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Neurobiological bases of rehabilitation

Abstract The adult brain maintains the ability to reorganise throughout life. Motor cortical representations can reorganise rapidly in response to different stimuli. Important mechanisms for mediating reorganisation in the cerebral cortex involve the unmasking of existing, but latent, horizontal connections and modulation of GABAergic inhibition and synaptic efficacy. Interfering with these mechanisms can either block or enhance reorganisational processes. Following injury to the motor cortex alterations of the neurotransmitter system regulation, recruitment of additional undamaged brain areas even remote from the injury, and anatomical alterations such as axonal sprouting and synaptogenesis in the brain tissue surrounding the lesion or in the homotopic motor area of the non-affected hemisphere occur. The understanding of cortical reorganisation may enable us to apply principles of plasticity to the rehabilitation of patients after brain injury.

Key words Plasticity · Recovery · Rehabilitation · Motor cortex

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Introduction

During the past two decades experimental studies in animals, and neurophysiological and neuroimaging studies in humans have demonstrated that the adult brain maintains the ability to reorganise throughout life. Primary motor cortical representations can reorganise rapidly in response to different stimuli, such as peripheral nerve lesion [1, 2], ischaemic nerve block [3] or motor performance [4, 5]. The important question for restorative neurology of whether such plasticity also operates after damage to the brain was approached in specific ablation experiments. Nudo et al. [6], observed that the cortical finger representations adjacent to partly damaged finger representations became enlarged with rehabilitation, while they remained unchanged in the untreated monkeys. These experiments indicate that use-dependent plasticity in perilesional intact neuronal tissue is one mechanism operating in recovery of function after injury to the brain.

This review will focus on use-dependent plasticity of the adult primary motor cortex (M1) because evidence from animal and human studies suggest that post-injury use of the affected limb is a major modulator of plastic changes that take place in the undamaged brain tissue and that contribute to the recovery of function. For the discussion of mechanisms underlying and enhancing recovery of function after brain injury this review will refer to data from patients after infarction of the brain because it represents a well defined localised lesion to the brain with a clear temporal onset and is in this sense comparable to the lesion experiments in animals. In the first part of this review I will describe data available from experiments in animals and healthy humans pertaining to the mechanisms of reorganisation of M1 in response to use. In the second part of the review I will discuss data obtained from animal lesion experiments and humans after stroke. As the changes following unilateral injury to the motor output system are different for the affected and non-affected hemisphere, the two sides will be discussed separately.

Mechanisms of use-dependent plasticity in intact M1

Three main mechanisms are thought to mediate cortical reorganisation: (1) the unmasking of existing, but latent horizontal connections [1, 2], (2) the modulation of synaptic efficacy, such as long-term potentiation (LTP) [7, 8] or long-term depression (LTD) [9], and (3) experience-dependent increases in dendritic spines and synaptogenesis [10–12].

These mechanisms are based on the idea that M1 contains multiple overlapping motor representations [13–15], functionally connected through an extensive horizontal network [16]. While connections are abundant *within* somatic representations, they are sparse *between* them [16]. By changing the strength of horizontal connections between motor neurons, functionally different neuronal assemblies can form, allowing dynamic motor output zones to form. Unmasking horizontal connections provides a means for rapid dynamic modulation of motor output zones in M1 [1, 2]. However, modification of synaptic strength by LTP and LTD provides more stable changes of horizontal connections within M1 [17, 18]. The neurotransmitter systems involved in mediating LTP and LTD effects include the inhibitory g-aminobutyric acid GABAergic system [8, 19] and excitatory glutamatergic system with activation of N-methyl-D-aspartate (NMDA) receptors [7, 8]. Induction of synaptic modification, e.g. LTP, is related to morphological changes of dendrites and synaptogenesis, linking cortical neurophysiological and morphological changes [12, 20]. In *intact* human M1, mechanisms underlying use-dependent plasticity include changes in the balance of excitation and inhibition [21]. This is influenced by NMDA, muscarinic and alpha-adrenergic receptor function, as well as GABAergic neurotransmission [21–23]. Therefore, use-dependent plasticity in the intact human brain is mediated by mechanisms that share similarities with LTP as both activation of NMDA receptors [8] and down-regulation of GABA can facilitate LTP in M1 slices [7, 8].

Plasticity after lesion to M1

The affected hemisphere

In *lesioned* M1, one mechanism of mediating recovery is reorganisation of adjacent intact tissue, i.e. new regions taking over function of the injured area [24]. This process appears to be use dependent [24]. Similar to mechanisms involved in plasticity of *intact* human M1, regulation of excitatory and inhibitory neurotransmitter systems may play a role in this reorganisation process in *lesioned* M1. Most evidence is derived from the rat photothrombosis model, where small focal cortical lesions led to perilesional changes leading to altered spontaneous activity and stimulus response characteristics within the *lesioned* hemisphere. These perilesional changes included increased stimulation threshold and decreased GABAergic intracortical inhibition [25, 26], up-regulation of NMDA-receptors [27] and facilitation of LTP induction [28], which persisted over many months. Perilesional anatomical changes include axonal sprouting and synaptogenesis that are to some extent dependent on use [10, 12]. In humans there is some evidence that intracortical inhibition is decreased in the perilesional area as demonstrated using transcranial magnetic stimulation (TMS). First, a shortened silent period occurred after infarctions within M1 [29, 30], indicating increased excitability of the stimulated area. Second, increased paired pulse excitability of M1 was seen in patients with stroke involving the motor output system either cortically or subcortically [31]. Functional imaging studies showed regional reorganisation of cortical representations. For example, a systematic posterior shift of the activation was observed after recovery from stroke [32, 33]. Furthermore, there was also evidence that following infarction in M1, the activation related to sensorimotor activity occurred in somatosensory cortex [34].

Practice-dependent reorganisation of M1 after infarction

Behavioural experience has a clear impact on limb representation in *lesioned* M1 [12, 20, 24, 35]. In adult monkeys, the effect of training the affected limb on the reorganisation of viable M1 neuronal tissue spared by a small lesion to the hand area of M1 (perilesional reorganisation) was studied. Monkeys receiving post-infarct behavioural training showed retention of the undamaged hand representation with expansion to the elbow and shoulder representation in some cases [24]. In contrast, in monkeys not receiving post-infarct behavioural training the remaining, undamaged hand representation decreased in size [24]. There is some evidence that this principle of promoting use of the affected limb results in improvement of motor function and maintenance of its cortical representation applies to humans. In stroke patients, training consisting of repetitive finger and wrist movements of the affected hand or enhanced walking by treadmill training improved the kinematics of the trained movement that generalised to improvement of overall function [33, 36–38]. Another example of promoting use of the affected limb is the concept of constraint-induced therapy. This encourages use of the affected limb by constraining the non-affected limb and has been shown to improve motor function when applied to stroke patients [39–42]. Training-induced improvement of motor function was associated with changes in the motor representation of the affected limb in one study [41] and increased perilesional M1 activity [33]. Reduction of GABAergic inhibition enhanced training-induced increases in M1 excitability and behavioural improvement in chronic stroke patients [37]. This points to similarities with use-dependent plasticity in intact M1, thereby further supporting the evidence that use-dependent reorganisation operates in recovery of motor function after stroke.

The non-affected hemisphere

In rats, following an ischaemic lesion in the primary motor cortex, long-term changes in the inhibitory and excitatory neurotransmitter systems of the homotopic cortex of the non-affected hemisphere have been described and implicated as processes relevant for functional recovery after stroke. More specifically, following a lesion to the primary motor cortex, down-regulation of $GABA_A$-receptor function and up-regulation of NMDA-receptor function has been described in the non-affected contralateral motor cortex (for review [43]). Furthermore, use-dependent dendritic growth followed by dendritic pruning, synapse formation and changes in the specific structure of synaptic connections was described [35, 44].

Several lines of evidence support the functional relevance of the non-affected hemisphere in recovery of function in humans after stroke. First, in neuroimaging studies of stroke patients increased recruitment of the non-affected hemisphere when moving the paretic limb was evident [45–47]. Second, an increase of excitatory activity in the non-affected motor cortex was seen in patients after stroke [48–50]. This increase in excitability correlated with good recovery of function as it was not seen in patients who remained plegic [50]. However, the role of M1 of the unaffected hemisphere is still under debate requiring more detailed studies regarding the time of study in reference to the insult [50, 51], lesion location and possible combination of different techniques [52].

Pharmacological enhancement of motor recovery after infarction

Pharmacological manipulation represents one strategy used to promote recovery of motor function after stroke. D-amphetamine (AMPH), a drug that increases the presynaptic release of the monoamines noradrenaline, dopamine and serotonin and inhibition of their re-uptake from the synaptic cleft, enhanced the beneficial effects of physical therapy after cortical injury in animals and patients post-stroke [53–56]. The underlying mechanisms are not known, but may include modulation of central norepinephrine pathways [57, 58] with secondary alleviation of injury-induced functional depression of structures remote from the injury site (diaschisis) [59, 60]. Additionally, there is some evidence that AMPH paired with motor training facilitates induction and retention of use-dependent plasticity in healthy humans [22] – a type of plasticity that is probably mediated by LTP-like mechanisms [21]. This evidence is in line with reports of its facilitatory effect on behaviourally assessed memory storage [61–65] through its effect on memory consolidation [63] and facilitatory effect on LTP *in vitro* [66, 67]. As use-dependent plasticity is thought to contribute to the functional recovery after brain injury [24, 36] (B.5), the facilitatory effect of AMPH on this form of plasticity may contribute to the reported beneficial effect of AMPH on the functional outcome after brain injury in patients [55, 56]. However, there are studies on stroke patients that did not find such beneficial effects [68, 69].

The interpretation of studies with AMPH is hampered by the involvement of different monoamines. More recent studies use drugs that interact specifically with a single neurotransmitter system, to address the question of their relative contribution to the enhancing effect of AMPH. A beneficial effect of increasing dopaminergic [70, 71] and serotonergic [72] transmission in stroke patients undergoing physical therapy was already reported, but the underlying mechanism remains unclear. These data demonstrate the importance of the pharmacological approach in the rehabilitation of stroke patients.

Non-invasive stimulation of M1

Several reports demonstrated that cortical TMS could enhance the beneficial effects of motor training on performance, cortical plasticity and motor cortical excitability [73–77]. Anodal transcranial DC stimulation (tDCS) appears to exert effects comparable to those of excitatory TMS when applied to cortical regions engaged in a practice or learning task. Several reports have recently documented performance improvements in visuo-motor coordination [78, 79], implicit motor learning [80] and probabilistic classification learning [81]. Altogether, it appears that tDCS and TMS may represent useful tools to modulate motor cortical excitability in regions engaged in practice or learning tasks. This approach has been used in patients with chronic stroke. tDCS can be applied continuously and safely for up to 30 min [75, 82–84]. Together with TMS, anodal tDCS applied to the affected hemisphere of chronic stroke patients, preferably in association with motor training, appears to benefit aspects of motor performance [75–77].

Summary

In sum, there is accumulating evidence that mechanisms known to operate in potentiating synaptic efficacy share similarities with mechanisms operating in use-dependent cortical reorganisation in *intact* and *lesioned* human M1, and that this form of plasticity plays an important role in motor skill acquisition of healthy subjects or patients post-stroke. TMS and tDCS of M1 and drugs that enhance monoaminergic transmission are means to enhance use-dependent cortical reorganisation.

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