Pharmacology of Motor and Somatosensory Skills in Humans

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Abstract: The pharmacological basis of changes in human behaviour and associated cortical reorganization remains poorly understood. Different paradigms have been introduced to alter motor and somatosensory skills in humans. The underlying changes in synaptic efficacy can be modulated by pharmacological agents acting to gate synaptic plasticity. Non-invasive imaging techniques offer the possibility to assess parallel changes in cortical processing.

Cellular studies suggest that there might be only few, but very basic mechanisms that control regulation of synaptic transmission. In particular, the γ-aminobutyric acid (GABA) and the N-methyl-D-aspartic acid (NMDA) receptor, a specific subtype of the glutamatergic receptors, are thought to be crucial in synaptic plasticity. Thus, the application of benzodiazepines facilitating the binding of GABA on GABA(A) receptors, and NMDA receptor blockers, were found to prevent learning and associated cortical reorganization.

While there are many approaches to block plastic processes, less is known about drugs, which enhance learning and cortical plasticity. Growing evidence from human studies support the suggestion that learning is subject to amplification by amphetamine. Amphetamine however acts non-specific by increasing centrally the levels of dopamine, serotonin, and noradrenaline. Thus, first approaches that intend to scrutinize the apparently ubiquitous role of only one of these neurotransmitter systems used more specifically acting pharmacological agents.

In this review we focus on studies that aimed to investigate the pharmacology of the motor and somatosensory system. First, we introduce standards for testing potential effects of a substance. Then, we focus on biochemical mechanisms of learning, before discussing different motor and somatosensory paradigms which were introduced to elicit changes in cortical excitability or organization in animals and humans. Emphasis is placed on the role of inhibitory and excitatory pharmacological agents acting to gate synaptic plasticity in healthy subjects and patients. It is concluded that future studies that investigate the interaction between artificially modulated receptor activity and specific patterns of behaviour in various neurological disorders may help to improve our understanding of how to support recovery of motor and somatosensory function pharmacologically.

Key Words*:* Cortical reorganization, behaviour, dopamine, serotonin, noradrenaline, γ-aminobutyric acid, N-methyl-D-aspartic acid.

INTRODUCTION

Pharmacological agents with a well-defined mode of action on a neurotransmitter system may be used to investigate physiological mechanisms of motor and somatosensory skills in humans. Considered standards for testing potential effects of a substance, double-blinded placebo-controlled crossover studies provide reliable findings that are free of bias introduced by either the patient or the researcher. In this type of study, neither the subject nor the researcher conducting the study knows whether the active drug or a placebo has been administered. Usually, the supervisor randomly divides the participants into two groups. The randomization code will then be kept by the supervisor and broken at the end of the study. The "blindness" of the study is crucial. It eliminates the possibility of a participant's personal beliefs to undermine the study's validity, as well as the researcher's expectations to influence the test results. To ensure that the subject cannot violate the "blindness", the placebo and the test substance must look, smell and taste similar.

In this context, “crossover” means that both groups undergo the same motor or somatosensory task twice, one time under placebo and one time under verum condition. The comparison of both conditions by using a reassigned statistical test may then reveal the pharmacological influence on the tested skills. Trials that use subjective outcomes often require large sample sizes because detection of a drug effect must compete with other causes of individual variation in outcome. Much of this between-patient variation can be eliminated by using a crossover design, in which treatment comparisons are largely or entirely within the same patient. Because of this reduction in variance, and because each patient is used several times, crossover studies often have greater statistical power than parallel group designs that include 5 or 10 times the number of subjects. This is

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1570-159X/05 $50.00+.00 ©2005 Bentham Science Publishers Ltd.

generally an important practical advantage, particularly when studies are performed in a single centre [40, 49, 79].

An optimized study could be designed as follows: one group starts under placebo, the other under verum condition. After a well-defined interval of several days or weeks, the groups are reversed. Generally, the length of this interval is crucial because it should avoid the occurrence of any task dependent carry-over effects which may cause artificially enhanced cortical and behavioural effects. In this case, parallel group designs are more sufficient, but they also require a larger number of subjects and they miss the possibility to assess intra-individual changes.

During the last decade, studies that combine psychophysical tasks with modern non-invasive imaging methods, e.g. magnetic source imaging or functional magnetic resonance imaging (fMRI) provided deeper insights into neuronal correlates of motor and sensory skills [6, 20, 23, 38, 60, 84]. Obviously, this parallel assessment of cortical and psychophysical changes offers the possibility to extend the explanatory power of a study by correlating changes of the investigated skills with alterations of those regions in the brain which are responsible for the processing of changes in the input statistics.

This review summarizes recent studies which were performed to study the pharmacological basis of changes in human behaviour and associated cortical reorganization. First, we focus on biochemical mechanisms of learning. Then, particular attention is given to different motor and somatosensory paradigms, which were introduced to elicit changes in cortical excitability or organization. Emphasis is placed on the role of inhibitory and excitatory pharmacological agents acting to gate synaptic plasticity in healthy subjects and patients. It is concluded that future studies that investigate the interaction between artificially modulated receptor activity and specific pattern of behaviour in more detail may help to improve our understanding of how to support recovery of function in neurological disorders pharmacologically.

BIOCHEMICAL MECHANISMS OF LEARNING

More than 50 years ago, Donald Hebb already hypothesised that individual neurons could participate in different cell assemblies and be involved in multiple functions and representations [31]. This was the first step into a new era of neuroscience as the brain now appeared to be adaptable to environmental changes. Strengthening of synaptic connections following coincident pre- and postsynaptic activity was proposed by Hebb as a cellular mechanism for learning. Thus, contemporary models assume that multiple synapses must act cooperatively to induce the postsynaptic activity required for Hebbian synaptic plasticity.

Regarding crucial biochemical mechanisms of plasticity and learning, neurophysiological and imaging studies suggest a role for dendritic calcium signals in the induction of long-term potentiation (LTP) and long-term depression (LTD) in hippocampal and cortical neurons [41, 50, 58], for a detailed review see [64]. In particular, when an excitatory postsynaptic potential (EPSP) precedes a postsynaptic action potential (AP), the calcium transient in dendritic spines, where most excitatory synaptic connections occur, was observed to be larger than the sum of the calcium signals generated by the EPSP or AP alone, causing LTP; on the other hand, when the EPSP occurred after the AP, the calcium transient was found to be a sublinear sum of the signals generated by the EPSP or AP alone, resulting in LTD [41, 45, 58]. Possible sources contributing to the spinous calcium transient include calcium ions entering through N-methyl-D-aspartate (NMDA) receptors [3, 41], voltage-gated calcium channels in the dendrites [74], and calcium-induced calcium release from intracellular stores [21].

LTP of synaptic transmission in the hippocampus is the primary experimental model for investigating the synaptic basis of learning and memory in vertebrates. Among other glutamate receptor types, notably the metabotropic glutamate receptors, the best understood form of LTP is induced by the activation of the aforementioned NMDA receptor complex. This subtype of glutamate receptor endows LTP with Hebbian characteristics, and allows electrical events at the postsynaptic membrane to be transduced into chemical signals which, in turn, are thought to activate both pre- and postsynaptic mechanisms to generate a persistent increase in synaptic strength [3]. In particular, L-glutamate as an excitatory neurotransmitter activates two classes of ionotropic receptor, named AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) and NMDA. During low frequency transmission the EPSP is mediated predominantly by AMPA receptors. NMDA receptors play a minor role because their ion channels are substantially blocked by Mg^{2+}, and this block is intensified by γ-aminobutyric acid (GABA)-mediated synaptic inhibition [12]. But during high-frequency transmission, mechanisms are evoked that provide sufficient depolarization of the postsynaptic membrane to reduce this block through which calcium enters the dendrites of the postsynaptic neurons to initiate a cascade of biochemical processes which ultimately result in enhanced synaptic efficiency. This critical depolarization is enabled because during high-frequency transmission GABA depresses its own release by an action on $GABA_B$ autoreceptors, which permits sufficient NMDA receptor activation for the induction of LTP [15].

LTP of synapses can be induced in Hebbian fashion by pairing weak presynaptic stimulation with strong postsynaptic depolarization (for a review see [25]). One mechanism for the implementation of this cooperation is action potential firing, which begins in the axon, but which can influence synaptic potentiation following active backpropagation into dendrites. Backpropagation is limited, however, and action potentials often fail to invade the most distal dendrites. Recently, Golding *et al*. showed that long-term potentiation of synapses on the distal dendrites of hippo-campal CA1 pyramidal neurons does require cooperative synaptic inputs, but does not require axonal action potential firing and backpropagation. Rather, locally generated and spatially restricted regenerative potentials (dendritic spikes) contribute to the postsynaptic depolarization and calcium entry necessary to trigger potentiation of distal synapses. Furthermore, they found that this mechanism can also function at proximal synapses, suggesting that dendritic spikes participate generally in a form of synaptic potentiation

that does not require postsynaptic action potential firing in the axon [29].

DRUGS THAT PREVENT LEARNING AND ASSOCIATED CORTICAL REORGANIZATION

Somatosensory Skills

Effects of $GABA_A$ receptor agonists and NMDA receptor antagonists

Cellular studies on synaptic plasticity suggest that there might be only few, but very basic mechanisms that control regulation of synaptic transmission, like the GABA [15] and the NMDA receptor [3]. In humans, benzodiazepines that modulate $GABA_A$ receptor through an allosteric binding side like alprazolam are used for anxiety, insomnia, and seizures. It is evident that these drugs may impair performance in a variety of skills in healthy volunteers as well as in patients [85]. They worsen memory, especially in large doses. In micromolar concentrations, benzodiazepines have been shown to reduce LTP, which could be a cellular basis for their amnesic action [17, 22].

Regarding effects of benzodiazepines on perceptual learning in humans, Dinse *et al*. introduced a specific paradigm to modulate the sensory input statistics [26, 27] and we investigated if this is subject to GABAergic [19] and NMDA mechanisms (Fig. **1**) [20]. The idea was to induce perceptual learning by Hebbian coactivation of the skin of the tip of the right index finger (IF). Stimuli were presented at different interstimulus intervals between 100 and 3000 ms in pseudorandomized order; average stimulation frequency was 1 Hz, and duration of each pulse was 10ms. To transmit the coactivation stimuli to one point of the skin, a small solenoid (diameter 8 mm) was mounted to the tip of the right IF. It stimulated simultaneously (coactivated) receptive fields of the skin portion of the IF under its position. Stimuli were applied at supra-threshold intensities over 3 hours. Pulses were recorded on tape and were played back *via* portable tape recorders. Subjects were instructed not to attend stimulation. In fact, all subjects resumed their normal day work. The basic idea was to coactivate in a Hebbian manner receptive fields to strengthen their mutual interconnectedness through the induction of LTP-like processes [19, 20, 26, 27, 59, 60]. Under placebo conditions, tactile 2-point discrimination was improved on the coactivated, but not on the left IF. This augmentation was completely blocked by the benzodiazepine lorazepam, a $GABA_A$ receptor-positive allosteric modulator [19], and the NMDA receptor antagonist memantine (Fig. **1**) [20]. No drug effects were found on the left IF indicating that the drugs had no effect per se on performance. These findings impressively document that perceptual learning and parallel reorganization of the somatosensory cortex are subject to pharmacological gating by basic mechanisms known to mediate and modulate synaptic plasticity.

Motor Cortex Excitability and Motor Skills

Effects of Modulating Glutamatergic Synaptic Transmission on Motor Cortex Excitability

Further studies provide evidence that the neurotransmitter glutamate is mainly involved in facilitatory mechanisms in the motor system, and therefore might enhance cortical plasticity. Liepert *et al*. studied the effect of the glutamate antagonist riluzole on excitatory and inhibitory phenomena in the human motor system by transcranial magnetic stimulation (TMS) and peripheral electrical nerve stimulation. The motor threshold, the intracortical inhibition and intracortical facilitation as assessed by paired TMS, the cortical and peripheral silent periods, F wave amplitudes and F wave latencies were measured. Riluzole suppressed the intracortical facilitation whereas other parameters remained unchanged [43]. In another study, Schwenkreis *et al*. used transcranial magnetic stimulation (TMS) during 7 days of riluzole administration to correlate these effects with riluzole plasma levels. Nine healthy volunteers received a dose of 100 mg riluzole from day 1 to 7 of the study period. Electrophysiological examinations were performed on day 1 before and 2 h, 5 h and 8 h after riluzole administration, on day 2, day 3 and day 5 before riluzole administration, and on day 8. Plasma samples were taken simultaneously. The excitability of the motor cortex, supraspinal and spinal motor pathways was tested by studying intracortical facilitation and inhibition, the cortical silent period and motor threshold after TMS, as well as the peripheral silent period and F-wave amplitudes after electrical peripheral nerve stimulation. The authors found a significant reduction of intracortical facilitation, which correlated significantly with riluzole plasma levels. To a lesser extent, intracortical inhibition was enhanced on day 1, motor threshold was increased on day 8 and F-wave amplitudes were reduced. These changes did not correlate with riluzole plasma levels. The authors concluded that the main effect of riluzole is a reduction of intracortical facilitation, which is closely related to the drug's level in the plasma. The most probable mechanism involves an effect on glutamatergic synaptic transmission [75].

Effects of NMDA Receptor Antagonists on Motor Cortex Excitability

Wolters *et al*. tested the corticomotor excitability of the representation of the abductor pollicis brevis (APB) muscle before and after repetitively pairing of single right median nerve simulation with single pulse transcranial magnetic stimulation (TMS) delivered over the optimal site for activation of the contralateral APB (paired associative stimulation (PAS) protocol). Following PAS, depression of TMS-evoked motor-evoked potentials (MEPs) was induced only when the median nerve stimulation preceded the TMS pulse by 10 ms, while enhancement of cortical excitability was induced using an interstimulus interval of 25 ms, suggesting an important role of the sequence of cortical events triggered by the two stimulation modalities. Experiments using F-wave studies and electrical brainstem stimulation indicated that the site of the plastic changes underlying the decrease of MEP amplitudes following PAS (10 ms) was within the motor cortex. MEP amplitudes remained depressed for approximately 90 min. The decrease of MEP amplitudes was blocked when PAS(10 ms) was performed under the influence of the NMDA receptor antagonist dextromethorphan. The physiological profile of the depression of human motor cortical excitability following PAS(10 ms) suggests long-term depression of synaptic efficacy to be involved. This study suggests that strict

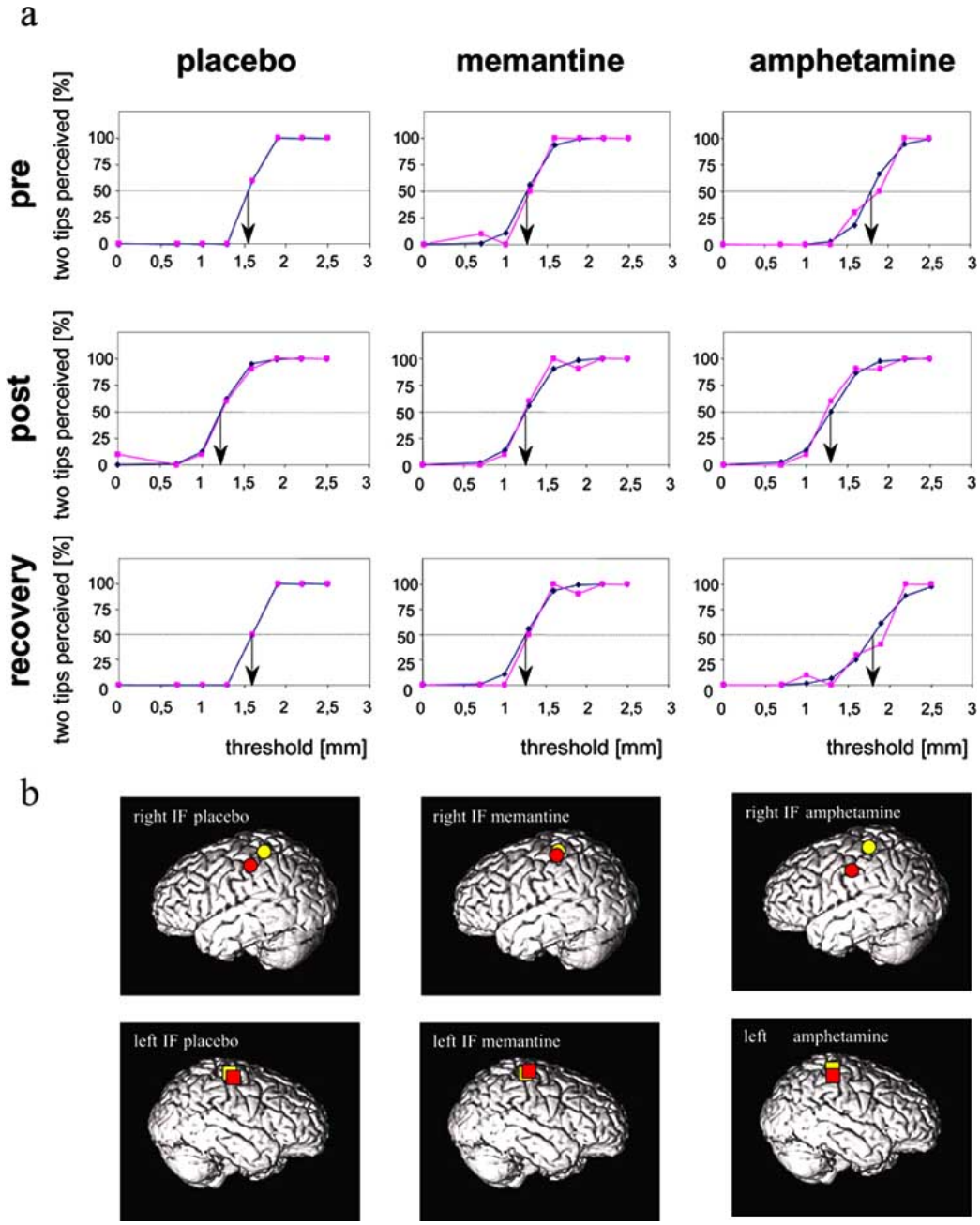

Fig. (1). a. Ref. [20]. Psychometric functions illustrating the coactivation-induced effects on discrimination threshold for an individual subject from each group (placebo, memantine, and amphetamine). Correct responses in percent (pink symbols) are plotted as a function of separation distance together with the results of a logistic regression (blue line). Top row: pre-condition before coactivation; middle row: post-condition, immediate after coactivation; bottom row: recovery after 24 h. 50 % level of correct responses is indicated (dashed line) together with resulting thresholds (arrows). **b.** Schematic projection of the average locations of the single equivalent N20-dipoles of the IF pre (yellow symbols) and post (red symbols) coactivation onto a 3D reconstructed MRI dataset of an individual subject. Note the coactivation-induced shift towards the lateral and inferior aspects of the postcentral gyrus in the placebo-controlled group, which is nearly doubled in the amphetamine group, but blocked under memantine. Comparable effects are lacking on the not-coactivated hemisphere (bottom row).

temporal Hebbian rules govern the induction of long-term potentiation/long-term depression-like phenomena. The depression of corticomotor excitability moreover appeared to be subject of NMDA mediated mechanisms [90].

Schwenkreis *et al*. also studied motor excitability in humans and if this can be modulated by the ingestion of the NMDA receptor antagonist memantine. Seven healthy volunteers received memantine or placebo, respectively, over a period of 8 days. At day 8, transcranial magnetic stimulation (TMS) was performed using a paired pulses paradigm in order to assess intracortical inhibition and facilitation. Additionally, motor threshold and silent period duration after TMS were measured as well as M waves, F

waves and peripheral silent period after electrical peripheral nerve stimulation. Intracortical inhibition was enhanced, and intracortical facilitation reduced after memantine ingestion in comparison to placebo, whereas no significant difference could be observed regarding the other neurophysiological parameters [78]. Similar findings were reported by Ziemann *et al*. who studied the influence of dextrometorphan on human motor cortex excitability [92]. These findings provide further evidence that the NMDA receptor is involved in the regulation of excitability of intracortical interneuronal circuits.

Effects of $GABA_A$ Receptor Agonists and NMDA Receptor Antagonists on Motor Skills

Motor practice leads to changes of trained representations in the motor cortex. Evidence, mainly based on animal experiments, indicates that the activity of GABA-related cortical inhibition is important in controlling the extent to which plasticity may occur. Also in humans movements result in changes in performance and in plasticity of the motor cortex. For example, if human subjects undergo a training period of voluntary thumb movements, it causes changes in the direction of thumb movements evoked by TMS and in TMS-evoked electromyographic responses [11]. To identify the underlying mechanisms, Bütefisch *et al*. studied use-dependent plasticity in human subjects premedicated with drugs that influence synaptic plasticity. Use-dependent plasticity was reduced substantially by dextromethorphan and by lorazepam. These results identify NMDA receptor activation and GABAergic inhibition as mechanisms operating in use-dependent plasticity in intact human motor cortex and point to similarities in the mechanisms underlying this form of plasticity and LTP [8].

In another study, Ziemann *et al*. also tested the role of GABA in modulating practice-dependent plasticity in the human motor cortex. A decrease in GABA-related cortical inhibition was achieved by ischaemic nerve block (INB) in the hand by deafferentation/deefferentation and an increase was achieved by administration of the $GABA_A$ allosteric potentiater. In Experiment 1, healthy subjects performed motor practice (MP), consisting of repeated ballistic contractions of the biceps muscle in the absence (MP alone) or presence of INB (MP+INB). Changes in the biceps motor cortex representation were assessed by transcranial magnetic stimulation (TMS). MP+INB resulted in a dramatic increase in the size of the motor evoked potential (MEP) and in cortical excitability compared with mild or no changes in the MP-alone and INB-alone conditions. In Experiment 2, this dramatic increase in biceps representation induced by MP+INB was replicated when subjects were pretreated with placebo, but this increase was prevented or even switched to a decrease when subjects were pretreated with lorazepam. These findings indicate that a decrease in GABA-related inhibition facilitates practice-dependent plasticity in the human motor cortex, whereas an increase depresses it. In Experiment 3, practice-dependent plasticity (assessed by transTMS, as in the first two experiments) was also tested at the behavioural level. The dramatic increase in biceps MEP size induced by MP+INB was paralleled by an increase in peak acceleration of the fastest elbow flexion movements. Similarly, the lack of change in MEP size in the MP-alone condition was paralleled by a lack of change in peak acceleration. The authors proposed that changes in GABA activity may be instrumented to modulate plasticity purposefully; for instance, to enhance plastic change and recovery of function after a lesion in neurological patients [93].

In 1999, Tegenthoff *et al*. [82] introduced a motor task consisting of a simultaneous Hebbian co-contraction of the abductor pollicis brevis (APB) and the deltoid muscle. Immediately before and after motor learning motor output maps of the APB muscle were assessed my means of TMS in order to get insight into plastic changes of the muscle representation. After subjects completed the motor task, TMS mapping revealed a substantial medial shift of the APB representation toward the presentation of the deltoid muscle. These reorganizational changes could be blocked by the administration of lorazepam indicative for the role GABA ergic mechanisms gating the observed plastic changes. Furthermore, they found that the observed shifts in cortical representation are subject of NMDA receptor activity as the application of the NMDA-receptor antagonist memantine also led to an abolishment of cortical reorganization (Schwenkreis *et al*., unpublished data).

Effects of Modulating Cholinergic Neurotransmission on Motor Skills

Despite of these aforementioned studies investigated the modulation of GABA and the NMDA receptor activity in order to prevent learning of motor and somatosensory skills, less is reported about the modulatory role of cholinergic neurotransmission.

Beside of modulation of motor or somatosensory skills, classical conditioning in animals specifically modifies receptive fields in primary and secondary auditory cortical areas to favor the frequency of a tone signal over other frequencies, including tuning shifts toward, or to, this frequency [88, 89]. This plasticity of receptive fields is associative and highly specific, can develop very rapidly, can be expressed under anesthesia and can be maintained indefinitely [88]. Muscarinic receptors in the cortex may be involved in this development of receptive field plasticity [89]. Using the method of functional magnetic resonance imaging, Thiel *et al.* showed that experience-dependent plasticity, evident in hemodynamic changes in human auditory cortex, is modulated by acetylcholine as they found that experience-dependent plasticity, expressed as a conditioning-specific enhanced fMRI response, was evident in auditory cortex in the placebo group, but not with scopolamine (a muscarinic receptor antagonist) [83]. Given the influence of cholinergic substances on learning and memory processes, Sawaki *et al*. evaluated the effects of scopolamine on use-dependent plasticity and corticomotor excitability in humans (detailed information about the task, see [11]) in a double-blind placebo-controlled randomized design study. The magnitude of use-dependent plasticity was substantially decreased by scopolamine in the absence of global changes in corticomotor excitability. Although these findings may occur as a consequence of arousal mechanisms in thalamus and cortex, they suggest a facilitatory role also

for cholinergic influences in use-dependent plasticity in the human motor system [71].

Interconnectedness in the Sensorimotor System

Effects of $GABA_A$ Receptor Agonists and NMDA Receptor Antagonists

Many brain mapping studies have described changes of somatosensory cortex after the execution of a motor task, which supports the idea of a profound interconnectedness in the sensorimotor system. The strict division between motor and somatosensory systems might therefore be less distinct than previously thought. Thus, somatosensory stimulation results in increased corticomotoneuronal excitability to the stimulated body parts. Kaelin-Lang *et al.* recorded motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) from abductor pollicis brevis (APB), first dorsal interosseous (FDI), and abductor digiti minimi (ADM) muscles. MEP amplitudes, recruitment curves (RC), intra-cortical inhibition (ICI), intracortical facilitation (ICF), resting (rMT) and active motor thresholds (aMT) were recorded before and after a 2-h period of ulnar nerve electrical stimulation at the wrist. Somatosensory input was monitored by recording somatosensory evoked potentials. To differentiate excitability changes at cortical vs. subcortical sites, supramaximal peripheral M-responses and MEPs to brainstem electrical stimulation (BES) were recorded. In order to investigate the involvement of GABAergic mechanisms, lorazepam, dextromethorphan and placebo were administered in a double-blind design. The authors found that somatosensory stimulation increased MEP amplitudes to TMS only in the ADM. This effect was blocked by lorazepam but not by either dextromethorphan or placebo and lasted between 8 and 20 min in the absence of (i) changes in MEPs elicited by BES, (ii) amplitudes of early somatosensory-evoked potentials or (iii) M-responses. The authors concluded that somatosensory stimulation elicited a focal increase in corticomotoneuronal excitability that outlasts the stimulation period and probably occurs at cortical sites. The antagonistic effect of lorazepam supports the hypothesis of GABAergic involvement as an operating mechanism [37].

Recently, we reported experiments in which we investigated the opposite interconnectedness. We used somatosensory evoked potentials (SSEPs) mapping to assess reorganizational capacities in primary somatosensory cortex before and after the Hebbian repetitive co-contraction task of the thumb and arm (see previous paragraph) [82]. We investigated the susceptibility of SI plasticity to the pharmacological modulation of the GABA-neurotransmitter system by application of lorazepam. We found that repetitive training induced stable motor learning characterized by a significant improvement of performance. The time differences between the onset of contraction of the deltoid muscle and the abductor pollicis brevis were progressively shortened. The process of motor learning was accompanied by plastic changes in the primary somatosensory cortex as indicated by a significant increase in the dipole strength and a significant shift of the median nerve dipole on the hemisphere contralateral to the exercised side [76]. The individual shifts of median nerve dipole location were correlated with the individual improvement in motor performance. After administration of lorazepam, motor

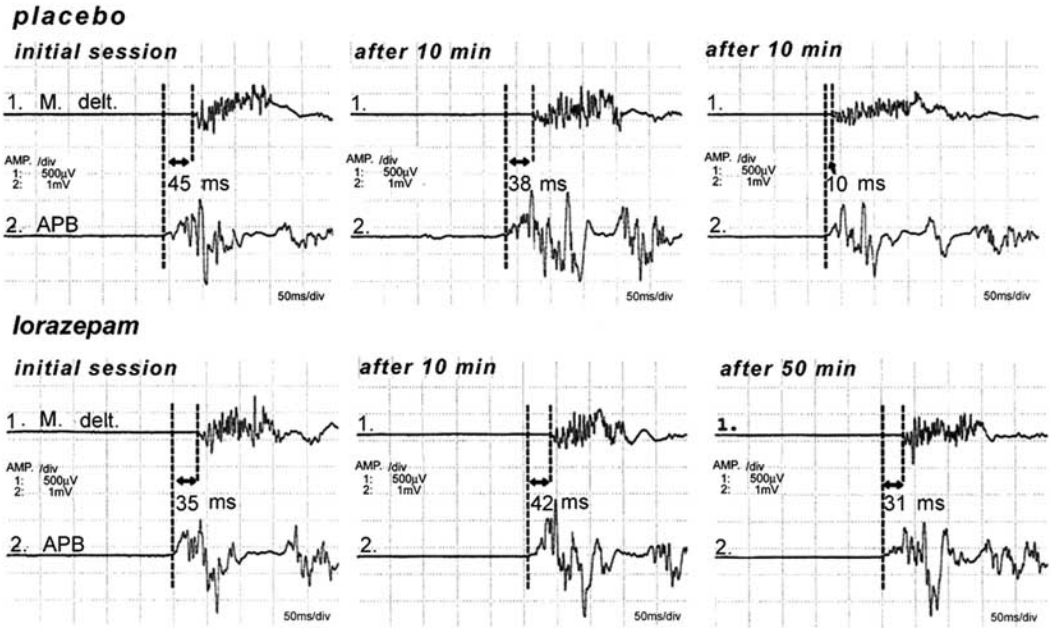

Fig. (2). Ref [61]. Time-differences between the onsets of contraction of the deltoid and APB muscles were determined using non-continuous EMG-monitoring. The figure illustrates EMG data during motor learning at three different sessions (initial session, after 10 and after 50 minutes). Vertical dashed lines indicate onset of EMG, numbers under each arrow indicate time between the onsets of EMGs in ms. Top: placebo condition showing a substantial shortening of the time difference between the onsets of EMGs of both muscles. Bottom: Effect of lorazepam suppressing the shortening of the time differences observed under placebo conditions. Calibrations of EMG signals were 500 µV/div for the deltoid and 1 mV/div for the APB muscles.

learning was significantly suppressed (Fig. **2**). The behavioral effect was accompanied by an abolition of the N20 dipole shift and an unchanged dipole strength. These results imply that motor learning leads to a profound reorganization in SI which is also subject to pharmacological suppression with the $GABA_A$ modulator lorazepam [61].

DRUGS THAT ENHANCE LEARNING AND ASSOCIATED CORTICAL PLASTICITY

Somatosensory Skills

Effects of Modulating Adrenergic Neurotransmission

While there are many approaches to block plastic processes, less is known about drugs, which enhance learning and cortical plasticity.

Amphetamine, when administered peripherally, increases centrally the level of dopamine, serotonin and noradrenalin. These monoamines modify long-term changes in synaptic function [28, 42] with serotonin being more potent than noradrenalin [4]. Many studies provided evidence for the facilitating role of amphetamine on learning processes that might relate to the induction of LTP [28]. Delanoy *et al*. tested the effects of amphetamine on LTP produced by high frequency stimulation of the perforant path in rats. In fact, the results indicate that amphetamine can enhance the development of LTP. The authors further assumed that studies of the neurobiological bases by which central and peripheral catecholamines modulate memory storage may be augmented by examinations of catecholamine effects on a specific form of long-lasting changes in brain function. Similarly, the ability to manipulate LTP may prove to be an important aid in examinations of neurobiological correlates of this phenomenon [18].

In a previous study we investigated human subjects and showed that using a single dose of amphetamine the effect of Hebbian coactivation of the skin of the tip of the right index finger [19, 26, 27, 59, 60] was boosted both perceptually and neurophysiologically providing evidence that perceptual learning in the somatosensory cortex is subject to amplification by amphetamine (Fig. **1**) [20].

Motor Cortex Excitability and Motor Skills

Effects of Modulating Adrenergic Neurotransmission on Motor Skills

In rats, Bourdelais *et al.* found that forty minutes following peripheral administration of amphetamine the extracellular concentration of GABA was significantly reduced, in parallel with a significant elevation in motor activity. These data indicate that a decline in GABA transmission in the ventral pallidum may also be important in the initiation of amphetamine-induced motor activity [5].

To assess behavioral consequences of these facilitatory effects on brain function, Mayfield *et al*. tested amphetamine for its influences on the reaction time response in rats. Animals were shaped to release a lever in response to an auditory/visual stimulus to avoid mild foot shock. The characteristics of the reaction time response of primary interest were percent successful avoidance and response latency. Successful avoidance was not affected by amphetamine treatment. However, response latencies were dose-dependently decreased in response to amphetamine. The authors concluded that dopamine receptor stimulation produces effects on the characteristics of the reaction time response without affecting the response latencies [53].

Bütefisch *et al.* investigated if administration of d-ampheta-mine facilitates the effects of motor training on use-dependent plasticity. Healthy human volunteers underwent a training period of voluntary thumb movements under the effects of placebo or d-amphetamine in different sessions in a randomized double-blind, counterbalanced design. The endpoint measure of the study was the magnitude of training-induced changes in TMS-evoked kinematic and electromyo-graphic responses in the d-amphetamine and in the placebo conditions. Motor training resulted in increased magnitude, faster development and longer lasting duration of use-dependent plasticity under d-amphetamine compared to the placebo session. These results document a facilitatory effect of d-amphetamine on use-dependent plasticity, a possible mechanism mediating the beneficial effect of this drug on functional recovery after cortical lesions [7].

Repetitive synchronized movements [61, 77] lead to short-term plastic changes in the primary motor cortex, which can be assessed by transcranial magnetic stimulation (TMS) [44, 82]. Cortical plastic changes observed after 1 h of training were more pronounced with amphetamine, whereas motor performance did not differ between training sessions with and without amphetamine. These findings provide further evidence that amphetamine is able to enhance training-induced motor cortex plasticity. This effect could be due to its known influence on the GABAergic and glutamatergic system, but might also result from its role as an indirect catecholaminergic agonist [81]. In another study, Sawaki *et al*. studied six subjects in whom training alone failed to elicit behavioral effects. Administration of a single dose of 10 mg of D-amphetamine preceding training however, caused use-dependent plasticity in a subgroup of these subjects. They concluded that pharmacologic interventions to enhance the effects of motor training might therefore help rehabilitative efforts in patients in whom training alone fails [72].

In fact, several animal and human studies provide evidence that amphetamine with motor training/physical therapy promotes recovery of motor function after brain injury or stroke [13, 16, 32, 34, 86]. For example, Crisostomo *et al.* conducted a double-blind study of 8 patients with established cerebral infarction to evaluate the effect of a single dose of amphetamine on recovery of motor function. Four patients received amphetamine; the rest were given placebo. All underwent a session of physical therapy. Patients treated with amphetamine obtained greater increments in motor scores than the controls. Along with animal studies, these findings may allow the development of a pharmacological approach to stroke rehabilitation [13].

Amphetamine however acts non-specific by increasing centrally the levels of dopamine, serotonin, and noradrenalin. Thus, first approaches that intend to scrutinize the apparently ubiquitous role of only one of these neurotransmitter systems

used more specifically acting pharmacological agents. For example, it has been proposed that norepinephrine plays a critical role in the modulation of cortical excitability, which in turn is thought to influence functional recovery from brain lesions. Plewnia *et al*. investigated if it is possible to modulate cortical excitability with the selective norepinephrine reuptake inhibitor reboxetine in intact humans. Recruitment curve and intracortical facilitation, assessed by transcranial magnetic stimulation, were increased after oral intake of 8 and 4 mg reboxetine, in the absence of changes in motor threshold, intracortical inhibition, M-response, F-wave or H-reflex. These results demonstrate that reboxetine enhances cortical excitability and raise the possibility that it could act as a plasticity enhancing substance potentially useful in combination with neurorehabilitative strategies geared to enhance neurorehabilitation [63].

Effects of Modulating Serotonergic Neurotransmission on Motor Cortex Excitability and Motor Skills

Adding serotonin to cell cultures causes long-term facilitation of sensorimotor synapses due in part to growth of new presynaptic varicosities [25]. On behavioural level, several animal experiments showed that serotonin has the capacity to modulate purposeful motor responses [1, 2, 9, 51, 52]. In rats serotonergic neurons were activated in association with increased muscle motor activity, especially if the motor activity is in the repetitive or central pattern generator mode [36]. Serotonergic neurons seem therefore to promote motor output if it is generated in Hebbian fashion. In humans, the serotonin reuptake inhibitor fluoxetine accumulates in the brain relative to the plasma and promotes an amplified serotonin concentration [39, 80]. Recently, we investigated the effect of a single dose of fluoxetine on Hebbian motor learning and associated cortical changes in healthy right-handed subjects in order to get deeper insight into its facilitating influence on human motor cortex [62]. Subjects performed repetitive synchronized movements of the abductor pollicis brevis (APB) and the deltoid muscle [61, 77, 82] with and without fluoxetine in a placebo-controlled double-blinded crossover study design. Immediately before and after motor learning motor output maps of the APB muscle were assessed in order to get insight into plastic changes of the muscle representation. We found a significantly improved motor performance under both conditions without having substantial differences between placebo and fluoxetine. After the completion of the motor task there was a medial shift of the APB muscle motor output map. Only after the administration of fluoxetine the sum of MEP amplitudes (SOA) increased and the motor output map enlarged (Fig. **3**). These findings provide evidence for a use-dependent facilitating effect of fluoxetine on cortical excitability but not on motor performance [62]. Using TMS, Ilic *et al*. investigated the effects of the selective serotonin reuptake inhibitor sertaline on human motor cortex excitability in healthy subjects [35]. Under the influence of

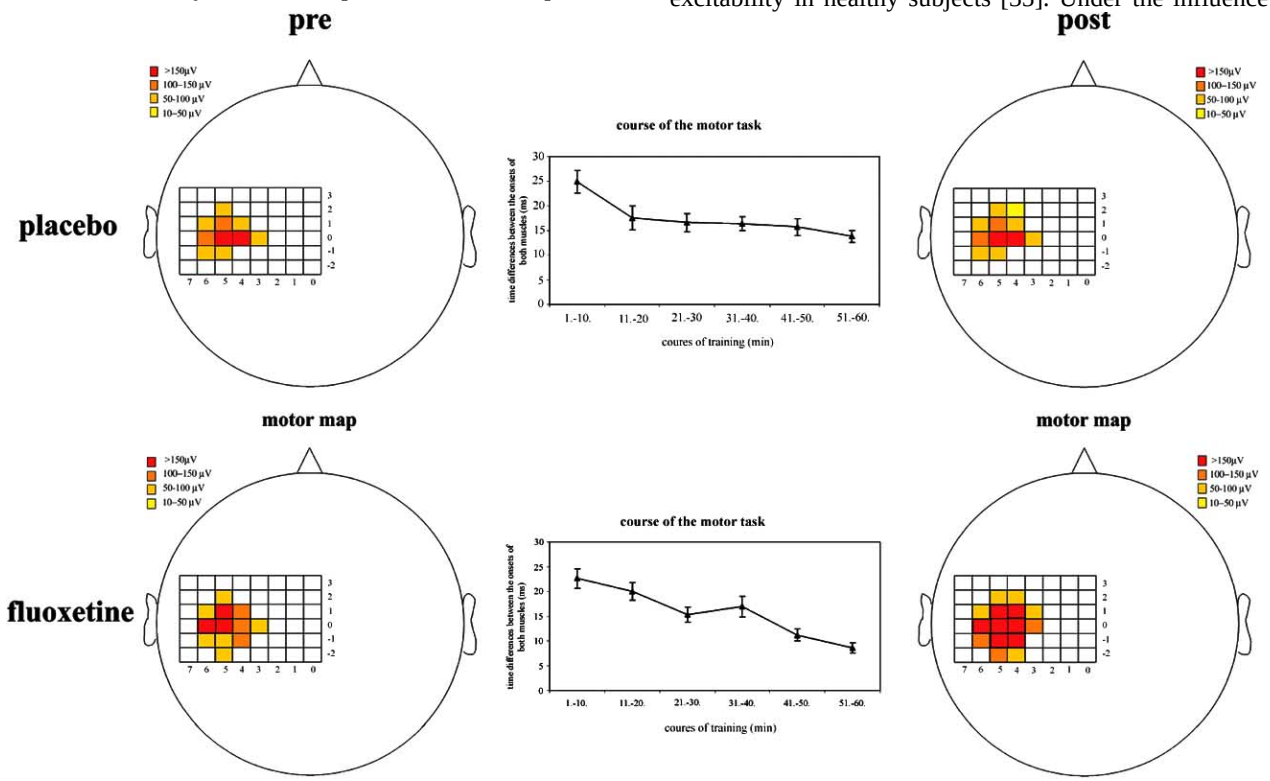

Fig. (3). Reprint from Ref. [62], with permission from International Federation of Clinical Neurophysiology. Single-subject co-contraction effect: Shown are the results of the TMS mapping performed before and after the co-contraction task under both conditions (placebo: above; fluoxetine: below). The graphs between both motor maps show the changes in motor performance during the course of the task (placebo: from 24.9 ± 2.3 (mean values ± standard error) to 13.8 ± 1.2 ms, paired t-test 0.-10. *vs*. 51.-60. min $p<0.001$; fluoxetine: from 27.5 ± 2 to 15.8 ± 1 ms; $p<0.001$). Note the differences of changes in motor maps between placebo (above) and fluoxetine condition (below), especially the enlargement of the area and the gain in.

sertaline, they found a steeper intensity curve suggesting an increased excitability of the cortico-spinal neurone. In our study, under the influence of fluoxetine, repetitive co-contraction of the APB and the deltoid muscle resulted in an increase of the SOA and an enlargement of the APB representation. Selective serotonin reuptake inhibitors like sertaline and fluoxetine seem therefore to have complex influences on different parameters of cortical excitability [35, 62].

Also Loubinoux *et al*. evidenced a putative role of monoamines and, more specifically, of serotonin in the regulation of cerebral motor activity in healthy subjects. The effects on cerebral motor activity of a single dose of fluoxetine and fenozolone, an amphetamine-like drug, were assessed by functional magnetic resonance imaging. Subjects performed sensorimotor tasks with the right hand. Functional magnetic resonance imaging studies were performed in two sessions on two different days. The first session, with two scan experiments separated by 5 hours without any drug administration, served as time-effect control. Drug effects were assessed in a second, similar session, with the drug being administrated after the first scan. A large increase in evoked signal intensity occurred in the ipsilateral cerebellum, and a parallel, large reduction occurred in primary and secondary motor cortices. Both drugs elicited comparable effects, that is, a more focused activation in the contralateral sensorimotor area, a greater involvement of posterior supplementary motor area, and a widespread decrease of bilateral cerebellar activation. These findings provide further evidence for a direct or an indirect involvement of monoamines and serotonin in the facilitation of cerebral motor activity [46]. Regarding these facilitating influence of fluoxetine on motor cortex activity, it is conceivable that it may influence outcome after ischemic brain injury in humans [14]. In order to determine the influence of a single dose of fluoxetine on the cerebral motor activation of lacunar stroke patients in the early phase of recovery, Pariente *et al*. conducted a prospective, double-blind, crossover, placebo-controlled study on 8 patients with pure motor hemiparesia. Each patient underwent two functional magnetic resonance imaging examinations: one under fluoxetine and one under placebo. The first was performed 2 weeks after stroke onset and the second a week later. During the two fMRI examinations, patients performed an active controlled motor task with the affected hand and a passive one conducted by the examiner with the same hand. Motor performance was evaluated by motor tests under placebo and under fluoxetine immediately before the examinations to investigate the effect of fluoxetine on motor function. Under fluoxetine, during the active motor task, hyperactivation in the ipsilesional primary motor cortex was found. Moreover, fluoxetine significantly improved motor skills of the affected side. They found that a single dose of fluoxetine was enough to modulate cerebral sensory-motor activation in patients. This redistribution of activation toward the motor cortex output activation was associated with an enhancement of motor performance [56].

Our findings [62] are not in line with these experiments in poststroke patients as we found no gain in motor performance after a single dose of 20 mg fluoxetine. The lack of any behavioral effects in our approach could however emerge from the low dosage we applied as Loubinoux *et al*. investigated the dose dependant effects of SSRIs and found that changes in human brain function and motor improvement were dose dependent [47, 48]. Nevertheless, long-term treatment may additionally improve motor function by upregulating serotonergic [10, 33, 91] and also β-adrenergic receptors [55]. Further studies investigating the influence of long-term treatment with selective serotonin reuptake inhibitors as an adjunct to physical therapy may therefore provide deeper insight into their possible therapeutical efficiency in poststroke patients.

Effects of Modulating Dopaminergic Neurotransmission on Motor Cortex Excitability and Motor Skills

Despite of these encouraging results of amphetamine and SSRIs in improving human motor and sensory skills less is known about the modulatory role of dopaminergic substances. Ziemann *et al*. used TMS to probe the acute effect of a single oral dose of various dopaminergic (levodopa, selegiline, bromo-criptine) and antidopaminergic drugs (sulpiride, haloperidol) on motor cortex excitability in healthy volunteers. Motor threshold, intracortical inhibition and intracortical facilitation were tested in the abductor digiti minimi muscle. The latter two parameters were studied in a conditioning-test paired stimulus paradigm. The principal findings were an increase in intracortical inhibition by bromocriptine, and, conversely, a decrease in intracortical inhibition and an increase in intracortical facilitation by haloperidol. Effects peaked at delays consistent with the pharmacokinetics of the two drugs and were fully reversible. The authors concluded that dopamine receptor agonists and antagonists can be considered inverse modulators of motor cortex excitability: the former enhance inhibition while the latter reduce it [94].

To ascertain whether levodopa could enhance the efficacy of physiotherapy after hemiplegia, Scheidtmann *et al*. did a prospective, randomised, placebo-controlled, double-blind study in which they enrolled 53 primary stroke patients. For the first 3 weeks patients received single doses of levodopa 100 mg or placebo daily in combination with physiotherapy. For the second 3 weeks patients had only physiotherapy. Motor recovery was significantly improved after 3 weeks of drug intervention in those on levodopa compared with placebo, and the result was independent of initial degree of impairment. The advantage of the levodopa group was maintained at study endpoint 3 weeks after levodopa was stopped. A single dose of levodopa is well tolerated and, when given in combination with physiotherapy, enhances motor recovery in patients with hemiplegia. In view of its minimal side-effects, levodopa will be a possible add- on during stroke rehabilitation [73].

SUMMARY AND CONCLUSIONS

The pharmacological basis of changes in human behaviour and associated cortical reorganization remains poorly understood. Different motor and sensory paradigms have been introduced in order to modulate motor and sensory skills in animals [30, 65-70] and humans [11, 27, 54, 57, 87]. The underlying alterations of synaptic efficacy can be

modulated by pharmacological agents acting to gate synaptic plasticity. Non-invasive imaging techniques offer the possibility to assess parallel changes in brain activity [6, 20, 23, 38, 60, 84].

In this review we focussed on studies that aimed to investigate the pharmacology of the motor and somatosensory system. Considering pharmacological agents that prevent learning, emphasis was placed on the role benzodiazepines facilitating the binding of GABA on $GABA_A$ receptors, and memantine, which blocks NMDA receptors. Both agents were found to block the induction of LTP, prevent learning and parallel changes of human brain function. These findings support cellular studies on synaptic plasticity emphasising the role of the GABA [15] and the NMDA receptor [3] in controlling LTP as a basic mechanism of learning.

While there are many approaches to block plastic processes, less is known about drugs, which enhance learning and cortical plasticity. Growing evidence from human studies support the suggestion that learning and training is subject to amplification by amphetamine [7, 20, 72, 81]. Its use to enhance the effects of motor training might also help rehabilitative efforts in patients in whom training alone fails [13, 16, 86]. Amphetamine however acts non-specific by increasing centrally the levels of dopamine, serotonin, and noradrenaline. Thus, first approaches that intend to scrutinize the apparently ubiquitous role of only one of these neurotransmitter systems used more specifically acting pharmacological agents. In animals, serotonin has the capacity to modulate purposeful motor responses [1, 2, 9, 51, 52]. Selective serotonin-reuptake inhibitors (SSRI), like fluoxetine, that enhance serotonin concentration in the human brain cause facilitation of use-dependent cortical excitability [62] and motor skills, not only in healthy subjects [46] but also in stroke patients [56].

Despite of these encouraging results of amphetamine and SSRIs in improving human motor and sensory skills less is known about the effects of dopaminergic substances. However, it has been shown that a single dose of levodopa, when given in combination with physiotherapy, enhances motor recovery in patients with hemiplegia. In view of its minimal side-effects, levodopa may become a possible add-on during stroke rehabilitation [73].

In summary, studies that used substances with a known mode of action emphasised the role of different types of neuroreceptors in controlling synaptic plasticity. More importantly, it was shown to which extend different agents are able to facilitate or block specific pattern of behaviour. In fact, the possibility to control neuroreceptor activity substantially may be instrumented to alter plasticity purposefully; for instance, to enhance plastic changes and recovery of function in neurological disorders [24, 93]. Emphasis should however be placed on the fact that the mentioned studies only provided first insights into basic mechanisms of synaptic plasticity. Before we can initiate discussions of how to revise established clinical standards of neurorehabilitation, further studies are necessary investigating ensemble acting of substances with a specific mode of action and specific pattern of behaviour in various neurological disorders.

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Received: 17 January, 2005 Accepted: 18 February, 2005

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