

## Normal and Abnormal Development of Motor Behavior: Lessons from Experiments in Rats

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### ABSTRACT

**In this essay a few relevant aspects of the neural and behavioral development of the brain in the human and in the rat are reviewed and related to the consequences of lesions in the central and peripheral nervous system at early and later age. Movements initially are generated by local circuits in the spinal cord and without the involvement of descending projections. After birth, both in humans and in rats it seems that the development of postural control is the limiting factor for several motor behaviors to mature. Strong indications exist that the cerebellum is significantly involved in this control. Lesions in the CNS at early stages interfere with fundamental processes of neural development, such as the establishment of fiber connections and cell death patterns. Consequently, the functional effects are strongly dependent on the stage of development. The young and undisturbed CNS, on the other hand, has a much greater capacity than the adult nervous system for compensating abnormal reinnervation in the peripheral nervous system. Animal experiments indicated that the cerebellar cortex might play an important part in this compensation. This possibility should be investigated further as it might offer important perspectives for treatment in the human.**

### KEYWORDS

neuro-ontogeny, motor development, compensation, plasticity, peripheral nerve lesions

### INTRODUCTION

The consequences of brain damage in human babies during the perinatal period differ importantly from those at later age. The behavioral disturbances as they become apparent after brain damage at early age often change with age. In addition, the abnormalities as they ultimately emerge, often are different from those after similar lesions at adult ages. In adults in contrast, the effects of brain lesions generally appear soon after the inflicting incident and the symptoms often might be fairly well predicted on the basis of the size and the site of the lesion.

The delayed emergence of handicaps after lesions at early age may be related to the circuitries in central brain areas not being fully established yet and fiber projections from the damaged areas not having reached their final target areas. Lesions at adult age, however, disturb well-balanced sets of circuitries with specific functions. Another aspect is that it often is difficult to relate the severity of motor handicaps to the size of the damage which has occurred at young age. Large

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lesions sometimes only lead to minor symptomatology, while in other cases severe disturbances may occur which are difficult to explain from the minute abnormalities on the fMRI-images or PET-scans. These discrepancies might be due to what often is referred to as an increased plasticity of the young nervous system. The ill-defined term 'plasticity' refers to the modifiability of neuronal interactions by changes in neural circuitry or in synaptic efficacy and a high degree of plasticity generally is taken to be beneficial for compensating the functional effects of brain damage. However, brain regions with their fiber projections still growing also might be more vulnerable to disturbances and aberrant synaptic connections might easily develop by virtue of this increased plasticity.

Plasticity of the brain after lesions at early and later age obviously are related to the developmental stage and knowledge of the early development of the nervous system and the time tables of its fundamental processes are prerequisites for understanding and interpreting the differential reactions of the young and older nervous system to damage. The aim of this essay is to review a few of the relevant aspects of the neural and behavioral development of the brain and on that basis to discuss the results from studies into the consequences of lesions in the central and peripheral nervous system at early and later age. Motor development in the human is compared to that in the rat and the rat's development, in turn, is discussed in the perspective of some aspects of its neurobiological development.

Rats are often selected for investigations into the normal and experimentally disturbed development of the nervous system, as they are born at an early stage of brain development. This allows to study aspects of their early development in the postnatal period. However, this very aspect has to be taken into account when extrapolating rat data to human development: the stage of brain development in

rats at 10 to 13 days after birth is analogous to that in term babies (Romijn et al., 1991). Another obvious consideration should be to acknowledge the important differences between the properties of the nervous systems of primates and rats. The function and the neuro-anatomy of the cortico-spinal tract illustrates this point. In primates, pyramidal neurons in the motor cortex are monosynaptically connected to the spinal motoneurons innervating the hand and wrist muscles thus enabling so-called fractionated finger movements. In rats, however, pyramidal fibers predominantly terminate in the dorsal laminae of the spinal cord and their function probably mainly is to influence the processing of afferent input (Lemon et al., 1997). Studies on the effects of motor cortex lesions in rats, therefore, only can answer part of the questions which we have, e.g. in relation to Cerebral Palsy in the human.

## NORMAL DEVELOPMENT

### **Prenatal development of motor behavior**

The first movements in human fetuses can be observed by ultra-sound scanning from the onset of the 7th week of post menstrual age (PMA; De Vries et al., 1982) and this is shortly before the stage when Hooker (1952) in aborted fetuses firstly could elicit neck and trunk movements by tactile stimulation. The spontaneously occurring 'just discernible movements' initially only involve minor head and neck movements, but a few days later also trunk and extremity movements participate (De Vries et al., 1982). In the weeks thereafter, a repertoire develops of arm and leg as well as trunk and head movements and specific patterns such as sucking and breathing movements (for details see, De Vries et al., 1982; Prechtl, 1984; Prechtl, 2001). So-called General Movements, consisting of a complex and variable pattern of trunk and

extremity movements, is the most frequently occurring movement pattern and these occur from the 9<sup>th</sup> week PMA, throughout pregnancy, and until about 5 months after birth (Prechtl, 1997; 2001).

In rats, the first movements can be elicited at the 15<sup>th</sup> embryonic day (Angulo y Gonzalez, 1932), and the following day (E16) movements emerge spontaneously. Movements in trunk, head, fore and hindlegs occur with increasing frequency in the next days (Narayanan et al., 1971; Smotherman & Robinson, 1988). The head moves in lateral directions and uncoordinated wriggling movements of the trunk, as well as foreleg movements may be observed. The vigorousness of the movements increases gradually in the days to follow and from E20, the first signs of coordination between the extremity-segments have been observed (Bekoff & Lau, 1980). However, coordination between the individual limbs does not occur in rats prior to birth (Narayanan et al., 1971).

The motor development in the human fetus and in the rat shows some striking similarities. Both in the human and in the rat, movements from the onset are part of patterns in which several groups of muscles are involved. In both species, the first movements occur in the neck-region. In the rat, the emergence of fore- and hindleg movements follow a clear-cut cephalo-caudal trend, while movements of the mouth and the tongue develop relatively late. In the human, however, such a trend does not seem to occur. In the human, the first movements emerge shortly before reactions can be elicited by tactile stimulation. In the rat, movements can be elicited half a day before the onset of spontaneous motility and this indicates that in both species, afferents (indirectly) connect to the motoneurons at about the time when motoneuronal axons reach the muscles.

Movements also occur in anencephalic human fetuses (Preyer, 1885). Also rats, after transection of the spinal cord or after decapitation, keep

moving (Hooker, 1930; Narayanan et al., 1971), and these observations indicate that the spinal cord is able to autonomously generate motility. Ultrasound scanning of movements in 7 anencephalic human fetuses with gestational ages varying from 16 to 35 weeks PMA indicated that such movements lack the fluency and variability of those movements in normal fetuses (Visser et al, 1985). This investigation also showed that the absence of the pontine region is accompanied by a disturbed temporal distribution of motility. This indicates that, at least from the 16<sup>th</sup> week PMA, brain stem projections modulate fetal activity in the human fetus.

#### **Some aspects of rat neurobiological development before birth**

*Motoneurons and segmental afferents.* The neuroblasts in the spinal cord, which later differentiate into motoneurons, are proliferating between E11 and E13. It is noteworthy that the motoneurons which later innervate extremity muscles are generated a day earlier than those which will innervate the (filogenetically older) trunk muscles (Altman & Bayer, 1984). After migrating to their final destination along radially oriented glial cells (Henrikson & Vaughn, 1974), the motoneurons differentiate between E12 and E14, and this process follows a rostro-caudal gradient (Altman & Bayer, 1984). Roots emanating from the ventral horn have firstly been demonstrated at E12, and the motoneuronal axons have reached the intercostal muscles at E14 (Dennis et al., 1981). From that age, muscle contractions can be elicited by electrical stimulation. Remarkably, this is almost 2 days before the stage when Angulo y Gonzalez (1932) firstly could elicit reactions by tactile stimulation. As at early stages the transmitter release is low (Dennis et al., 1981), this possibly could explain this discrepancy. The release of AcetylCholine (ACh) only begins to

increase substantially when the multiple innervation of muscle fibers has been eliminated (Diamond & Miledi, 1962).

The proliferation of neurones in the dorsal ganglia (between E12 and E15) virtually coincides with that of the future motoneurons (Altman & Bayer, 1984). From E13, the first sensory fibers were observed to penetrate the limb bud, and afferents reach the dorsal horn of the cervical cord at E14.5 (Vaughn & Grieshaber, 1973) and in the thoracic cord at E15.5 (Smith & Hollyday, 1983). Around that stage, tactile stimulation may elicit movements (see above). Proprioceptive reflexes, on the other hand, which are partly mediated by monosynaptic connections between afferent fibers and motoneurons, develop a few days later. Muscle spindles have been demonstrated already before birth (Milburn, 1973), and Kudo & Yamada (1985) could elicit the myotatic reflex of the triceps surae muscle in rats from E19.5.

*Movements and pattern generators.* Fetal movements, both in the human and in the rat, emerge at a stage when the descending projections, e.g., from the brainstem, have not yet developed. This implies that at those stages they are generated by endogenous activity in local spinal cord-circuits. It is striking that from early stages onwards, these movement patterns involve several muscle groups, and this implies patterned activity in adjacent spinal cord segments connected by propriospinal interneurons. Particularly interesting are the motor patterns, such as rhythmic mouth movements, breathing movements, and leg movements. For such rhythmical movement patterns, a specific spinal circuitry termed a Central Pattern Generator (CPG) has been implied on the basis of experiments by Graham Brown (1914) and others since (e.g., Grillner, 1975). Already at early stages of development and only a few days after the motoneurons have migrated towards their localization in the spinal cord, synchronous and rhythmical bursts of activity can be recorded in these circuits. This is

even before any activity in the muscles is obvious and before sensory fibers have reached the dorsal horns of the spinal cord (Cazalets et al., 1995; for a review see Cazalets, 2001). At later stages when brain stem projections have developed, excitatory amino acids (EAA) and serotonin (5-HT) act together in the modulation of the rhythmic CPG activity.

*Descending projections.* Descending projections from the brain stem reach the caudal spinal cord in the rat already a few days before birth. This holds, e.g. for the medially descending projections, from the reticular formation and the vestibular nuclei. These have reached lumbar levels from E16 (for review, Lakke, 1997) and shortly after their arrival at segmental levels, these fibers make provisional synaptic contacts. Vinay & Clarac (1999) have demonstrated that electrical stimulation at the lower brain stem already on the first postnatal day induces responses in the ventral roots, but important changes occur thereafter, indicating that still important changes in circuitry occur during further development.

Spinal projections of the Limbic Motor System (Kuypers, 1982; also termed the Emotional Motor System, Holstege, 1991) containing noradrenergic and serotonergic fibers have reached lumbar spinal cord levels before birth as well (Rajaofaetra et al., 1989; 1992). The medial portions of this motor system influence the excitatory state of interneurons, motoneurons, and probably CPGs via diffusely projecting monoaminergic fibers. As the serotonergic terminals initially are present widespread but later on only in the dorsal and ventral horn, Rajaofaetra et al., (1989) hypothesized that 5-HT containing fibers at early stages might play a role in the stabilization of terminals from other projections in the spinal cord.

*In summary.* Motility develops early, from the moment when motor axons reach their muscles. These movements initially are generated by local circuits in the spinal cord and without the involvement of descending projections. Descending

projections only develop later, and they initially may subserve functions which differ from those at adult age.

### **Motor development and postural control after birth**

Human babies, immediately after birth, start breathing; they start sucking, vestibular reflexes emerge, but particularly from the second month onwards, the repertoire starts to expand significantly (Prechtl, 1984). Goal directed arm movements, head movements, and smiling occur which play a role in the social interaction with the environment. An important prerequisite for these newly emerging behaviors is adequate postural control (for review, Hadders-Algra, 2001; see also, Hadders-Algra, this issue). Prechtl (1989) studied neck muscle activity in babies in prone and supine positions during external perturbations, and he and his coworkers observed that direction-specific activity in the neck muscles develops from the 8th to 10th postnatal week onwards. More recent results on EMG recordings in neck and trunk muscles of babies during reaching support this conclusion (Van der Fits & Hadders-Algra, 1998; Van der Fits et al., 1999a). Successful reaching movements in infants develop around 4 to 5 months of term age. These movements are accompanied by contractions in trunk and neck muscles (Van der Fits et al., 1999a), but it lasts until after 15 months, when the activity in postural muscles consistently anticipates reaching movements, being suggestive for a feed-forward control of the activation of postural muscles (Van der Fits et al., 1999b).

A stepping response can be elicited in the first weeks after birth, and these movements probably are the remains of the fetal pattern of alternating leg movements. Walking movements only reappear at the onset of the development of unsupported walking, when the babies are 7 to 9 months old.

The alternating leg movements in the fetal and neonatal period and those during walking at later ages probably both are produced by a CPG in the lumbar spinal cord (Forssberg, 1985). Unsupported walking, however, only develops by virtue of advanced levels of postural control and equilibrium maintenance. Assaiante and Amblard (1995) hypothesized, on the basis of their own results and those of others, that from this age until about 6 to 8 years, postural control mechanisms still are occupied with mastering the intricate balance problems and that then an ascending temporal organization of balance control prevails, while only in the years thereafter the adult type of postural control gradually develops.

In rats, locomotion in their first 2 or 3 days is effected by crawling movements with the forelegs, and also head movements in the horizontal plane may occur (Geisler et al., 1993). At the end of the first week, rats may lift their ventral body surface off the floor and make a few staggering steps (Geisler et al., 1993; Gramsbergen & Mulder, 1998). This pattern strikingly changes at P15. In the course of 1 or 2 days, the immature locomotion pattern is replaced by adult-like walking, characterized by fluent and swift movements (Altman & Sudarshan, 1975; Westerga & Gramsbergen, 1990). Then, rats are able to stand on their hindpaws (rearing) for extended periods of time, and head movements may occur when walking. This transition is accompanied by changes in the EMG recorded from hindlimb and back muscles (Westerga & Gramsbergen, 1993). Until P14, recordings from the gastrocnemius and the tibialis anterior muscles show irregular patterning of the EMG, with co-contractions during walking but from P15 to P16, the EMG changes into an interference pattern with clearly delineated bursts.

Circumstantial evidence indicates that from that age, descending projections impinge (indirectly) upon motoneuronal pools. EMG bursts in the long

back muscles from this same age become closely linked to the leg movements during walking (Geisler et al., 1993; Gramsbergen, 1999).

Experiments in rats involving vestibular deprivation from P5 indicated that a change in postural control mechanisms probably is instrumental to this sudden shift into the adult-like walking pattern. Plugging the horizontal semi-circular canals (which prevents the endolymph to circulate) leads to a retardation in postural development. The emergence of rearing (standing on the hindlegs without support) e.g., is delayed by 5 days (Geisler et al., 1996). Pertinent to our reasoning is that the adult type of walking is delayed as well (Geisler et al., 1996) and even, that a 3-day delay occurs in the development of EMG patterns in the back muscles (Geisler & Gramsbergen, 1998). These results therefore indicate that the development of postural control is the limiting factor for the development of the efficient and smooth movement patterns.

### **Neuroanatomical aspects of postural development**

The question is which development might explain the sudden shift in motor behavior around the end of the second week in rats. Changes in the properties of motoneuronal membranes, sudden shifts in the force production of hindleg muscles, or a relation with the opening of the eyes (in rats, around P14) could be refuted (for a discussion, see, Gramsbergen, 1998; Kernell, 1998). Another possibility is that the establishment of synaptic connections between descending projections and motoneuronal pools is causally related to this transition in motor behavior. The corticospinal tract in rats starts to grow from E16 and at the day of birth, the first pioneer fibers have descended as far as the cervical intumescence (Schreyer & Jones, 1982; Joosten et al., 1987). Between P7 and P10 they have descended along the extent of the spinal cord, but it is not known when the ultimate

synaptic terminals in the spinal cord are established. In the adult rat, the tract mainly terminates in the dorsal horn and therefore, its main role probably is to modulate sensory input (Porter & Lemon, 1993). A minority of the fibers indirectly connect to motoneurons (Liang et al., 1991) and lesioning of the corticospinal tract affects fine digital flexion movements in rats (Castro, 1972), but motor cortex lesions do not interfere either with the transition in motor behavior around P15 or with postural control mechanisms (own observations).

The rubrospinal tract has descended to the caudal spinal cord segments already at E17 (Lakke & Marani, 1997). Unilateral ablation of a cerebellar hemisphere at early postnatal stages leads to serious motor handicaps from P15 (see also, below), and the delay between the descent of the rubrospinal tract and the functional consequences of cerebellar lesions would imply a prolonged waiting period between the descent and the establishment of synaptic connections at segmental levels. A more likely possibility is that developmental changes at central levels parallel this shift in postural control and motor development. In the cerebellum, important changes occur in cortical circuitry and in olivary-cerebellar interactions during the first 2 postnatal weeks and these indeed may explain the behavioral changes (see, Gramsbergen, 1984).

Also other evidence points to the cerebellum being elementary for the coupling of the movement performance and postural control (see, Grillner, 1975 referring to animal species; Forssberg, 1985 referring to human babies). For this reason, much experimental research is invested now in elucidating the involvement of the cerebellum, the precerebellar nuclei, and the basal ganglia in the linkage of postural control and the planning and execution of movements (e.g., Houk & Wise, 1995). In the human, deficient postural control has been claimed to be a major factor in cases of CP (Aicardi & Bax, 1992). Insight in this aspect therefore is important

for understanding not only normal development but also deviant motor development.

*In summary.* Both in humans and in rats it seems that the development of postural control is the limiting factor for several motor behaviors to mature. In rats, the developments of posture and movements initially proceed more or less independently. Only at later postnatal stages both these aspects become intimately linked to effect feed-forward control of movements. Strong indications exist that the cerebellum is significantly involved in this control.

## EARLY BRAIN LESIONS AND PLASTICITY

### Introduction

Disorders in human motor development are relatively common. It is estimated that around 2 individuals per 1000 are suffering from CP, an umbrella term covering a group of non-progressive but often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development. In contrast with the clinical and social dimensions of the handicaps involved, is the still widespread notion that brain lesions at neonatal age have less severe consequences for later functioning than similar lesions at adult age. This was supported by experimental research in young and adult monkeys by Margaret Kennard (Kennard, 1936; Kennard & Fulton, 1942). The advent of modern fiber tracing methods and sensitive neurophysiological techniques were of great help in studying neuroanatomical changes after brain damage, and careful behavioral observations have demonstrated that the new connections which may develop after lesions at early age not always are beneficial for functioning. Remodeling processes are not restricted to young ages, and new fiber connections termed collateral sprouts also may develop after lesions at adult age

(Tsukahara, 1981; Tsukahara et al., 1983). The rearrangements after such lesions, however, seem to be much less extensive compared to those after early lesions. Recent research has indicated that repair of lesions in certain brain areas might also be effected by dormant neuroblasts induced to differentiate as a consequence of the lesion, even at later stages of development (see, Kolb, this issue).

### Cerebellar hemispherectomy in young and older rats: A case in point

The cerebellar hemispheres play an important role in the regulation of muscular activity in the extremities, in linking postural control and movements and also in motor learning. In a series of investigations we studied the behavioral and neuroanatomical effects of the removal of one cerebellar hemisphere, including its deep nuclei at neonatal and older ages in rats. Ablations were performed at P2 when the proliferation of granular cells in the cerebellum just has started; at P5 and P10 when the cerebellar circuitry is being established, and in young adult rats (at P20 and at P30). An unexpected result from these experiments was that in rats lesioned at P5 and P10, the first neurological handicaps became apparent only around P15 (Gramsbergen, 1982; also see above). We also showed that the effects on locomotor behavior in the rats operated at P20 or P30 were distinctly less severe compared to those after lesions at P5 or P10. Neuroanatomical investigations which were started in order to explain these discrepancies revealed that unilateral cerebellar hemispherectomy only before P10 leads to extensive neural remodeling (for review, see Gramsbergen & IJkema-Paassen, 1984). For example, Castro (1978), Gramsbergen & IJkema-Paassen (1982), and others found an aberrant projection from the remaining deep cerebellar nuclei onto the ipsilateral red nucleus after early lesioning (in normal rats, only contralaterally projecting cerebello-

rubral fibers occur). Another example is the re-routing of the spinocerebellar fibers at the side of the lesion (Castro & Smith, 1979). These fibers, which normally project onto the parallel fiber system in the cerebellar cortex, now make synaptic contacts with neurones in the vestibular nuclei. The common denominator in all these experiments is that neuronal rearrangement is restricted to animals which were lesioned until the 10<sup>th</sup> day of life. Lesioning beyond this age does not lead to extensive remodeling.

The nature of the normal (contralaterally projecting) and aberrant (ipsilaterally projecting) cerebellorubral projections was studied with the double-labeling technique (Gramsbergen & IJkema-Paassen, 1982). This investigation showed that the aberrant fibers were not collaterals from the normally projecting fibers but that they stem from separate parent cells in the remaining cerebellar nuclei. One of the most plausible possibilities seemed that the aberrantly projecting neurons emanate from supernumerary neurons in the deep cerebellar nuclei; neurones which normally die during early development. This possibility was investigated by inventarising cell death patterns in the deep cerebellar nuclei from P2 until P20 (Gramsbergen & IJkema-Paassen, 1987). In normal rats, neuronal cell death in the cerebellar nuclei stops at about the 15<sup>th</sup> day, but after a cerebellar hemispherectomy at P2, this process ends already at P8. The interpretation of these results is that neurons in the deep cerebellar nuclei escape physiological cell death by making aberrant connections in the ipsilateral red nucleus (Gramsbergen & IJkema-Paassen, 1991).

*In summary.* Motor handicaps after cerebellar lesions at early stages (i.e. before the 10<sup>th</sup> day) only become apparent from the 15<sup>th</sup> day. This late expression probably is due to the immaturity of the cerebellum itself or to its descending projections until this age. Lesions at early stages, interfere with fundamental processes of neural development,

such as the establishment of fiber connections and cell death patterns. The functional effects are strongly dependent on the stage of development.

## PERIPHERAL NERVE LESIONS, MOTOR OUTPUT AND COMPENSATION

### Introduction

In contrast to the limited capacity to neuro-anatomical reorganization after lesions in the adult CNS is the aggressive outgrowth of peripheral nerves after transection. Outgrowing nerve fibers from the proximal nerve stump after transection may cover considerable distances, e.g. to a target muscle, but functional recovery generally is poor. This has been demonstrated after regeneration of the oculomotor nerve in a human patient (Bender & Alpert, 1937). This nerve carries axons to the levator palpebrae muscle; the inferior oblique; the medial, superior, and inferior rectus muscles. When the patient, after regrowth of the nerve, was asked to move his eyes in a specific direction, this led to inadequate eye movements and eyelid contractions at the affected side. This result indicated that the severed motor axons randomly reinnervate the respective muscles.

A similar inability of nerve fibers to relocate their muscles of origin has been demonstrated after transection of the sciatic nerve in adult rats (e.g., Bodine-Fowler et al., 1997). This inability is in contrast with the amazing pathfinding and recognition properties of outgrowing axons at embryonic stages of development. From this perspective, the suggestion that peripheral nerve lesions at young age have less deleterious functional consequences (Hardman & Brown, 1987) is of great interest. The specific question is whether the greater compensational capacity after peripheral nerve transection at young ages is due to still effective pathfinding capacities of the out-

growing nerves. Another possibility is an increased capacity for functional compensation in the CNS.

In order to unravel these differential effects and its neuro-anatomical and neurophysiological substrates, we studied the consequences of lesions in the sciatic nerve at adult and at young age in rats. The sciatic nerve innervates a multitude of hindleg muscles which are involved in extension and flexion of the knee and ankle joint.

#### **Peripheral nerve lesions at adult and at young age**

In adult rats, a gap (12 mm) was made in the sciatic nerve in the left hindleg, proximal to the bifurcation into the tibial and common peroneal nerve, and this gap was repaired with the removed nerve segment in a reversed orientation (Meek et al., 1999). Neurological assessments after recovery periods up to 21 weeks after the operation indicated a return of sensory functions to some degree, but walking remained severely disturbed throughout the observation period, as indicated by abnormal foot placing and dragging of the leg (Meek et al., 1999).

In another group of nine rats, we studied the locations of the motoneurons which, after reinnervation, innervate a few of the hindleg muscles which are particularly important for walking. Fifteen or twenty one weeks after transection of the sciatic nerve and after reinnervation, the gastrocnemius, soleus, and tibialis anterior muscles at the right and at the left side were injected with retrogradely transported Cholera Toxin subunit B (CTB). The results indicated that the motoneurons innervating the respective muscles were dispersed over much wider areas than at the unoperated side (Gramsbergen et al., 2000).

In still another group of six rats, we implanted EMG electrodes in the gastrocnemius and the tibialis anterior muscles and the activation patterns were recorded during walking 15 and 21 weeks after the transection. Normally, the EMG recordings in the gastrocnemius muscle show tonic bursts

during the stance phase but at the affected side, the EMG was markedly irregular. The burst onset increased more slowly and sometimes activity continued during the swing phase. The tibialis anterior muscle normally is only active with a brisk burst at the onset of the swing phase. At the left side, however, we often recorded irregular and badly phased bursts during the swing phase and even more remarkably, we regularly observed activity during the stance phase, indicating that the tibialis anterior and the gastrocnemius muscles are coactivated during the stance phase.

Results described by Luff and Webb (1985) in cats support our results. They cross-innervated the (tonic) soleus muscle with the nerve which normally innervates the (phasic) extensor digitorum longus muscle. After recovery, they recorded EMG patterns during walking, and often they observed burst activity in the soleus muscle, similar to that what normally is observed in the extensor digitorum muscle. Our observation of a coactivation of the tibialis anterior and the antagonistic gastrocnemius muscle and the histological evidence indicate that the motoneurons after transection aselectively have reinnervated these two muscles (and, undoubtedly all other muscles which were severed from innervation by the transection).

In order to study whether transections at early age have less deleterious effects, in a second set of experiments we transected the sciatic nerve at the 10<sup>th</sup> postnatal day. The walking behavior of the rats was assessed at regular intervals after the operation on the basis of qualitative criteria, such as the nature of hindleg movements, foot placement, leg abduction, etc. Results indicated that after 8 to 10 weeks, a near-to-normal walking pattern had reappeared and, only incidentally, we observed abnormal foot placing or irregularities in walking.

In another group of six rats which were treated similarly, we recorded the EMG during walking. Quite unexpectedly, we found that the EMG patterns during walking showed marked abnormalities in the

activations of the gastrocnemius and tibialis anterior muscles. These patterns closely resembled those patterns which we detected after transection at adult age. EMG bursts were irregular and both in the gastrocnemius and the tibialis anterior muscle we observed coactivation during all phases of the stepcycle. These abnormalities lasted at least until 21 weeks after transection. The results strongly suggest that also after a transection at the 10<sup>th</sup> day, the outgrowing axons in the sciatic nerve randomly reinnervate their muscles, and this is currently the object of further investigation.

Our hypothesis to explain a near-to-normal walking pattern in conjunction with severely disturbed EMG patterns is that subtle readjustments are effected in the force recruitment in the respective muscles, despite a random reinnervation by the motoneurons. A corollary to this hypothesis obviously is that such readjustments are particularly outspoken after a sciatic nerve transection at early age. A likely site for a compensatory modulation of force recruitment is the cerebellum. It is well known that the cerebellar hemispheres are intimately involved in modulating motor output to extremity muscles on the basis of ascending information from the spinal cord and also in motor learning. In a pilot experiment, we explored whether such compensatory mechanisms in the cerebellum might account for these findings. In our groups of three rats each, the left sciatic nerve was transected at their 10<sup>th</sup> day. After 8 weeks, their motor behavior was recorded on videotape and assessed, and this showed that walking was very similar to that in the other groups of early transected rats (see above). Thereafter at around the 50<sup>th</sup> day, in one group of three rats the left cerebellar hemisphere was ablated and in another group the right cerebellar hemisphere; still in another the left sensory-motor cortex was removed, and in the last group the right sensory-motor cortex. After another recovery period of 30 days, their behavior in the walking alley was again recorded and evaluated. The preliminary results of

this experiment indicated that the rats with lesions in the sensorimotor cortex at either side did not show overt abnormalities when walking. Rats after a cerebellar hemispherectomy at the right side had an atactic gait and signs of a hyperextension in the hindleg at the right side, but those rats in which the cerebellar hemisphere was removed at the left side, in addition to signs of the cerebellar ataxia, also showed a marked deterioration of step cycle characteristics at the left side, the side of the sciatic nerve transection.

These experiments need further elaboration, but the results indicate that the cerebellar hemisphere indeed plays a role in the compensation after peripheral nerve lesions at early stages. If so, the exploitation of these processes, which might be homologous to motor learning, might open new perspectives for a goal-directed treatment.

*In summary.* The young central nervous system in rats has a much greater capacity than the adult nervous system for compensating abnormal reinnervation in the peripheral nervous system. The cerebellar cortex might play an important part in this via processes which might be homologous to motor learning. This perspective should be investigated further as it might offer important perspectives for treatment.

## EPILOGUE

Experimental research has elucidated many fundamental aspects of the neuroanatomical and neurophysiological consequences of lesions at early and later ages in the central nervous system in the rat, and this can to some extent be extrapolated to human development. Our knowledge on developmental processes in the brain and behavior in rats now offers a sound basis to test the possibilities of implanting stem cells in damaged areas, the mobilization of silent primordial cells in the CNS in order to repair lesioned areas, or new

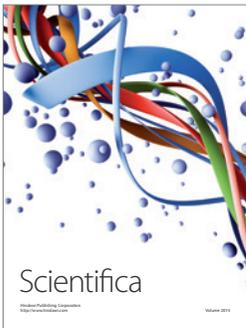
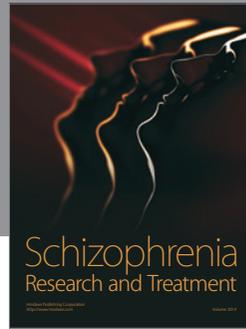
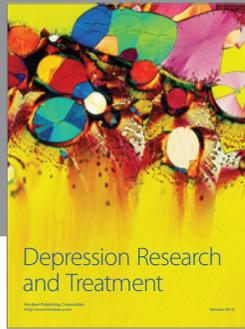
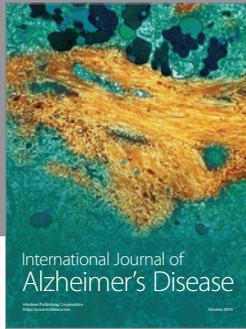
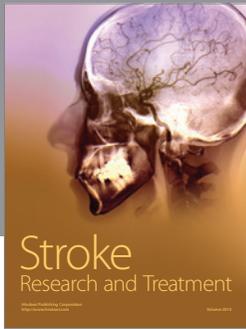
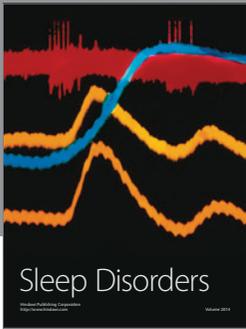
compensational strategies by motor learning. This ultimately may lead to new strategies in treating the effects of brain lesions in the human, acquired in the perinatal period.

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