Introduction
The term brain plasticity was introduced around 100 years ago. It is used to describe how the structure and function of neural circuits are modified (1) during development, (2) by experience and learning, and (3) in response to brain lesions. In the middle of the last century, Donald Hebb postulated that cortical neural connections, i.e. synapses, are strengthened and remodelled by experience (Hebb et al 1994). He also showed that rats reared in the rich environment of his own house were much better learners and had better memory capacity than rats living in laboratory cages. The molecular mechanisms behind neural plasticity are complex and not yet fully understood, but numerous studies have shown various mechanisms underlying the activity-dependent modification of synaptic connectivity, including increased number of synapses by changed turnover of dendritic spines, long-term potentiation (LTP) and long-term depression (LDP) (Calverley and Jones 1990, Jenkins et al 1990, Buonomano and Merzenich 1998, Feldman et al 1999, Luscher et al 2000, Trachtenberg et al 2002, Malenka 2003). The latter two mechanisms are important for storage of information in the central nervous system (CNS) and involve several neurotransmitter systems, including glutamate (NMDA and AMPA receptors) and GABA (Myers et al 2000), as well as the monoamine systems (dopamine, noradrenalin and serotonin), which are involved by modulating the transmission in the other neurotransmitter systems (Bao et al 2001, Gu 2002).

Neuroimaging methods used to study brain plasticity
The first studies on neural plasticity were performed in experiments on animals. More recently, the development of new powerful imaging techniques has made it possible to study neural plasticity in the human brain as well. Magnetic resonance imaging (MRI) is the most widely used method and enables studies on both structure and function. Volume-based morphometry (VBM) can measure the volumes of critical grey or white matter structures, while diffusion tensor imaging (DTI) measures the integrity of the white matter, i.e. myelinization, size and order of nerve fibres in the neural pathways. By special algorithms of the DTI signal, the tracts of the neural fibres can be estimated (tractography). In functional MRI (fMRI) the synaptic activity in local neural circuits is indirectly measured. In reality it is changes in the blood oxygenation (BOLD signal) that are recorded. Increased metabolism in neurons that are synaptically active induces increased flow of oxygenated blood.
In PET studies, radiolabelled agonists or antagonists are used as ligands. When injected, these attach to available receptors and transporters involved in the chemical transmission between pre- and postsynaptic neurons. PET thus measures the availability of these receptors, i.e. a function of the number of receptors and the endogenous release of the transmitter substance. PET can also be used to measure metabolism and blood flow to specific regions.

TMS is a non-invasive technique in which a focused magnetic field pulse, passing through the cranium, is used to evoke electrical discharges of cortical neurons. By stimulating over the motor cortex, the motor area (map) evoking EMG responses in recorded muscles can be defined. With MEG (or multi-electrode EEG) the electrical activation of neural circuits involved in specific actions can be localized with high time resolution.

Plasticity in the developing brain
One of the first descriptions of neural plasticity during development was by Hubel and Wiesel, winning them the Nobel Prize (Hubel and Wiesel 1970, Le Vay et al 1980). They studied the ocular dominance columns in the visual cortex of kittens and monkeys. The visual cortex receives information from both eyes. The right and left eye columns are normally evenly distributed in the primary visual cortex. This organization is not present at birth and takes several weeks to develop in kittens. When Hubel and Wiesel interfered in the development by suturing the eyelid of one eye, thereby only allowing vision from the other eye, the result was an uneven distribution of ocular dominance columns. The columns innervated by the seeing eye expanded at the expense of the non-seeing eye.

These experiments revealed two important principles which have been confirmed in several systems in many different species, including humans. First of all, development of
the CNS is not predetermined, but depends on interaction with external factors. Secondly, development is dependent on the activity in the neural circuits. Nerve cells and neural circuits that are frequently used strengthen their connections, while those that are not used are weakened. The phrase ‘use or lose’ reflects this principle and indicates how an exuberant number of nerve cells and neural pathways which exist in early phases of development are discarded because they are not used. Interestingly, these exuberant neurons and pathways that typically disappear during development may remain after central lesions or peripheral damage blocking the sensory inflow. When there is no competition from lesioned neural circuits, these nerve cells and pathways have less competition and will be used and can survive.

There seems to be an extensive capacity for cross-modal plasticity between auditory and visual areas as a result of lesions/disturbances in early childhood. For example, in congenitally blind humans, speech and auditory processes may activate the visual cortex, and, indeed, blind people localize sound sources better than sighted people (Weeks et al 2000, Roder et al 2002). Sign language activates different brain regions in deaf and hearing individuals (Bavelier et al 2001). After unilateral lesions of the corticospinal system in the human fetus, leading to hemiplegic cerebral palsy, there seem to be exuberant ipsilateral pathways that are maintained and that connect the (undamaged) ipsilateral motor cortex to the (paretic) upper extremity (Carr 1996, Vandermeeren et al 2003b, Staudt et al 2004, Staudt 2007).

**Plasticity in the somatosensory system**

Studies on cortical synaptic plasticity are partly based on ‘cortical maps’, i.e. representations of different sensory and motor systems at the primary sensory and motor cortices (Buonomano and Merzenich 1998). In animals, it is possible to investigate the cutaneous innervation of the primary sensory cortex from the hand, by stimulating the fingers and recording from cortical neurons by microelectrodes. Using this procedure, a map of the cortical area that is innervated from each finger can be produced. In monkeys, it was possible to show that the cortical map of the fingers changed after training (Fig. 1.1). In one study, monkeys used two fingers in a tactile discrimination task daily for 5–20 minutes over three weeks (Jenkins et al 1990). The maps of the two fingers that had been used expanded, while those from the fingers not used shrank. These results revealed that more cortical nerve cells were activated by the fingers that had been used frequently, i.e. use-dependent plasticity. A similar phenomenon has been described in blind Braille readers, in whom the maps of the ‘reading finger’ expanded (Pascual-Leone and Torres 1993). Indeed, the plasticity seems to be quite dynamic since the maps fluctuate with the daily reading activity (Sadato et al 1998).

Studies on amputees have shown that absent sensory input may change the cortical maps as well (Pascual-Leone et al 1996). In such cases there is a lack of activity, and other neural circuits that are active can take over cortical nerve cells that are no longer used. In individuals with low amputations, the cortical representation of the remaining upper part of the arm had expanded and occupied the area originally used for the distal part of the arm. In individuals with high amputations, the representation of the face had been extended to
the lost arm and hand areas. Sensation of ‘the phantom hand’ could in some cases be elicited by touching the face or the upper arm in these patients (Flor et al 1998), which indicates that the perception of the body scheme partly remains although innervated from other parts of the body.

Fig. 1.1  Cortical maps of the primary sensory cortex in non-human primates before (normal) and after tactile stimulation of the tip of the index finger. The innervation maps showing the cortical sensory neural representation of the fingers are produced by striking the skin of each finger and at the same time recording from the sensory cortex. The area of the stimulated part of the index finger is indicated by stippling in the schematic area of the hand, and in the two drawings of the cortical maps. Note that after a period of differentiated stimulation of the tip, there was a substantial enlargement of the cortical map of the index finger, in particular of the stimulated area.

Plasticity in the motor system

Similar forms of the neural plasticity seen in the sensory system are also present in the motor cortex. Nudo studied the cortical maps of the upper limbs in monkeys before and after training in specific motor tasks (Nudo et al 1996a, Nudo 1999). In this case the cortical neurons are stimulated by TMS and the muscle activity is recorded by EMG. When the monkeys picked up pellets from a small cup for 15 minutes every day during a 10-day period, the cortical representation of the finger muscles used to pick up the pellet was enlarged, while it was reduced for more proximal muscles of the arm. When the same monkeys trained in another motor task, which required repeated movements of the wrist and elbow, the representation for these more proximal muscles increased, while the distal finger muscle representation was reduced. Thus, when a movement is performed repeatedly, the synaptic connectivity is strengthened in the cortical circuits activating the muscles required for the movement, leading to expanded cortical motor maps for these muscles.

Several studies have shown similar activity-dependent plastic changes in the human motor cortex. In badminton players, the hand of the racket arm has been shown to have a larger cortical representation compared with the other hand. Several studies have been performed with professional musicians, who spend extensive time in motor skill training. One study reported increased cortical sensory-motor representation of the fingers of the left hand in string players, with correlations found between cortical map size and the age at which the player began to play (Elbert et al 1995, Pantev et al 2001). This indicates an interaction between age and activity – the earlier the musician began training and the more intensive the training, the larger the effects. A similar effect on the myelinization of the corticospinal tract has recently been shown in professional piano players in a DTI study (Bengtsson et al 2005). DTI measures the white matter characteristics in the neural pathways. A high anisotropy indicates large and well myelinated nerve fibres, which are known to give fast conduction velocities and fatigue resistance. In this study, the pianists had higher anisotropy in the corticospinal tract through the internal capsule than control participants. This difference could have been due to a genetic disposition among the pianists, actually allowing them to be more technically skilled. However, within the pianist group the anisotropy correlated positively to the amount of training the pianist received before 11 years of age. This suggests that intensive training during childhood, during the period when the corticospinal system is myelinated, may influence the organization, and probably also the function, of the pathways.

Learning of new motor skills

The plastic changes of the maps in the sensory and motor cortices mentioned above were caused by sensory input or enhanced motor activity. The fingers, the hand or the arm were used more frequently than normal, but also the same movement patterns were used repeatedly. This form of practice is different from learning and practising new motor skills. Initially the new movement has to be carefully learned. With time, the movement can be performed more fluently, until it becomes automatized and performed without the person paying attention to the different sequences of the movement. After a longer training time even complicated movements can be automatized, e.g. a secretary can type perfectly while
talking with somebody else. The learning process can be divided into two phases: an early learning phase with rapid improvement of performance, beginning from the first training sessions; and a second more extended phase including several training sessions for days/weeks during which a gradual improvement proceeds and the movement becomes automatized (Ungerleider et al 2002). During the early learning phase there is a consolidation of the learned movement. This means that the movement is improved and stabilized during the rest period between training sessions, partly during sleep. If the rest period is disturbed (e.g. no sleep) the consolidation of the movement is negatively influenced (Shadmehr and Holcomb 1997, Karni et al 1998, Fischer et al 2002).

The brain activity changes underlying learning of new motor skills have been studied in humans by means of fMRI. The results suggest that in general the same areas are synaptically active both during the early learning phases and after the movement has become automatized (Wu et al 2004). Thus, there is no support for a previous hypothesis that new circuits and new areas are activated when the movement becomes automatized. On the other hand, the amount of neural activity decreased as the movement became more automatized. In an attempt to make a simple neural model of motor learning, Ungerleider and coworkers (Ungerleider et al 2002) suggested that there are two different categories of motor learning. One includes learning of new motor programmes (e.g. new sequences of finger tapping). The other involves adaptation of already existing motor programmes to new forms of movement patterns or to a new environment. When new motor programmes are learned (category 1), a large neural network is involved including sensory and motor cortices in the frontal and parietal lobes, basal ganglia and cerebellum. The whole network is active in the beginning of the learning. In later phases the basal ganglia continue to be active, while the activity in the cerebellum ceases. Interestingly, the opposite occurs when the motor learning involves adaptation (category 2). A cortico-cerebellar network continues to be active, while the activity in the basal ganglia is reduced during later phases.

In one of the earliest motor learning studies, changes in the motor cortex were studied in healthy adults before and after a four-week training period (Karni et al 1995). The research paradigm required participants to learn a specific sequence in which they opposed different fingers against the thumb in a specific order. After each training week the learned sequence could be performed faster. The fMRI recordings indicated increased activity in the motor cortex when the learned sequence was performed, as compared to a different, not learned sequence. This study indicated that there might be plastic changes taking place also in the primary motor cortex during learning of motor sequences. However, it has so far not been confirmed by other researchers, and it does not tally with later studies showing a general reduction in activity after the learned sequence has been automatized. Although the new imaging techniques have allowed us to study what is happening in the brain during motor learning, we are still only in the early stages of understanding the interplay between various networks and how the information of the learned motor skills is stored.

In addition to changes of synaptic activity during motor performance after training, there seem to be structural changes in the grey matter. In a recent study in healthy adults, participants were instructed to learn a classic three-ball cascade over a period of three months (Draganski et al 2004). The brain changes in the participants were investigated by MR
volumetry before and after the training period learning a new motor skill. Results showed volumetric expansion in the grey matter of these individuals in certain areas of the temporal and parietal lobes. The expansion correlated with the skills the participants learned, indicating a growth of the neural circuits that are used. The grey matter areas which were changed in this study are not directly involved in motor coordination and motor planning, but have important roles in receiving and integrating visual and somatosensory information that serves as a foundation for subsequent motor programming.

**Plasticity of the young damaged brain**

The plasticity present during development and during learning and training is probably also an important factor supporting rehabilitation after a brain lesion. Nudo and colleagues (Nudo et al 1996b, Nudo 1999) have shown that recovery of motor functions after a cortical lesion in monkeys is dependent upon extension and expansion of the cortical maps post-lesion. Monkeys who were trained after lesions in the hand area of the primary motor cortex exhibited a better recovery than those who were not, and also had a larger expansion of their cortical map. This and other experimental studies give hope, since they show that specific training produces both functional improvements and structural reorganization of the motor cortex. Several clinical imaging studies in adult patients have shown considerable neural reorganization post-stroke (Hallett 2001). In the acute phase of stroke rehabilitation, changes have a multifactor background and thus attributing progress solely to the training is difficult. However, there are now several training studies showing good results also during the chronic phase of the stroke, when most other factors are no longer present. The functional improvements in these individuals are associated with changed brain activity as measured by fMRI (Lindberg et al 2007).

Brain lesions affecting the sensory-motor system during development often result in different types of motor dysfunction compared with those that are seen in the case of adult brains with similar lesions. During development, various neural systems are competing for synaptic space. In the absence of competing circuits, due to lesions or altered neural activity, other neural circuits and pathways, which typically disappear during development, may remain and become functionally active. Whether the outcome of early lesions in children results in better or worse function than in adults is not obvious, however. In some cases outcomes are better, in others worse (Kolb and Whishaw 1998, Kolb et al 2000).

One clinical example is the brain development in children with an early (fetal) lesion in one hemisphere leading to hemiplegic cerebral palsy. Recent studies by several groups using TMS and fMRI in children with hemiplegic cerebral palsy have shown that the cortical circuits and the corticospinal pathways from the motor cortex to the hand muscles do not develop as they do in typically developing children (Carr et al 1993, Carr 1996, Vandermeeren et al 2003a, 2003b, Staudt et al 2004). When a small lesion mainly affecting the primary sensory-motor cortex occurs in these children, secondary motor areas in the premotor cortex and supplementary motor cortex typically take over arm/hand functions (see Fig. 1.2). These areas also have neurons projecting to the spinal cord through the corticospinal system. After a large lesion, however, which also includes these secondary motor areas, hand motor control is transferred over to the undamaged hemisphere on the
ipsilateral side of the paretic hand. In such cases, motor control is probably exerted through remaining exuberant ipsilateral connections from the primary cortex to the hand muscles. Interestingly, these plastic changes are not solely beneficial, but may give some problems during bimanual tasks. In children with hemiplegic cerebral palsy, there is a clear relationship between the presence of ipsilateral corticospinal pathways and mirror movements. These may be very disturbing, in particular in bimanual movements, when the two hands have different tasks and are required to move differently to successfully perform desired skills.

Clinical considerations
Knowledge about use-dependent neural plasticity has already influenced theories and thinking around rehabilitation of individuals with functional limitations due to lesions in the nervous system. Although it has already had an influence on clinical interventions, greater implementation in clinical practice is essential for advancing rehabilitation in the future.

Fig. 1.2 Major principles of neural reorganization of the cortical hand motor system after early congenital lesions resulting in hemiplegic cerebral palsy of varying degrees of severity. After a small lesion limited to parts of the primary sensory-motor cortex (A), recovery involves adjacent perilesional areas. After a larger lesion in the same area (B), direct control of hand movements migrates to other frontal motor cortical areas (premotor cortex, supplementary motor area, cingulate motor area), conveyed to the spinal cord via parts of the corticospinal pathways originating from these areas. An even larger lesion, including these other frontal motor areas (C), initiates, in some cases, a transition of direct motor control to the contralateral undamaged hemisphere. In this case, otherwise exuberant ipsilateral corticospinal pathways remain and are used to convey motor signals to the spinal cord.

Source: Adapted from Vandermeeren et al 2003b.
A lesion in the CNS of an individual will have a direct effect on the neural circuits involved in the sensory-motor control of, for example, his or her hand dexterity. However, in addition, as a secondary effect, the actual hand which is affected will not be used to the same extent as that of a peer without a disability. According to what we now know about use-dependent plasticity, circuits that are intact, but not used, will be down-regulated by decreased synaptic strength. By stimulating the child to use the limb, the down-regulation of the circuits might be prevented and the synaptic connectivity strengthened. This strengthening of synaptic connectivity is actually precisely what is done in various forms of constraint-induced movement therapy (CIMT) in children and adults with hemiplegia (Taub and Wolf 1997). The CIMT method was first developed for adults post-stroke in whom the neural circuits developed during childhood and were used until the stroke occurred. Training of the hand in the chronic phase after the stroke may thus restore the neural circuits that had been down-regulated by the patients not using the limb (Lindberg et al 2007).

In children with hemiplegic cerebral palsy, the condition is somewhat different, since there is no, or different, activity in the undamaged neural circuits due to the limb not being used or used in a non-typical way. In certain conditions this also leads to a non-typical organization of the descending motor pathways (see above and Fig. 1.2). However, in less severe lesions, when the motor control remains in the affected hemisphere, it is not known to what extent the cortical infrastructure in non-lesioned areas is influenced by not being used during development. There are now several studies in hemiplegic cerebral palsy showing that periods of intense training and use of the affected hand improve the motor function of the hand (Eliasson et al 2005, Bonnier et al 2006, Charles et al 2006). Thus, it seems that the basic infrastructure of cortical neural circuits essential for sensory-motor control is still in place, although it has not been used during typical development. The ‘glove’ or the ‘sling’ used to prevent movement of the dominant hand is, of course, the obvious means to stimulate the person to use the affected hand. In the future, new training methods in which the actual hand can be trained by some other means will probably be developed.

In general, the existence of use-dependent neural plasticity prompts us to stimulate self-initiated active movements and to develop training programmes that involve the affected limb and prevent non-use. One longstanding clinical question is: how important is it to start early training and treatment? The first studies on the visual system described ‘critical periods’ during the first few weeks after birth when activity in the visual pathways was needed in order to support proper development of the ocular columns. More recent studies on cortical sensory and motor maps describe dynamic mechanisms functioning well also in adults. These results indicate that therapy based on activity-dependent plasticity can be used at all ages. This concept has also been demonstrated by the effects of constraint-induced movement therapy in both children and adults. However, the neural plasticity that takes place during development, and in response to task-specific activity in the sensory and motor system, is probably important for accurate development of the neural circuits. This would seem to indicate the importance of early intervention, aiming at encouraging the infant with signs of hemiplegia to use the affected arm. Early intervention has been part of the treatment in many schools of therapy, but so far we lack any clinical evidence that age is critical for
starting the intervention. However, with our new knowledge of use-dependent plasticity during development and after CNS damage, there are now good theoretical grounds for initiating studies on the effectiveness of early intervention.

The emerging imaging data on brain activity during different phases of motor learning are fascinating and indicate that the learning of new motor sequences engages the ordinary sensory-motor parts of the brain, and that the level of activity is reduced after the movements have been automatized. Clinically, it might be useful to divide intervention into two categories: (1) the learning of new motor skills – for example, moving the fingers in a special sequence, e.g. playing a tune on the piano; and (2) already existing, but impaired, motor skills – for example, moving only one finger quickly up and down, e.g. playing the same note. The former is dependent on developing a higher order motor programme including temporal and spatial parameters. The latter is mainly dependent on the already existing infrastructure of the neural circuits, which might be underdeveloped by not being used. While the training of the latter might improve connectivity in the existing neural circuits and improve motor capacity of finger movement in any motor task, the motor learning programmes seem to be very task-specific with little transfer to other programmes. In clinical terms, this means that it is important that the motor learning and training are task-specific. Patients should be instructed to specifically train the motor behaviour that needs to be achieved.

REFERENCES


