Clumsiness and Disturbed Cerebellar Development: Insights from Animal Experiments

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ABSTRACT

Cerebellar functioning has been implied in the fine adjustments of muscle tone, in the coordination and the feed-forward control of movements and posture, as well as in the establishment and performance of motor skills. The cerebellar cortex in mammals develops late in neuro-ontogeny and an extrapolation from experimental results indicates that in the human the proliferation of the granule cells and the development of circuitry in the cerebellar cortex starts only in the last trimester of pregnancy and lasts until beyond the first birthday. This late development makes the cerebellar development particularly vulnerable to situations like an insufficient supply of nutrients, which may follow placental dysfunction, or to side effects of pharmacological treatments like the administration of corticosteroids in the postnatal period. We studied whether such situations might also lead to motor impairments. In rats, the effects of undernutrition during the brain growth spurt were investigated as well as those of corticosteroids administered in a period that is analogous to the 7th to 8th month of pregnancy in the human. Both these interferences affect cerebellar development and our results in rats indicate that they also lead to retardations in the emergence of certain reflexes, as well as to longer lasting motor impairments during locomotion. Extrapolation of these results strongly suggests that a disturbed cerebellar development should be considered as an important etiological factor in clumsiness in human children.

INTRODUCTION

Clumsiness and motor impairment are among the terms that are used to characterize the unskillful and awkward movements which cause a variety of problems in a considerable percentage of children. The lack of fluency and efficiency ultimately is caused by maladjusted recruitment of motoneurones and badly phased coordination of agonist and antagonist muscle groups but the underlying causes for such impairments generally have to be found at higher levels in the brain. It is the heterogeneity of the motor impairments that excludes a single or even a few factors in the pathophysiology of clumsiness (see for example, Sigmundsson, 2003—this issue p. 27). When theorizing on the basic problems that might be involved in the neurophysiology of clumsiness, ill processing of sensory information, inefficient motor programs sometimes based upon deficient movement concepts, and abnormalities in descending and ascending influences on the neuromuscular effectors are among the main factors underlying clumsiness.
Skillful motor behavior only develops years after birth when the neurobiological processes governing the aspects mentioned above have matured and match the tasks to be met. By the standards of the efficiency of movements at later ages, those in young children might be called 'clumsy' (although age-adequate). Reaching movements at two months of age initially are ill directed with several acceleratory and deceleratory phases along the trajectory (for example, Von Hofsten, 1991). The immaturity of perceptional processes, the inadequate recruitment of forces in arm muscles during the movement, and the lack of anticipatory adjustments in postural control are among the factors contributing to these irregularities. In the months to come, new possibilities emerge, such as directing the arm more precisely and moving the fingers independently ('fractionated' finger movements, Kuypers, 1982; Lemon et al., 1997) and these enable delicate manipulative skills to develop. The development of vestibular functioning, newly acquired postural control strategies and the neuromuscular maturation of antigavity muscles are among the factors allowing the baby a few weeks after birth to keep its head upright for longer periods, a few months later to sit, and still later to stand. In the years thereafter, fluent bipedal walking develops (Forssberg & Dietz, 1997), as well as reaching and grasping movements (Hadders-Algra, 2001) by virtue of feed-forward programs for leg and arm movements in conjunction with postural control. This development continues at least during the first decade of life (Massion, 1998; Assaiante, 1998). These developments ultimately lead to skillful motor behaviors. From this perspective, it seems that global or partial retardations of the neurobiological processes involved in motor skills should be considered possible etiological factors of clumsiness.

For a long time, cerebellar functioning has been implied in the fine adjustment of muscle tone and in the coordination of movements at adult age (Dow & Moruzzi, 1958). Later, Eccles (in his "dynamic loop hypothesis of movement control", Eccles et al., 1972) stressed the role of the cerebellum in the feed-forward control of movements. Neuroanatomists, making use of tract tracing techniques and antibody staining unraveled many details of the reciprocal connections between the cerebellum and other motor areas in the brain and the spinal cord, and this provided the blueprint for this and more recent neurophysiological evidence (for reviews Voogd et al., 1990; Voogd, 1995; Voogd & Glickstein, 1998). Indeed, strong indications now exist for a key role of the cerebellum in the production of programmed and skilled movements; for its role in the fine adjustment and timing of motoneuronal activation, and in the feed-forward regulation of postural adjustment along with extremity movements (Brooks et al., 1973; Grillner, 1975; 1981; Brooks, 1979; Massion & Sasaki, 1979; Ito 1984; 1998; 2001; De Zeeuw et al., 1998; Gramsbergen, 1998).

The cerebellar cortex develops late during neuro-ontogeny. Research by Dobbing and Sands (1973) has demonstrated that the spurt in brain growth in the human starts in the last trimester of pregnancy and continues in the first year of life. Further analysis has shown that the fast and late development of the cerebellum is the main contribution to this growth spurt (Dobbing, 1981). In rodents, this phase of cerebellar development occurs in the postnatal period (Smart & Dobbing, 1971), and neuroanatomical studies have shown that this involves neuronal and glial proliferation, the outgrowth of axons and dendrites, the establishment of synaptical contacts, as well as myelination (Altman & Bayer, 1997). The results of these studies on the one hand indicate that the cerebellar structures that are involved in regulating the delicate and skillful movements develop late in neuro-ontogeny. On the other hand the results point to the possible vulnerability of this development, for example, to iatrogenic side effects of
medical treatments or to insufficient supply of nutrients in the perinatal period.

From this background we studied in rats the effects of an experimentally manipulated cerebellar development on motor performance. The specific question is whether clinical situations, as early undernutrition or the administration of synthetic corticosteroids, which are known to influence cerebellar development, might lead to motor impairments. The experimental situations were chosen in analogy to the clinical conditions of intrauterine growth retardation (IUGR) and to the treatment with dexamethasone for respiratory problems.

To appreciate the role of cerebellar processing in the performance of skillful motor behavior, its connections with other motor areas and the basics of cortical circuitry are briefly reviewed.

CEREBELLAR MORPHOLOGY AND CIRCUITRY

In the human, the afferent and efferent fiber connections of the cerebellum or details of the cerebellar circuitry have not been studied with modern techniques, and therefore most of our knowledge is based upon extrapolations from animal studies, notably in rats and cats. Macroscopically, the flocculonodular lobe at the caudal end of the cerebellum is closely connected with the vestibulum and the vestibular nuclei and this part in particular is involved in eye movement control and in postural control. The vermis, the rostro-caudally oriented worm-like structure in the middle with the adjoining strips of the cerebellar hemispheres, or, the spinocerebellum is reciprocally connected to the spinal cord. This part receives massive afferent input from the spinal cord, for example, via the ventral and dorsal spinocerebellar tracts. The first tract conveys information from interneurons around the motoneurons and the second from interneurons in the dorsal horn. The information on motor commands from the premotor interneurons on the one hand, as well as on the effects of these motor commands from the interneurons in the dorsal horn on the other, are considered the basis for motor learning (see Brodal, 1992). In addition to these tracts, several indirect spinocerebellar pathways transport information to the cerebellum via the so-called precerebellar nuclei as the lateral reticular nucleus and the inferior olivary nucleus. The hemispheres, or, the cerebrocerebellum, receive massive information from the motor cortices and also from the visual cortex and other areas, mainly via the contralateral pontine nuclei and also via the inferior olivary nuclei, and the output from these parts reaches the cerebral cortex via several thalamic nuclei.

A remarkable feature of cerebellar organization is that the number of afferent fibers entering the cerebellum far outnumbers those leaving the cerebellum (Brodal, 1992, refers to a factor of 40). The processing of the immense stream of information is effected in the cerebellar cortex by the interaction of the mossy fiber and the climbing fiber systems (for a schema of the afferent and efferent cerebellar connections, as well as of the basic circuitry of the cerebellar cortex see for example, Brodal, 1992). Each Purkinje cell, at adult age, is contacted by one climbing fiber. The fibers stem from the inferior olivary nucleus (which in turn receives input from the spinal cord, brain stem, and the cerebral cortex) and each fiber makes thousands of synaptic contacts with its Purkinje cell. The other afferent system is the so-called mossy fiber system. Afferents from the spinal cord and from the cerebral cortex terminate on the granule cells and the axons of these cells head toward the superficial layers of the cerebellar cortex. There they bifurcate and course in parallel to the cortical surface over long distances. These so-called parallel fibers contact several thousands of Purkinje cells on slender spines (for a review on
the cerebellar ‘micocircuitry’ see, De Zeeuw et al., 1998). The key features in cerebellar processing are the immediate synaptic influences of these two fiber systems on Purkinje cell output, as well as longer lasting modulations in their synaptic efficacy. A long-term depression (LTD) in synaptic transmission on Purkinje cells in the flocculus, in the vestibulo-ocular reflex, was found by pairing the activation of the vestibular mossy fibers and the stimulation of the climbing fibers (Albus, 1971; Ito, 1982). Long term-depression is considered one of the main factors involved in processes such as motor learning (for recent reviews see, Linden & Connor, 1995; Daniel et al., 1998; Ito, 2001). The Purkinje cell is central in cerebellar processing, and its axon is the sole (inhibitory) output reaching the deep cerebellar nuclei. The neurons in the nuclei project onto thalamic nuclei and the red nucleus, on the way to the motor cortex or to the spinal cord.

The amazing feature of the cerebellar circuitry is the seemingly simple layout of the basic circuit, which is repeated endless times and which is involved in so many quite different motor acts. This “paracrystalline lay-out” of dendritic trees of Purkinje cells in one plane, perpendicular to the direction of the parallel fibers, has also been considered to play a role as a timing device (Braitenberg, 1977; De Zeeuw et al., 1998; see also Ivry, 2003—this issue). Much is understood from the neurophysiological interactions in this circuit, but the relevance of this processing for motor learning and adjusting motor acts is not yet fully solved.

The cerebellum shares with a few other regions in the brain a remarkably stretched developmental history. The neuroblasts for the deep cerebellar nuclei and those for future Purkinje cells are among the first in the brain to proliferate and to migrate from the central germinative matrix. Much later, in the human in the last trimester of pregnancy and in rats even after birth, groups of proliferative cells migrate and form a layer over the Purkinje cell layer. After arrival, at a late stage of development, the cells start proliferating. Amazingly, the main efferent projections such as the cerebellorubral and the rubrospinal tract are established even before the proliferation of the granular cells has started and this seems to indicate that the function of these tracts must change during neuro-ontogeny (Altman & Bayer, 1997; Gramsbergen, 2001).

WHY STUDY CLUMSINESS IN RATS

Rats are born at an early stage of development. By the end of the second week of life, brain development in the rat is similar to that in a human baby at term age (Romijn et al., 1991). Therefore, the early phases of neural development can be studied postnatally in this animal. When studying clumsiness, the differences between rats and humans in motor competence and motor repertoires obviously have to be taken into account. The human is a bipedal species and specialized to use its arms and hands for the performance of fluent and skillful movements requiring delicate postural adjustments during such operations. The corticospinal tract in primates plays a key role in producing the so-called fractionated finger, hand and wrist movements (Lawrence & Hopkins, 1976; Lemon et al., 1997). The feed-forward adjustment of postural reactions to extremity movements by medially descending projections are tailored to these abilities. Although rats basically are quadrupedal animals, they, more than cats or dogs, can ably manipulate smaller and larger objects, even when standing on their hindfeet, as has been demonstrated for example, by the elegant experiments of Whishaw and colleagues (see for example, Whishaw, 2003, this issue). In the rat, the rubrospinal tract has a primary role in steering extremity movements (Grillner, 1981; Kuypers, 1982), whereas corticospinal tract is primarily involved in modulating and
gating afferent proprioceptive and exteroceptive input (for references and discussion see, Lemon et al., 1997). Despite the differences in behavioral repertoire and neural functioning, the rat is considered the most convenient animal for investigating the factors interfering with normal motor development.

**GROWTH RETARDATION**

A frequently occurring condition in the last period of pregnancy is a diminished supply of nutrients due to placental dysfunction. Experimental research, mainly in rats and also in pigs, has demonstrated that such a condition during the brain's growth spurt leads to a decreased brain growth (Smart & Dobbing, 1971). This finding has led to the formulation of the vulnerable period hypothesis (Dobbing, 1981) comprising that the brain is most vulnerable to a restriction of nutrients during its growth spurt. In the human, the brain growth spurt lasts from the beginning of the last trimester of pregnancy until after birth, and brain growth continues until well after the end of the first year of life, as demonstrated in a neuropathological investigation in an impressive series of human fetuses, babies, and children (Dobbing & Sands, 1973).

Extrapolating from experimental research, supposedly also in the human a restricted supply of nutrients in this period leads to abnormalities in brain growth. The cerebellum grows extremely rapidly around term age, and supposedly circumstances interfering with optimal placental functioning, or complications and inferior nutritional conditions in the postnatal period particularly affect the development of this structure, thus leading to a distorted brain growth (Dobbing, 1981). Data on intrauterine growth retardation per se in relation to changes in normal motor development are scarce as growth retardation in the human often is confounded by other adverse conditions during pregnancy. Still, a wealth of data and circumstantial evidence indicates that IUGR on its own leads to motor impairments and developmental retardations, and also certain evidence points to a decreased brain growth being related to such deviations (for reviews, Allen, 1984; Bos et al, 2001). From this background our research is reviewed on the effects of growth retardation in developing rats on motor development.

A restriction of the daily food intake to the mother during a rat's brain growth spurt leads to a smaller cerebellum containing less neuronal and glial cells, less synapses and decreased myelination, whereas other parts of the brain are less seriously affected (for reviews, Dobbing, 1981; Smart, 1989). Developmental trends in reflexes (as their emergence or disappearance) indicate a retardation of functional development (Smart & Dobbing, 1971), and the question in the present essay is whether undernutrition during this period also leads to delays or to abnormalities in motor development.

Fourteen rats from two litters were undernourished by providing restricted amounts of food to their mothers. The mothers received 7 g standard rat chow from the 5th day of gestation (E5); this amount was gradually increased to 17 g from postnatal day 15 (P15) until P21, amounts approximating 40% of the daily food intake during pregnancy and the lactation period. Locomotor development was studied daily from P10 until P20, at P25, and at P30 and compared with that in control rats. The rats were recorded when moving in a perspex walking alley (100 x 15 x30 cm high) with a mirror underneath. This apparatus allowed the simultaneous observation of the lateral and the ventral views (via the mirror) of their stepping movements. Their walking was recorded (Panasonic type F11 VHS video camera featuring a stroboscopic shutter at 25 frames/sec and Panasonic AG 6200 videotape recorder) and then analyzed during play back runs. Attention was directed toward the
pattern of locomotion and qualitative changes with age.

Locomotion patterns could consist of (a) crawling with either the forepaws alone or with all four paws; (b) locomotion with the ventral body surface in contact with the floor, or (c) free from the floor, as well as a staggering or a fluent walking pattern. We also noted the presence or absence of (a) a postural tremor and the posture of the trunk; (b) hindlimb abduction or adduction during the stance phase; and (c) the absence or presence of horizontal and vertical head movements while walking (for further details see Westerga & Gramsbergen, 1990). In addition, we analyzed the characteristics of the stepcycle in a frame-to-frame analysis as the duration of the step cycle and the swing phase, stride length, and walking speed.

The birth weights of the rats were within the range of those of normal pups but thereafter the weight increases in undernourished rats decreased, such that at P12 the rats weighed less than 60% of the weight of normal rats; at P20 the weight had recovered to only about 65%.

Normal rats in their first week of life crawl only with their ventral body surface on the floor. From P8 to P9 they can stand freely and make a few steps. At these ages, they slide with their chin on the floor and this, with unsecure leg movements and an irregular and long stepcycle until P10 gives their walking a staggering appearance. From that age, the head and the belly is kept off the floor for longer periods and slowly walking may continue during several steps. A sudden change in the walking pattern occurs at P14 to P15. From that age, the hindfeet remain adducted during walking and the speed increases, but the most striking change is that suddenly, locomotion has become remarkably fluent.

In undernourished rats, we observed a paucity of movements. They crawled less and at later ages walked for only a few steps. At least until P15, walking was sluggish and staggering, and only from P16 did we observe a change in quality. From then, the speed of walking increased, although many rats still swayed and in others a striking postural tremor appeared, a phenomenon that

![Graphs showing step cycle and swing phase duration](image)

**Fig.** Left panel: mean and SD of the step cycle duration in undernourished and control rats; durations in ms; age in days. Right panel: mean and SD of the swing phase duration. Note that at P20, P25 and P30 the data on both groups are nearly identical (from Gramsbergen and Westerga, 1992, and Westerga and Gramsbergen, 1990 respectively).
had never been observed in normal rats. Until P17, the rats still walked only scarcely and although they walked more often and for longer periods thereafter, the walking still made a clumsy impression because of a marked tilting of the pelvis and limited flexion in the talo-metatarsal joint. From P20, walking became faster but still not fluent, particularly at low speeds, because of an unusual brisk onset of walking, a slightly unsteady gait, and non-fluent bending of the hindpaws.

With respect to quantitative aspects of the step cycle, it appeared that until P15, the mean step cycle duration was increased in comparison with normal rats (see, Figure). Thereafter, it decreased but this steep decrease was retarded by 1–2 days in comparison with control rats. The duration of the swing phase was increased until P15. Thereafter, it decreased (as in normal rats), but a stable level of around 150 msec was reached only by P18, a few days later than in normal rats. The velocity of walking increased both in normal and in undernourished rats, but the sudden increase—which in normal rats takes place around P14 to P15—occurred one or two days later.

In sum, the results described here indicate that undernutrition during the brain growth spurt leads to a retarded and a prolonged transition from the immature type of locomotion into the fluent adult-like walking pattern. Walking, even at P20 and P25, still showed traits of immaturity. By P30 these symptoms had disappeared but walking kept signs of clumsiness, particularly at slow speeds (Gramsbergen, 1992). One explanation for this delay and the long-lasting abnormalities is that a retarded muscular development or a diminished force production might be instrumental in the motor impairments. Research into the effects of severe undernutrition on muscle composition, by providing the mothers with only 30% of the daily food intake during a normal pregnancy, indeed points to a significant reduction in the number of secondary myotubes while the primary myotubes remain unaffected. The question of whether such changes contribute to retardation in motor development, however, is not yet solved. Another possibility is that a disturbed cerebellar development is causally related to these deviances. Bedi and coworkers (1982) have shown that the number of granular cells is permanently decreased, and they also found a poor arborization of the Purkinje cells. A decreased number of synapses per cerebellar granular cell (a decrease that wanes later on) might contribute to the abnormalities during development (Bedi et al., 1980; Thomas et al., 1979). Earlier we demonstrated that the feed-forward control of posture during the rhythmic walking movements of extremity movements is the limiting factor for the shift into the fluent walking pattern (Gramsbergen et al., 1999; Gramsbergen, 2000). This shift does not occur after surgical ablation of the cerebellar hemispheres at early age (Gramsbergen, 1993). From this evidence we conclude that a disturbed cerebellar development caused by early undernutrition is an important factor in the retardation of motor development and clumsy motor behavior.

CORTICOSTEROID TREATMENT IN RATS

Respiratory problems related to premature birth is a threatening condition in the neonatal period. Synthetic corticosteroids (such as dexamethasone) are widely used in clinical practice to enhance lung maturation. Corticosteroids administered before birth proved to significantly reduce morbidity and mortality from the respiratory distress syndrome and periventricular hemorrhage (Avery et al., 1985; Crowley, 1995). After birth, however, the effects of such therapy are equivocal (for review, Bos & Bambang Oetomo, 1996). A side effect of treatment before birth is interference with CNS development as indicated by a decrease in fetal body movements,
breathing activity, and fetal heart rate variability (Derks et al., 1995; Mulder et al., 1994; 1997; Bos et al., 1984), and in the neonate, on the quality of General Movements (Bos et al., 1998). Recent evidence obtained from brain reconstructions of MRI 'slices' obtained at term from babies who received dexamethasone after their premature birth indicated a decrease by about 35% in the gray matter of the cerebral cortex (Murphy et al., 2001).

In animal research, and particularly in rodents, steroid treatment during neuro-ontogeny has been reported to lead to abnormalities in brain morphology as a decreased proliferation of neural and glial cells in the cerebellum as well as to increased cell death and retarded myelination (Cotterell et al., 1972; Gumbinas et al., 1973). No data on the neurologic development and the development of motor behavior were available, however. For this reason, we decided to study the effects of synthetic corticosteroids, administered at a period analogous to the 7th or 8th month of gestation in the human fetus, on motor development. We focused on the development of walking behavior and on the neurologic reflexes of rats after dexamethasone treatment.

A group of 12 rats was injected with 0.2 mg/kg dexamethasone (0.04 mg/mL in saline) at P3 and P4, and their behavior was compared with that in a group of 12 control rats injected with an equivalent quantity of saline. This dosage and phasing in relation to brain development are analogous to that used in clinical practice. We recorded their locomotion from P5 until P21 and studied qualitative aspects of walking movements and shifts in patterns during repeated videotape playbacks (for details, see above). In addition, we studied their neurological development by testing a variety of reflexes and compared the results with trends in the control rats. The reflexes included the grasp reflexes at fore and hind paws, hopping reactions of fore and hindlegs, tactile placing, negative geotaxis and free-fall righting; see Table 1; for full details, see,

| TABLE 1 |

Age at eye opening, as well as reflexes included in the neurological examination, showing a disturbed development. Note that in the negative geotaxis reaction, no 10% values is given as more than 10% of the rats showed a positive reaction on P4.

| Physical sign     | Percentage | Age at which sign or reflex is positive | Score       |
|-------------------|------------|----------------------------------------|-------------|
|                   |            | Control rats | Dexamethasone |           |
| Physical sign     |            |                          |             |
| eye opening       | 50%        | P14.9          | P13.8        |
|                   | 10% to 90% | P13.9–P15.9    | P12.6–P15.9  |
| Reflexes          | Stimulus: rat placed with head downward on 30 degrees slope | Response: turns to face up the slope within 60 sec |
| negative geotaxis | 50%        | Before P4      | P4.5         |
|                   | 10% to 90% | Before P4      | P9.9         |
|                   | Stimulus: rat rat dropped, back down, from 20 cm on cotton wool | Response: lands on all fours |
| free-fall righting| 50%        | P15.0          | P18.7        |
|                   | 10% to 90% | P14.7–P17.9    | P16.7–P10.3  |
In Table 1, the age at which the sign or reflex is positive in 50% of the animals as well as in 10% and 90% of the group is given. Transitions in reflexes were characterized by the point at which the cumulative distributions of the changes in the group of animals reached the 50% level and also the 10% to 90% range was calculated. In the group of rats injected with dexamethasone, the results indicating a growth retardation of around 25% until the end of the 3rd week confirms earlier findings (Cotterell et al., 1972; Howard & Granoff, 1968). A remarkable finding was that the eyes of these rats had opened already at 13.8 days (range 12.6 to 14.5 days), which is more than 1 day earlier than in control rats (see Table 1). Slotkin and coworkers (1992) observed that the development of the norepinephrine turnover in rats after prenatal administration of dexamethasone was advanced during the weaning period. These and other data (Uno et al., 1994; Cotterell, 1972; Gumbinas, 1973) on certain processes that are accelerated while others develop abnormally or retardedly point to a complicated influence on metabolic processes after steroid administration during development.

The development of most reflexes was normal with two striking exceptions. The negative geotaxis reaction was retarded by more than 1.5 days as in 50% this reflex became positive only at 5.5 days. The other exception was the free-fall righting reflex, which was even retarded by 3 to 4 days (in dexamethasone treated rats 50% at P18.7 [range 16.7 to 20.3 days] and in control rats, 50% at P15.0 [range 14.7 to 17.9 days]). Both reflexes have been classically attributed to test vestibular perception, whereas for the motor reaction (particularly in the case of the free fall righting reaction) optimal cerebellar functioning is required.

The development of walking roughly followed the normal time scale but certain aspects were distinctly abnormal after dexamethasone treatment. The development of locomotion was slightly advanced compared with that in control rats, but the walking pattern in the second week of life was distinctly less elegant. Rats walked staggering until P14 with a markedly curved back and exaggerated hindlimb and trunk movements during the swing phase. Another striking feature was a postural tremor during walking, which disappeared when the rats were not moving (in a sense reminiscent to an intention tremor). The postural tremor, the irregular stride length, and the clearly insecure gait gave the walking pattern an awkward quality compared with fluent and elegant walking in normal rats. In the third week locomotion became more fluent but until P20 the hind feet remained markedly exorotated, leading to an increased gait width. This development of the adult type of walking depends upon the development of feed-forward control of posture (Geisler et al., 1993; Geisler et al., 1996; Gramsbergen et al., 1999).

Previously, Cotterell and colleagues (1972) demonstrated that cerebellar development is disturbed after corticosteroids treatment. Particularly from P14, the cerebellum plays an important role in the regulation of complex movement patterns (Gramsbergen, 1993). Apart from vestibular involvement, also abnormal functioning of the cerebellum should therefore be considered as a causal factor underlying a delayed development of these responses.

In conclusion, the results of this investigation indicate that dexamethasone, injected into young rats at a maturational stage comparable to that of prematurely born human babies of 27 to 34 weeks postmenstrual age, induces neurologic abnormalities discernible as a retarded development of vestibular reflexes and long-lasting abnormalities during the development of walking as postural tremor and clumsiness.

Gramsbergen et al., 1998).
EPILOGUE

The experimental studies described herein demonstrate that undernutrition during the brain growth spurt and the administration of corticosteroids at a period analogous to the 7th or 8th month of human pregnancy lead to long-lasting motor impairments. Both these experimental situations induce diffuse changes in cerebellar development. Undernutrition leads to a diminished number of neuronal and glial cells in the cerebellar cortex and to a temporary decrease in synapses, and the early administration of corticosteroids to changes in the timetable of differentiation and integration of the neuronal elements of the cerebellar cortex. The results of our studies indicate that such interferences can lead to retardation in motor development (in the case of undernutrition) and consistently to long-lasting impairments. Extrapolation from these results strongly suggests that a disturbed cerebellar development should be considered as an important etiological factor in clumsiness in human children.

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