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Recovery of function in humans: Cortical stimulation and pharmacological treatments after stroke

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Abstract

In this contribution, we first provide an overview of general principles of reorganisation in the human brain, and point out possible biomarkers of recovery. Subsequently, we expand on possibilities of adjuvant therapy in human rehabilitation using cortical stimulation and pharmacological treatments. Finally, we suggest future directions for research in this field.

Keywords

Neurorehabilitation; Stroke; Training; Transcranial direct current stimulation; Transcranial magnetic stimulation; Dopamine; Amphetamine; Anti-cholinesterase-inhibitors; G-CSF; EPO

Introduction

Stroke is the leading cause of adult disability in the United States and Western Europe (American-Heart-Association, 1997). Two thirds of stroke survivors suffer from residual neurological deficits and have to cope with chronic motor and language dysfunctions (Gresham et al., 1975). After completing standard motor rehabilitation, about 50–60% of stroke patients still experience some degree of motor impairment (Hendricks et al., 2002). Motor deficits impair activities of daily living, such as dressing, engaging in self-care, and communicating (Whitall et al., 2000). Persisting language deficits (aphasia) after stroke, affecting approximately 18% of stroke patients (Pedersen et al., 1995), contribute significantly to permanent disability and emotional suffering in patients (Pulvermuller and Berthier, 2008). Because of their communicative disability, the majority of patients with chronic aphasia are unable to maintain their previous jobs and suffer from a reduction of social contacts. Taken together, the motor and language sequelae of stroke greatly impact individual patients and their families, and put a large burden onto public health systems. So far, we have very limited effective therapies in spite of intensive research efforts and numerous clinical trials (Roundtable, 1999).

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Basic science has improved our understanding of the mechanisms underlying recovery of function following brain injury, and started to identify strategies to facilitate these mechanisms, an important one being intensive training (Kaas, 1991, Nudo et al., 1996, Taub et al., 2002, Jones et al., 2009). Human studies started to take advantage of this information, for example using constraint-induced motor therapy, or bilateral arm training (Luft et al., 2004, Wolf et al., 2006, Luft et al., 2008). In the language domain, functional gains could likewise be demonstrated with sufficiently intensive training involving more than 5 h per week (Bhogal et al., 2003), even when total language training lasted for merely two weeks (Pulvermuller et al., 2001, Meinzer et al., 2005). Overall, human studies have reached conclusions similar to animal work with regard to training and rehabilitation success (see for review (Shepherd, 2001, Floel and Cohen, 2006, Kent et al., 2008, Benowitz and Carmichael, 2010, Carmichael, 2010). Training-based interventions however have so far provided only partial improvements or were able to include only a subgroup of patients, who could actually train. Individuals with poorer function and therefore more in need of therapeutic interventions could not take advantage of these approaches (Buch et al., 2008). Clearly, facilitating the beneficial effects of training-based interventions would be important (Ward and Cohen, 2004, Cramer, 2008b).

Along these lines, it has been proposed that pharmacological neuromodulation and invasive and non-invasive brain stimulation in humans may lead to significant improvement in rehabilitative outcomes, consistent with experiments in animal models (Benowitz and Carmichael, 2010, Carmichael, 2010, Wittenberg, 2010). While proof-of-principle experiments in humans are presently under way, none of these options have yet been implemented into routine clinical practise. Reasons for this translational roadblock (Endres et al., 2008) include the need for optimising the particular parameters of stimulation or drug dosing and protocols in humans, and the fact that patient groups most suitable for each intervention have not been identified yet. Further translational studies in humans are needed to better understand the mechanisms underlying the beneficial effects of each intervention, to determine the neural structures that need to be intact for its implementation, and to adapt and optimise the approaches for humans (Taub et al., 2002, Floel and Cohen, 2006, Cramer and Nudo, 2008). It is expected that this information will lead to successful randomised controlled trials needed to bridge the gap between experimental work and the clinical realm, and bring these interventions into everyday clinical practise (Endres et al., 2008, Cheeran et al., 2009). In this review, we will provide an overview of some of the strategies proposed to facilitate training effects that are presently under investigation, including pharmacotherapy and brain stimulation.

Principles of reorganization; biomarkers of recovery

Responses to rehabilitative interventions show large inter-individual variation. Many different reasons may contribute to justify this like lesion size and location, magnitude of impairment, patients age or gender (Bagg et al., 2002, Weimar et al., 2002, Rossini et al., 2003), the ability for (re-) learning and the specific patterns of brain reorganization after the injury (Ward and Frackowiak, 2006, Cramer, 2008a), as well as genetic factors (Cramer, 2008b). A better understanding of the cellular and molecular events underlying recovery of function is likely to lead to the development of more rationale interventions. It has been

proposed that specific biomarkers can provide information on the ability of the CNS to respond to particular interventions (Milot and Cramer, 2008).

Brain activation

A biomarker of stroke recovery would be a measure that correlates with clinical status, clinical evolution or response to treatment. For example, brain imaging techniques such as functional magnetic resonance imaging (fMRI) have been used to visualise patterns of activity following stroke, and to characterize how these patterns change with spontaneous recovery or in response to rehabilitation (Saur et al., 2006, Ward and Frackowiak, 2006, Johansen-Berg, 2007). Here, valuable information has been gained on the contribution of the contralesional hemisphere in both motor and language recovery, at least in reference to the specific tasks evaluated. Further information has arisen from a combination of imaging with “virtual lesion techniques” like TMS, or investigation of motor evoked potentials from both hemispheres. Using these techniques in the motor domain, a number of studies confirmed significant contribution to function in the paretic hand for activation in the ipsilesional hemisphere (Netz et al., 1997, Werhahn et al., 2003, Fridman et al., 2004, Ward et al., 2006). Others have demonstrated that increased activity in the contralesional hemisphere might likewise contribute to functional improvement, particularly in less-well recovered patients (Johansen-Berg et al., 2002). These findings indicate that the same approach may not be appropriate for every patient in the same way. For example, while some patients may benefit from inhibition of areas (overactive) in the contralesional hemisphere (Mansur et al., 2005, Takeuchi et al., 2005), others might need these areas to implement at least some residual function (Johansen-Berg et al., 2002).

In the language domain, it has been demonstrated that the contribution of the two hemispheres changes over time: In the subacute phase, language improvement correlates with increased recruitment of homologue language areas in the right (contralesional) hemisphere, followed by further improvement and normalization of activation towards the left (ipsilesional) hemisphere (Saur et al., 2006). In the chronic phase, intensive training leads to an increase in activity of “classical” language regions, particularly middle and superior temporal gyrus bilaterally. The magnitude of this activation correlated with long-term training success (Menke et al., 2007). Other studies have identified activation in the contralesional hemisphere as detrimental for recovery (Heiss et al., 1997, Martin et al., 2004). Structural neuro-imaging studies, in combination with clinical and neurophysiological data, are starting to provide additional insights. For example, the integrity of the pyramidal tract appears to influence both spontaneous recovery, and effectiveness of adjuvant therapies (see Liepert, 2005, Newton et al., 2006, Schlaug et al., 2008).

Thus, some consensus is now emerging on patterns that are predictive of improved outcome, and therapeutic strategies are beginning to be guided by such findings.

Genetic factors

Variations in learning-relevant genes may be the basis for differences in learning ability and response to therapy between individuals. Studies about the influence of genetic

polymorphisms on therapeutic response have been conducted for genetic variants of neurotransmitter metabolism, particularly dopaminergic neurotransmission. Dependent on a genetic variant in exon 4 of the Catechol-O-Methyl-Transferase [COMT, Val158Met], modulation of dopamine transmission (by amphetamines) in the prefrontal cortex shows an inverted U-shape distribution, for both working memory performance and brain activation (Mattay et al., 2003). This study suggested that the effects of pharmacotherapies may be influenced by genetic predispositions. Motor map reorganization by training in healthy individuals (Kleim et al., 2006), as well as cortical excitability assessed using neurophysiological techniques (Cheeran et al., 2008), are influenced by a polymorphism in the brain-derived neurotrophic factor (BDNF) gene that is known to influence long-term potentiation (LTP) (Bramham and Messaoudi, 2005). LTP is expressed in the motor cortex (Hess and Donoghue, 1996), and is thought to play an important role in motor learning (Riout-Pedotti et al., 2000, Ziemann et al., 2004). A polymorphism in the KIBRA gene, which interacts with proteins involved in synaptic plasticity (Kremerskothen et al., 2003) and consolidation of LTP (Buther et al., 2004), may influence encoding in the verbal domain (Papassotiropoulos et al., 2006).

So far, this information has not been used to guide particular interventions. It is conceivable though that in the future subjects with specific genetic patterns might be identified as requiring additional or different rehabilitative interventions after brain injury. If so, biologically distinct patient subgroups might be characterized, the inclusion criteria into clinical trials might be improved in order to reduce variance in experimental results, and more effective interventional therapies might be applied for each patient (Cramer, 2008b). However, the idea of an “individually tailored” therapy for each patient (Mayor, 2007) is still a long way off.

Pharmacological approaches proposed to facilitate training effects

Drugs can be used to facilitate recovery from stroke and other diseases of the CNS (see recent reviews by Liepert, 2008, Rösler and Flöel, 2008). This principle has been most thoroughly explored in the motor system. The notion of using drugs to improve language deficits is relatively new and even more controversial than in the motor domain (Pulvermüller and Berthier, 2008). Both approaches build on similar basic neuroscientific principles, namely that modulation of specific neurotransmitter or neurotrophic systems may facilitate neuronal plasticity and LTP (Schabitz and Schneider, 2007, Rösler and Flöel, 2008).

Amphetamines

Studies in healthy humans demonstrated that pre-medication with amphetamines enhanced the effects of motor training on use-dependent plasticity (Butefisch et al., 2002). Clinical trials with amphetamines in hemiparetic stroke patients have been conducted as well, with initial promising results if the drug was combined with physical therapy (Crisostomo et al., 1988). However, subsequent controlled randomised clinical trials showed mixed results ((Martinsson et al., 2003), Cochrane review; (Long and Young, 2003, meta-analysis). For language, one controlled randomised clinical trial suggested beneficial effects on

communicative abilities if amphetamines were combined with 2-hours of speech therapy per week over 5 weeks (Walker-Batson et al., 2001). However, these results have not been replicated so far, and no significant benefit for drug-treated patients could be ascertained 6 months later. A crucial disadvantage, limiting the administration of amphetamines in clinical practise, are potentially serious side effects (Martinsson et al., 2003), most notably increased blood pressure and cardiac arrhythmias. Thus, the available evidence does not support routine use of amphetamine to improve recovery after stroke, but further research in this area seems justified (Goldstein, 2008).

Cholinergic agents

For cholinergic transmission, it has been demonstrated that motor memory formation with training was increased in healthy subjects by the acetylcholinesterase (ACE)-inhibitor tacrine, but reduced when a muscarinic receptor antagonist was given (Sawaki et al., 2002, Meintzschel and Ziemann, 2006). Verbal memory encoding was improved by ACE-inhibitors in individuals with multiple sclerosis (Krupp et al., 2004). For stroke, a case study reported dramatic improvements in sensorimotor function of hemiplegic lower limb and shoulder as a result of treatment with the ACE-inhibitor donepezil (Zorowitz, 2004). A subsequent trial that tested constrained-induced motor therapy with combined donepezil application, versus placebo application, demonstrated higher gains on the Wolf Motor Function Test in the donepezil group approaching statistical significance (Nadeau et al., 2004). Functions of everyday life were not significantly different between groups. No detailed information were available on lesion location for the patients included; therefore, the question if patients responded better if they had suffered lesions to the cholinergic projections from the nucleus basalis of Meynert to the cortex could not be answered. Donepezil also showed promising results in an open-label study in chronic aphasic patients after stroke (Berthier et al., 2003). A subsequent controlled trial combining donepezil with standard speech-language therapy replicated the open-label trial results on measures of overall aphasia severity, and further demonstrated significant improvements in communication skills and processing speed and accuracy (Berthier et al., 2006, Berthier and Green, 2007). Cholinergic substances are safe but have potentially troublesome side effects, such as nausea, anorexia, diarrhea, vomiting, and weight loss. These adverse events are often self-limited and can be minimized by slow drug titration. Thus, use of cholinergic drugs is certainly awaiting further evaluation.

Dopaminergic agents

Experimental studies in healthy humans showed that medication with levodopa as well as dopamine agonists preceding motor training improved the development of an elementary motor memory (Floel et al., 2005a, Meintzschel and Ziemann, 2006) and hand activities of daily living (Floel et al., 2008c). In subacute stroke patients, one study (Scheidtmann et al., 2001) reported significantly better motor function in patients who received physiotherapy and levodopa, compared to those that received physiotherapy only, but a subsequent study could only demonstrate a trend for improvement (Sonde and Lökk, 2007). However, the subgroup sample size in the trial by Sonde et al. was small, and treatment groups were heterogeneous with respect to their initial impairment. In chronic stroke patients, levodopa significantly enhanced the formation of a motor memory (Floel et al., 2005b), and

procedural motor learning (Rosser et al., 2008). As medication with levodopa carries no serious cardiovascular risks, compared to amphetamines (Rösner and Flöel, 2008), it may represent a useful adjuvant during a period of extensive exercise in neuro-rehabilitation.

In the language domain, experimental studies in healthy humans (Knecht et al., 2004) showed beneficial effects for levodopa. In aphasic patients, one recent study reported improved outcome, as assessed with the Boston Diagnostic Aphasia Examination test, in individuals receiving language training paired with levodopa, compared to placebo (Seniow et al., 2009). Another study found that intensive language training, paired with levodopa, was not more effective than intensive language training alone in chronic aphasic patients, as evidenced in test scores (Aachen Aphasia test), and Communication of Daily Life (Breitenstein et al., 2008). For dopamine agonists, presumably enhancing tonic dopaminergic drive, negative effects in experimental learning studies in healthy humans (Breitenstein et al., 2006) and randomised controlled trials in aphasic patients (Gupta et al., 1995, Sabe et al., 1995, Berthier, 2005) have been reported. Beneficial effects in some initial reports, see for example (Sabe et al., 1992), were most likely due to improvement of nonfluent output that was the consequence of a decreased drive to generate speech (Pulvermüller and Berthier, 2008).

Growth factors (e. g., neurotrophins)

Growth factors are pragmatically defined by their biological actions, that is, stimulating cell growth and differentiation. A large number of these cytokines act on brain cells, with effects on neuronal survival and regeneration (Maurer et al., 2008). Here, we will only discuss the clinically important group of hematopoietic factors erythropoietin (EPO) and granulocyte-colony stimulating factor (G-CSF). These hematopoietic factors, initially characterized by their non-neural actions, were shown to have additional neuroprotective, as well as neuroplastic, properties (Maurer et al., 2008).

EPO is a glycoprotein produced in the kidney (Jelkmann, 1992) and known to cross the blood-brain barrier (Brines et al., 2000). In clinical application, EPO has long been used for the treatment of renal anemia, also with the emphasis that deterioration of cognitive function in chronic kidney failure can be ameliorated by EPO. Over the last years, EPO has been studied for the use in neurological disorders. Extensive preclinical testing has been conducted, see Tonges et al. (2007) for recent review on experimental data, and EPO has been successfully introduced to experimental stroke treatment in the clinics in a pilot trial (Ehrenreich et al., 2002). Here, no safety concerns were identified for EPO given to acute or subacute stroke patients. Furthermore, efficacy data demonstrated that EPO treatment, compared to placebo, was associated with significantly better outcome, as assessed by the Scandinavian Stroke Scale and the Barthel index after one month, as well as reduced infarct size on MRI. Although still at an experimental stage, the study showed the safety and feasibility of EPO treatment for stroke. While in these original studies EPO was used to target acute brain diseases, exploiting its potent anti-apoptotic action, more data has recently been acquired that have found a high regenerative potential of EPO, extending to neurotrophic and plasticity modulating properties (see Siren et al., 2009 for review). Data from normal subjects showed enhanced hippocampal response during memory retrieval

during fMRI after one week of EPO treatment (Miskowiak et al., 2007). Additionally, studies in patients with chronic multiple sclerosis demonstrated plasticity-enhancing effects of EPO, both on neurophysiological measurements and behavioural scores (Ehrenreich et al., 2007). An ongoing clinical trial (ClinicalTrials.gov Identifier: NCT00604630), using EPO with and without concomitant rtPA treatment, now demonstrated that patients receiving EPO alone (without concomitant rtPA application) show smaller lesion volume, and lower morbidity, compared to patients that received placebo.

G-CSF is a glycoprotein originally proposed to promote differentiation in the granulocytic lineage. It has long been used in the clinic to counteract neutropenia, and for mobilizing hematopoietic stem cells from the bone marrow in stem cell transplantation (Nervi et al., 2006). New data from single cell studies and animal models of stroke have shown that G-CSF also acts on neurons, counteracts cell death, and promotes functional and structural regeneration of the CNS. Possible mechanisms include induction of proliferation and differentiation of neuronal stem cells into new neurons (for review, see Schabitz and Schneider, 2006). Clinical trials published to date have shown that G-CSF is safe in low (Sprigg et al., 2006) and high (AXIS trial; Schabitz et al., 2008) doses. Thus, G-CSF appears to be safe at high concentrations in patients with ischemic stroke; even if there is a rise in blood white cell count.

In addition, in the AXIS trial, G-CSF showed signs of clinical efficacy in patients with larger baseline diffusion MRI lesions: When exploring functional outcome, a stable statistical interaction was observed between the volume of the initial diffusion deficit and dose of G-CSF that significantly influenced outcome in all clinical scales, and had a trend influence on infarct evolution (Schabitz et al., 2008). The model used to analyse the data detected a beneficial influence of G-CSF on patients with diffusion lesions $N\ 14\text{--}17\text{ cm}^3$. The obtained data provide the basis for the design of a second trial aimed to prove efficacy of G-CSF on clinical endpoints (Schabitz, personal communication).

In the chronic phase after stroke, data of an ongoing trial (ClinicalTrials.gov Identifier: NCT00298597) will soon become available to answer if G-CSF may enhance activities of daily living and learning in the motor and language domain. In this trial, patients received either G-CSF, 10 $\mu\text{g/kg}$ body weight per day, for a total of 10 days, or placebo for a total of 10 days, both injected subcutaneously. Motor performance, as assessed with a task that measures hand function for activities of daily living, was considered as the primary outcome measure, verbal and motor learning as secondary outcome measures.

Brain stimulation

The basis for using brain stimulation in stroke rehabilitation is its potential to modulate cortical excitability and plasticity, as well as to facilitate the beneficial effects of training protocols. Two non-invasive techniques, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), and an invasive technique, epidural stimulation, are currently used.

TMS is a non-invasive technique based on Faraday's principle of electromagnetic induction. A brief pulse of current flowing through a coil of wire generates a magnetic field which, in turn, results in an electric field and currents that flow parallel to the plane of the coil (Roth et al., 1990). Due to the electrical conductivity of living tissue, the electric field leads to an electrical current in the cortex and subsequently to depolarisation of the underlying neurons (Hallett, 2007). Transcranial direct current stimulation (tDCS) modulates cortical excitability by application of weak electrical currents in the form of direct current brain polarization. Depending on direct current (DC) polarity, neuronal firing rates increase or decrease, presumably due to DC-induced changes in resting membrane potentials (Nitsche et al., 2003a). The after-effects of tDCS on cortical excitability appear to be influenced by N-methyl-D-aspartate (NMDA) receptor-dependent processes (Nitsche et al., 2004). High frequency rTMS and anodal tDCS may increase motor-cortical excitability while low-frequency rTMS and cathodal tDCS may decrease excitability. Furthermore, animal and human studies indicated that both techniques may influence LTP- and LTD-like mechanisms, increase neurotrophic substances, dopamine and serotonin levels, and modulate gene expression ("immediate early genes") (Liebetanz et al., 2002, Siebner and Rothwell, 2003, Strafella et al., 2003, Nitsche et al., 2004). For epidural stimulation, the exact mechanisms of action are not fully understood yet. Both facilitation of stimulated motor regions, similar to what has been shown for anodal tDCS or facilitatory rTMS, as well as inhibition of regions that have developed hyperactivity after stroke, have been hypothesized (Brown et al., 2006, Brown et al., 2008).

Two models of brain stimulation have been used in human stroke rehabilitation studies: First, brain stimulation can be used to increase cortical excitability or training-induced LTP-like mechanisms in the ipsilesional hemisphere. Increasing the excitability of neurons in a motor region may promote improvements in performance for the contralateral hand possibly by facilitating LTP-like processes between activated neurons (Okano et al., 2000, Liebetanz et al., 2002). Practising motor behaviours, such as finger movements, naturally heightens motor-cortical excitability (Garry et al., 2004, Koeneke et al., 2006). Therefore, increasing excitability with brain stimulation, whether directly or indirectly, may provide a means of inducing a physiological state that supports acquiring novel skills (Hummel and Cohen, 2005). It has been recently demonstrated that application of anodal tDCS over the primary motor cortex of healthy subjects, in addition to facilitating motor learning as measured 3 months later, does so through facilitation of off-line learning (Reis et al., 2009). Second, brain stimulation may be used to inhibit networks that interfere with performance, most notably the overactive contralesional hemisphere, thereby dampen inhibitory projections from the contralesional onto the ipsilesional motor cortex, releasing the injured motor cortex, and thereby improving its function.

Inhibition of the contralesional hemisphere

Changes in interhemispheric inhibition after stroke may under certain circumstances contribute to persisting dysfunction. Using a "TMS double-pulse paradigm", in which a conditioning pulse is first applied over the contralesional hemisphere, followed 10 ms later by a test stimulus over the ipsilesional hemisphere (Ferber et al., 1992), it was possible to determine persistent inhibition from the contralesional onto the ipsilesional hemisphere

when patients with chronic stroke intend to move the paretic hand (Murase et al., 2004). The magnitude of this inhibition correlated negatively with hand function (Murase et al., 2004), and a reduction of this interhemispheric inhibition correlated with improved hand functions in experimental human models of plasticity (Floel et al., 2008a). It is conceivable that this effect could be mediated through specific interactions between interhemispheric glutamatergic connections and local GABAergic intracortical inhibitory circuits (Perez and Cohen, 2008).

TMS

Building on this model of “interhemispheric competition”, Kobayashi et al. showed that inhibition of the ipsilateral (seen from the task hand) primary motor cortex (M1) with low-frequency rTMS accelerated performance of a digit finger sequence in healthy subjects (Kobayashi et al., 2004). This effect was associated with increased excitability of the unstimulated contralateral M1 (Plewania et al., 2003, Schambra et al., 2003). Stimulation of control areas (contralateral M1, ipsilateral premotor cortex, vertex) did not show this behavioural result.

Takeuchi et al. used a randomised, sham-controlled study design with low-frequency rTMS over contralateral M1 in 20 stroke patients (Takeuchi et al., 2005). Half were given sham (coil tilted vertically by 90%). With real rTMS, increased acceleration of a previously trained pinch grip of the paretic hand immediately after stimulation was observed, with a parallel reduction of MEP amplitude in contralesional M1, and decreased transcallosal inhibition. The latter correlated with improved motor function. Based on the same concept, Mansur et al. showed in a crossed-over, sham-controlled study in 10 patients that reaction time in simple and complex reaction time tasks, as well as the Purdue Pegboard Task, of the paretic hand could be improved by low-frequency rTMS over the contralesional hemisphere (Mansur et al., 2005). A study by Fregni et al. (2006) reported significant improvement in the Jebsen-Taylor Hand Function Test (JTT) after 5 consecutive daily sessions of rTMS over the contralesional hemisphere that outlasted the end of stimulation for at least 2 weeks.

In the language domain, the potential of rTMS to influence linguistic functions in healthy individuals was demonstrated in several studies, in which high intensity, high-frequency rTMS over left prefrontal cortex was used (Pascual-Leone et al., 1991). Studies from our own group showed that low-frequency rTMS over left and right prefrontal cortex leads to an inhibition of language functions in healthy individuals that is dependent on the language-dominant hemisphere, as determined by functional imaging (Knecht et al., 2002). In stroke patients, it was demonstrated that naming ability was significantly improved after stimulation with 1 Hz rTMS over 10 days in areas that showed hyperactivity in fMRI (Martin et al., 2004, Naeser et al., 2005). These open trials can be viewed as pointing to the possible use of inhibitory rTMS in language therapy. Large randomised, preferably multi-center, trials are needed to evaluate this possibility further.

TDCS

Several reports demonstrated improved function of one hand with cathodal tDCS over the ipsilateral hemisphere in healthy individuals (Vines et al., 2006, Vines et al., 2008b). In

stroke patients, a small study likewise suggested that inhibition of the contralesional M1 using cathodal tDCS improved hand activities of daily living (JTT; Fregni et al., 2005). Preliminary results from an ongoing trial involving 5 days of combined cathodal tDCS over the contralesional hemisphere with occupational therapy in a cross-over sham-controlled study (Nair et al., 2008) suggests significant improvement in motor outcomes that last for at least 1 week.

Facilitating the lesioned hemisphere

TMS—In healthy individuals, Kim et al. were able to demonstrate, using high-frequency rTMS over right M1, that learning of a finger sequence task (left hand) was significantly better under rTMS than under sham stimulation (Kim et al., 2004).

In chronic stroke patients, Kim et al. demonstrated that high-frequency rTMS over the ipsilesional motor cortex in 15 patients with chronic stroke induced an improvement (short lasting) of execution of complex finger movements (Kim et al., 2006). A randomised sham-controlled study (52 patients) by Khedr and colleagues demonstrated that 3 Hz rTMS over lesioned M1 for 10 days significantly improved the “Disability Scale” (Khedr et al., 2005). This effect persisted at least 10 days after the end of stimulation. The authors suggested that the stimulation initiated plastic processes that then exerted persisting positive effects even after the end of stimulation. Moreover, they hypothesized that dopamine release during rTMS in the striatum (Strafella et al., 2001) might have facilitated encoding.

In the language domain, a study in healthy subjects demonstrated that short trains of high-frequency rTMS with low stimulation intensity (Mottaghy et al., 1999) improve object naming, possibly by a pre-activation of underlying neural networks. However, the effects were rather small, showed high inter-individual variability, and were only short lasting. Trials using facilitatory rTMS to improve language functions in chronic aphasia have not been completed so far to our knowledge, but are currently ongoing at the university of Hamburg (Siebner, 2009).

tDCS—The ability of anodal tDCS over primary motor cortex to enhance motor learning (Nitsche et al., 2003b; Reis et al., 2009) and motor performance (Hummel et al., 2009) in healthy individuals has been well-established. In stroke patients, proof-of principle studies demonstrated that activation of the lesioned hemisphere with anodal tDCS lead to transient improvements in motor performance in chronic stroke patients (Hummel et al., 2005): Motor cortex stimulation for 20 min with 1 mA induced an improvement in a hand motor task that mimics activities of daily living (Hummel et al., 2005), and correlated with the increase in excitability of the ipsilesional M1 (rise in the slope of the recruitment curve, reduction in the short-interval intracortical inhibition). Application of tDCS over the course of several days prolonged this effect (Boggio et al., 2007). Another study, however, subjected patients to multiple sessions of anodal tDCS over the ipsilesional hemisphere in combination with a robot-assisted arm training protocol, and failed to find significant improvement (Hesse et al., 2007). A multicenter trial (ClinicalTrials.gov Identifier: <http://clinicaltrials.gov/ct2/show/NCT00909714>) assessing the combination of 10 days of physiotherapy with or without

anodal tDCS over the lesioned hemisphere in subacute stroke patients will be starting in July/August 2009 in Germany, Austria, Switzerland, and France.

In the language domain, anodal tDCS over the posterior part of the left perisylvian area improved learning of a novel vocabulary in healthy subjects (Floel et al., 2008b) and over left prefrontal cortex, improved learning of a novel grammar (de Vries et al., 2008). In aphasic patients, tDCS has so far only been used in a small uncontrolled trial, originally designed to test the effect of tDCS on motor symptoms in stroke patients. Here, an unexpected improvement was found in a language test in 4 out of 5 patients that also suffered from aphasia (Hesse et al., 2007). The study did neither include a control group nor a control stimulation. An ongoing trial at the university of Muenster (ClinicalTrials.gov Identifier: NCT00822068) examines the potential of combined intensive training and anodal tDCS to improve object naming abilities in chronic aphasia, but no data is yet available here.

Of note, recent studies in healthy individuals (Vines et al., 2008a) point to the possibility that stimulating both hemispheres simultaneously, e. g., with cathodal tDCS over the contralesional hemisphere and anodal tDCS over the ipsilesional hemisphere, may be a better montage for catalysing motor recovery. An alternative approach would be to combine anodal tDCS of the ipsilesional M1 with peripheral nerve stimulation of the paretic hand, which induced superior improvements in the motor domain relative to each of them alone and relative to sham (Celnik et al., 2009). It remains to be determined which of these approaches induce more benefits or if they are better fit to different patient populations or stages of the disease.

Epidural stimulation—In the context of clinical studies using epidural electrical stimulation for pain management, some of the patients subjectively reported improved upper limb function (Katayama et al., 1998). Subsequent pilot studies in stroke patients (unblinded, uncontrolled) that used epidural electrical stimulation around a functional magnetic resonance imaging “hot spot” in the perilesional area, coupled with simultaneous rehabilitative therapy, showed encouraging results (Brown et al., 2008, Levy et al., 2008). A randomized controlled clinical trial (EVEREST Trial of Cortical Stimulation) was then designed to test the safety and efficacy of epidural cortical stimulation delivered during rehabilitation for upper limb motor function in patients with ischemic stroke (Harvey and Winstein, 2009). Patients with hemiplegia at least 4 months after acute ischemic stroke were implanted with a cortical electrode and pulse generator and received 6 weeks of upper limb rehabilitation with subthreshold stimulation delivered during therapy, before being evaluated 4 months later. However, the EVEREST failed to meet the primary end points (upper extremity Fugl-Meyer score and the arm motor ability test at 4 weeks following treatment), and has now been aborted ([!><http://ir.northstareuro.com/releasedetail.cfm?ReleaseID=345646>!!]).

In summary, the studies discussed in this section show that both (1) facilitation of motor areas of the ipsilesional hemisphere and (2) inhibition of homologous areas of the contralesional hemisphere may have potentially beneficial effects if used in combination with behavioural therapy.

Future directions

Adjuvant therapies like brain stimulation and pharmacotherapy, operating through different mechanisms still under investigation, can facilitate performance and learning in the motor and the language domains. These effects have been documented in both healthy individuals and in small “proof-of-principle” studies in stroke patients. As desirable as it is to attempt a rapid movement of these interventions into routine clinical practise, further experimental studies are needed to elucidate which strategies are most effective, which patients could benefit more from each intervention, which stimulation parameters or dosing or timing of application is more effective.

No direct comparisons have so far been conducted to address these questions. However, some interesting indications have emerged. In a study using levodopa, patients in whom the dominant hemisphere (dominant and non-dominant as defined by handedness) was affected were able to benefit to a larger degree from the intervention than patients in whom the non-dominant hemisphere was affected (Rosser et al., 2008). Interhemispheric inhibition from the dominant hemisphere is stronger onto the non-dominant hemisphere (Baumer et al., 2007), and previous studies have indicated that inhibition from the contralesional onto the ipsilesional hemisphere may be overly persistent when stroke patients intend to move the paretic hand (Murase et al., 2004). Stroke patients in whom the non-dominant hemisphere is affected may suffer from a larger inhibition onto the ipsilesional hemisphere. Thus, they may receive lesser benefits from an intervention aimed at improving dopaminergic neurotransmission, but could rather benefit from interventions aimed at reducing interhemispheric inhibition. This hypothesis is supported by recent findings that motor performance in healthy subjects is only improved by decreasing excitability in the dominant, but not the non-dominant hemisphere, indicating that decreasing excitability in the contralesional hemisphere would be most effective for patients with damage to the non-dominant hemisphere (Vines et al., 2008b). And in fact, Fregni et al. (2005) noted that decreasing excitability in the contralesional motor area had the strongest effect when the damage was in the non-dominant hemisphere. Ongoing trials using brain stimulation techniques like tDCS will hopefully soon shed some light on the functional contribution of different fMRI activation patterns. In the language domain, our own group is conducting a trial where both left- and right hemisphere activated areas that were correlated with training success are stimulated (Menke et al., 2007), to further tease apart their contribution to recovery (ClinicalTrials.gov Identifier: NCT00822068). Future studies should also directly compare interventions that modulate interhemispheric inhibition with those that modulate neurotransmitter levels, in cohorts that include patients with damage to the dominant and patients with damage to the non-dominant hemisphere.

Another question concerns the use of inhibitory brain stimulation in stroke patients. Inhibition of the contralesional motor cortex should only show a beneficial effect in those patients in whom the contralesional hemisphere is actually “overactive” and thus inhibiting the injured hemisphere (Murase et al. 2004, Floel et al., 2008). This may not be the case in all patients: A number of studies have shown that activity in the contralesional hemisphere may contribute to residual function in the motor (Lotze et al., 2006) and the language

(Menke et al., 2007) domain in some individuals. Here, facilitation of the contralesional side might be a more promising strategy, a hypothesis that should be examined further.

Following these focused experimental trials, the effects would have to be replicated in large, randomised, placebo-controlled studies outside the experimental setting. Here, multi-center approaches are needed to recruit homogenous patient groups in sufficient numbers. Ideally, interventions should be combined with training (physiotherapy, occupational therapy, speech therapy), thereby augmenting training success, consolidating stimulation effects, and improving functional outcome in the long run.

Open questions

Which stimulation technique (pharmacotherapy, electrical brain stimulation) is most effective in which patient?

Which site, duration, and mode of stimulation (transcranial direct current, transcranial magnetic, epidural) stimulation shows the most pronounced effects?

Which patient group benefit most from each respective intervention? Are there “biomarkers” (see above) that allow patient selection, intervention selection, prediction of response to therapy (for example, which patient benefits from inhibition of the contralesional, which one from facilitation of the contralesional hemisphere?). Should combination with biomarkers be mandatory before intervention in each individual patient to identify areas of hyper-/hypoactivity?

Can treatment groups be stratified according to polymorphisms in candidate genes for learning and memory?

How long do the effects last? Does repetitive application of the respective intervention lead to more permanent effects?

Is training plus intervention in the subacute or in the chronic phase most effective? After which time-interval following the initial event should adjuvant therapy be commenced?

Safety issues: E.g. does facilitation of the ipsilesional hemisphere increases the risk for epileptic seizures?

Needed are large, randomised, placebo-controlled clinical trials to evaluate the available strategies (preferably multi-center; issue of financing?).

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