amplitude values measured

as the difference from the P200 peak, the SPP amplitude of the adults was significantly greater at all recording sites ($P < 0.01$) as compared with the Down syndrome subjects and the children, except for Pz in the comparison with the children. The SPP amplitude of the children was not significantly different from that of the Down syndrome subjects.

Discussion

The motor-perceptual task lies in carrying out ballistic bimanual and self-initiated movements. Its successful performance basically depends on a correct and accurate temporal sequence of movements. The limited temporal range of actions forces a temporal and motor programming of the whole task. Moreover, as subjects can evaluate the result of each test in real time owing to the visual feedback, they are also able to compare each time the obtained result with the preprogrammed motor strategy and to change it in the most suitable way to reach the target.

The preparation of a movement sequence like that required by such a bimanual task involves the development of a central clock which controls the temporal course through afferent and efferent systems (Hirsch and Sterrick 1964; Rosenbaum and Patashnik 1980). The performance improvement of this clock depends in part on the presence of proprioceptive and exteroceptive feedback as regards the accuracy of the performance. However, it does not eliminate the need for motor programming (Rosenbaum 1983), which plays a fundamental role in the organization of the temporal sequence of movements, which depends, in turn, on a higher age-related synaptic efficiency of the central nervous system (Craik 1947). In fact, the interval between two consecutive movements has been found to be often shorter than the time required for the proprioceptive and exteroceptive feedback of the first one to act as a trigger for the second one (Lashley 1951).

The performances of the Down syndrome subjects in our investigation show that the development of this central clock proceeds with difficulty. Down syndrome subjects, in fact, meet with great difficulties in carrying out the bimanual movement in the correct temporal sequence. They were found to be steadily slower in executing the task in comparison with both control groups. They showed the highest rate of trials with performance times above both 60 and 200 ms. Moreover, their performance time decreased greatly from the first block to the fourth, but the target performance rate remained practically unchanged and below that of the controls.

The children showed the highest increase in the target performance rate as the task proceeded, even though they did not reach the values of the adults. The adults did not improve with practice the target performance rate, which was already high in the first block, but they showed a greater increase in their performance accuracy as compared with children.

The performance accuracy of the Down syndrome subjects showed the same behavior as the target performances; the performance shift remained at steadily higher values throughout the task.

Therefore the adults were able to carry out their task more speedily and accurately throughout the test. The children proved able to utilize experience, progressively improving their performance, even though they did not reach the level of the adults. The Down syndrome subjects were permanently below the other two groups as regards accuracy and speed. Not only were the Down syndrome subjects slower and less accurate, but they were also unable to benefit from practice, unlike the other two control groups which were similar as regards mental or chronological age.

These findings agree with several previous studies showing that motor-perceptual functions of Down syndrome subjects appear to be greatly impaired in comparison with subjects with the same chronological or mental age (Cratty 1969). The difficulty in maintaining equilibrium or in executing tasks requiring it (Pesch and Nagy 1978), the markedly prolonged reaction time (Berkson 1960), and the inability to carry out rapid movement sequences (Frith and Frith 1974) are some of the motor-perceptual functions in regard of which Down syndrome subjects display worse performances than subjects affected by other forms of mental retardation.

Furthermore they meet with particular difficulties in carrying out tasks involving a temporal component and when the sequence of movements must be programmed so as to make the resulting action coincide with an external event (Henderson et al. 1981a). To make this possible, in fact, it is necessary for the movement to be programmed according to precise spatial and temporal parameters. The specific problem of motor programming in Down syndrome subjects seems to lie solely in the temporal component and not in the spatial one (Henderson et al. 1981b).

In parallel to motor performances, MRBMs also showed significant differences between Down syndrome sybjects and control subjects. The BP is characteristic of the premotor period (Kornhuber and Deecke 1965), when the organization of ideokinetic elements for the execution of the movement takes place (Chiarenza et al. 1982, 1983). Its clinical and neurophysiological characteristics make it an important index of cortical maturation. The BP appears, in fact, at about the age of 7 years in the frontocentral regions, and it progressively increases in amplitude until in adolescence it reaches that seen in adults (Chiarenza 1986a). It is absent or has a low amplitude in various clinical situations: chronic schizophrenia (Chiarenza et al. 1985), Parkinson's disease (Deecke et al. 1977), dyslexia-dysgraphia (Chiarenza et al. 1986), and learning disabilities (Chiarenza et al. 1982). In the current study the BP was present in the two control groups, with a greater amplitude in adults, whereas it was absent or greatly reduced in all cerebral regions of the Down syndrome subjects.

Warren and Karrer (1984) showed that during the execution of unskilled movements the BP is missing or appears as a positive deflection in young adults

affected by mental retardation. The absence of BP in Down syndrome subjects could therefore indicate the presence of a programming failure of motor-perceptual performance, both simple and complex.

It has been assumed that the BP is a cholinergic potential: its absence in Down syndrome subjects would therefore agree with the microscopic and histochemical findings showing a remarkable deficit of the central cholinergic system in Down syndrome subjects (Perry et al. 1985; Kitt et al. 1984; Price et al. 1982).

During the sensory-motor period the MCP was absent or had a reduced amplitude in the Down syndrome subjects. This potential is considered to be an index of reafferent sensory activity: it represents the elaboration in precentral and frontal regions of the kinesthetic information related to the executed movement (Papakostopoulos et al. 1975; Papakostopoulos and Crow 1984). Since suitable proprioceptive information is of fundamental importance for the preparation and correct execution of movements, the lack of elaboration of this sensory feedback, expressed by the MCP, could be responsible for the poor capacity for temporal organization which Down syndrome subjects show in carrying out complex motor acts. Animal experiments (Dubrovsky and Garcia-Rill 1973) and observations on patients with damaged posterior spinal columns have in fact shown that total or partial deafferentation prevents the temporal control of a motor sequence. Furthermore, it is important to observe that in the same experimental situation subjects over 60 also show slower performances and a steadily reduced MCP amplitude (Papakostopoulos and Banerji 1980). Since macro- and microscopic investigations are in agreement in proving, in Down syndrome subjects, an early onset of anatomopathological signs of cerebral aging, the reduced MCP amplitude could indicate a poor cortical reactivity to the reafferent sensory information. The lower MCP amplitude in children compared with adults could reflect, in contrast, a condition of relative immaturity of the sensory reafferent activity, with which lower speed and accuracy of execution as regards performances would correspond.

The N100 wave is considered the cerebral response evoked by the appearance of the sweep on the oscilloscope. Its latency is shorter in Down syndrome subjects, but in this study it was significantly reduced only for FPz and Pz in comparison with the children's group. This result is in agreement with the studies of BAEPs by Squires et al. (1981) and in contrast with those of cortical ERPs by Bigum et al. (1970), Marcus (1970), and Gliddon et al. (1975). These discrepancies can be attributed mainly to the different experimental paradigms used by these authors, their experiments being externally paced.

The shorter latency of N100 in the Down syndrome subjects in the task performed in this study could be attributed to a deficit of the central mechanisms responsible for the perceptive elaboration of sensory input. An analogous interpretation has been suggested for the flat recovery function of wave V of the BAEPs of the Down syndrome subjects (Squires et al. 1981; Otto et al. 1984). P200 is considered to be one of the late components of somatosensory potentials (Chiarenza et al. 1983). Its latency was greater in children than in the other two groups; there was no significant difference between Down

syndrome subjects and adults. As the latency of P200 has been found to decrease with age (Chiarenza et al. 1983), these findings would indicate that in Down syndrome subjects the neuronal systems subtended by this potential have reached a maturation comparable with that in normal adults, whereas they are still relatively immature in 10-year-old children. The lower amplitude of P200 in Down syndrome subjects could be an index of reduced elaboration of reafferent sensory input. This result is in agreement with other investigations of late sensory and cognitive components of cerebral evoked potentials in Down syndrome (Squires et al. 1979).

The presence of SPP on all recorded brain areas in Down syndrome subjects and the fact that its amplitude was similar, except for Pz, to that in subjects with the same mental age, but lower than that in subjects with the same chronological age, could indicate that Down syndrome subjects are able to recognize and evaluate the results of their motor-perceptual performances but that they do not manage to use such experience to improve their performances. In fact, the SPP is present only when, besides elaborating movement strategies, the subject can also evaluate from time to time the result of his performances and utilize the acquired knowledge to change or influence future actions (Papakostopoulos 1978; Chiarenza 1986a). If the possibility of evaluation is lacking, the SPP does not appear (Papakostopoulos 1980; Papakostopoulos et al. 1986). This potential has peculiar developmental characteristics: it is always present in the parietal regions and appears at the age of 9–10 years in the frontocentral regions. With age its amplitude in these areas increases until it reaches the adult amplitude in adolescence, whereas the latency decreases (Chiarenza et al. 1983). Children under 9–10 are likely to be unable to elaborate complex strategies based on formal and probabilistic thinking (Chiarenza 1986b). These results agree with, and extend to self-paced tasks, the previous observations of Karrer and Ivins (1976b), Squires et al. (1979), and Lincoln et al. (1986) with P300 experiments.

There is evidence to support the assumption that all surface-positive slow potentials, such as SPP and P300, originate from the hyperpolarizing inhibition of pyramidal neurons and the electrotonic diffusion of postsynaptic inhibitory potentials to apical dendrites (Creutzfeldt et al. 1966). The physiological tone of the cholinergic component of the ascending activating reticular system projecting towards thalamus and cortex is thought to play a predominant role in the genesis of such positive potentials (Marczynski 1978).

Since the SPP is considered a potential produced by cholinergic systems (Marczynski 1978), its low amplitude might reflect the cortical and subcortical cholinergic deficit shown by histochemical and microscopic studies in Down syndrome subjects (Perry et al. 1985; Price et al. 1982). Furthermore, these findings would suggest the SPP and BP are generated by different neuronal systems, both because they are differently distributed on the scalp and because they are differently involved in Down syndrome.

In conclusion, the pathological structural organization of the CNS, from brain stem to cortex, may be responsible both for the bad performance of the

Down syndrome subjects on this motor-perceptual task and for the abnormalities of MRBMs that are its electrophysiological equivalent.

Conclusions

Analysis of the performances during the execution of a motor-perceptual, self-initiated task shows that Down syndrome subjects have great difficulty in organizing correct temporal sequence of ballistic movements. Moreover, they are much slower in performing the task because of a defective timing of motor sequences. From a neurophysiological point of view, these behavioral aspects express themselves in a reduced preparation of the movement (absent or very low BP), a lack of elaboration of the reafferent somatosensory information (absence of MCP), and a reduced capacity for evaluating the outcome of the performance (presence of low SPP).

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