Improving hand motor functions in patients with chronic stroke:

Modulation of somatosensory input into non-affected hemisphere

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I Introduction

I.1 Stroke

I.1.1 Incidence, risk factor, classification

Incidence

Stroke is a heterogeneously used term, which includes ischemic as well as hemorrhagic cerebral events potentially leading to severe destruction of brain tissue and subsequent impairment of respective functions. Prevalence in the western world is between 2 and 8% for patients older than 45 years with increasing numbers in the elderly and with a preference of male gender (Di Carlo et al., 2000). An international comparison revealed an age- and gender-adjusted yearly incidence of about 5/1000 for 45-84 year olds (Sudlow & Warlow, 1997). Yearly incidence of first stroke in the elderly in Europe is between 7/1000 subject years (64-69 year olds) and 38/1000 subject years (older than 90 years olds) (Di Carlo et al., 2000). In a WHO-initiated study in Germany, incidence rates of 9/100000 (25-34 years), 27/100000 (35-44 years), and 118/100000 (45-54 years) were found for young males (Heinemann et al., 1998). Although stroke letality has declined over the last decades it is still between 10 and 20% within one year after the event in western countries (Bamford et al., 1990; Wolf et al., 1992). Two-thirds of those surviving the initial stroke event suffer from residual neurological deficits (Ferrucci et al., 1993).

Thus, stroke is a leading cause of death and despite recovery a major cause of long term disability among adults in Europe as well as in the United States. These facts underline that stroke is not only a potentially devastating event for the individual but additionally represents a major social and economic challenge to the society. Lifetime cost for each stroke in the USA was estimated more than US$ 100,000 in 1990 (Taylor et al., 1996). Loss or reduction of work power due to chronic impairment must be taken into account, in particular, for younger patients.

Risk factors

Major risk factors for stroke are hypertonus, cigarette smoking, heart diseases and high age. Therefore, despite attempts to reduce risk factors, stroke events will further increase with increasing life expectancy. However, as already pointed out, not only the elderly are affected by stroke. Further underlying conditions including diabetes mellitus, coagulopathias, vasculitis, vessel malformation, rheumatological diseases and oral contraception contribute to stroke in particular in young patients. Cardiogenic embolies – often based on heart diseases - represent a further important cause for stroke in younger patients.

Classification

The most common differentiation divides stroke into two main types: ischemic and hemorrhagic stroke (Elkind, 2003). The ischemic stroke occurs in 80-85% of the time hereby a blood vessel in the brain becomes clogged mostly thrombotic or embolic. With a hemorrhagic stroke a blood vessel in the brain bursts or leaks. Hemorrhagic stroke tend to be more serious with a death rate of up to 50%. Besides differentiation between ischemic and hemorrhagic lesions and further classification strokes can be classified by the brain’s anatomic blood supply and the localization of related brain structures. An additional criterion is the clinical significance of the stroke. If the clinical symptoms resolve within hours (less than 24 hours) the episode is called a transient ischemic attack (TIA).

Symptoms

Depending on stroke localisation and extent, many strokes cause neurological symptoms such as ataxia, paresis, impaired sensibility, incontinency, visus and hearing impairments and/or neuropsychological symptoms, such as attention deficits, apraxia, mnestic dysfunction, executive dysfunction, hemineglect, aphasia and/or psychiatric symptoms such as

depression anxiety or hallucination. Often, not a single symptom but a combination of several symptoms is found.

Symptoms- motor deficits

For present experiments movement deficits after stroke are especially important. Movement deficits in the upper and/or lower extremity are one of the most common and devastating disabilities following a stroke. More than 50% of surviving patients are left with residual motor deficits, especially affecting the hand (Duncan et al., 1992). Motor function of the limbs is often affected in case the stroke is located in the circulation areas of A. carotis interna, A. cerebri media, or A. cerebri anterior which supply the motor cortex. Motor disabilities do not only result in reduction of working efficacy but also in compromise of activities of daily living such as dressing, bathing, self-care, and writing, thus reducing functional independence (Whitall et al., 2003).
In the present experiments it is focused on reorganization in the hand motor performance because motor function of the arms and hands can be used to model recovery processes after stroke (Rossini et al., 2003).

The present work focuses on motor deficits in patients with cortical or subcortical stroke.

I.1.2 Current Therapeutic Concepts

A stroke patient undergoes several phases of professional treatment: emergency team, intensive care unit/stroke unit, early rehabilitation, and late rehabilitation. In particular, the establishment of centers specialized in the treatment of acute stroke patients in recent years, has substantially improved the clinical outcome of these patients (Treib et al., 2000). These so-called “stroke units” follow a multiprofessional concept engaging specialists in neurology, radiology, internal medicine, psychology, nursing, physiotherapy, vaso- and neurosurgery. Nevertheless stroke is a disease with limited treatment options.

I.1.2.1 Treatment acute phase

The acute phase after stroke onset is dominated by life saving and stabilizing measures if possible in an intensive care environment. The further therapeutic intervention depends on the cause of the stroke. For the ischemic stroke the introduction of systemic lysis with recombinant tissue plasminogen activator (rtPA), specifically targeting the stroke-causing clot has added some benefit (summarized in Hacke et al., 2004). Preliminary data also suggest a potential benefit for local lysis therapy using intraarterial application of prourokinase (del Zoppo et al., 1998; Jahan & Vinuela, 2003; del Zoppo 2004). However, although lysis therapy in stroke has brought some success, it is restricted to a limited patient subgroup (e.g., with very low bleeding risk) and it can only be used in a short time period after the stroke onset (approx. 3h); best results are achieved within 90 minutes after the event (Hacke et al., 2004). Besides local fibrinolysis, interventional neuroradiology offers a range of further potential treatment options for acute stroke (Schroth et al., 2003). Its major impact, however, is rather found in primary and secondary prophylaxis of strokes. After a stroke or a TIA, 5 to 20% of patients will suffer from a second stroke per year (Wilterdink & Easton 1992).

I.1.2.2 Treatment subacute and chronic phase

In the subacute phase a so called secondary prevention is administered. The secondary prevention helps to prevent a recurrent stroke. Since a previous stroke is a high risk factor for a recurrent stroke and most of the risk factors which lead to the first stroke are still evident, a prophylactic therapeutic intervention is necessary. The secondary prevention depends on the cause of the first stroke (i.e. hypertension, heart disease, diabetes mellitus, heavy alcohol consumption) and of the type of the first stroke (ischemic or hemorrhagic). Early pharmaceutical secondary prophylaxis of ischemic stroke includes treatment with heparin (International Stroke Trial IST, 1997) and thrombocyte aggregation inhibitors, such as ASS (Hass et al.,

1989). All these medications bear the risk of bleeding complication. Depending on specific underlying condition also more invasive approaches, such as for example vaso-surgical interventions, may be beneficial. Applied adequately, these treatments may help to reduce the risk for a second stroke.

Recovery after stroke does not only result from spontaneous recovery of partially damaged brain tissue and passive adaptation of the brain to the lesion, therapeutic intervention may also contribute to recovery. Optimally, very soon after general stabilization patient undergo rehabilitative treatment to improve affected functions after stroke. This treatment depends on the specific deficits and includes e.g. physical therapy, occupational therapy, speech therapy and neuropsychological treatment.

I.1.2.3 Treatment of motor deficits

After central nervous system (CNS) injuries such as stroke, the initial deficit in motor function is followed by a spontaneous recovery of function in most cases. However, the degree of recovery is highly variable. Across patients recovery assumes an exponential shape, with a faster initial recovery followed by a slower asymptotic pattern. Individually, there is variability in shape and outcome of recovery. Motor recovery occurs predominantly in the first three months but may continue throughout the first year. Until recently, it had been unclear whether interventions could improve function beyond the spontaneous process. In particular, spontaneous recovery of hand function plateaus in about 1 year, and most patients will remain at that level for the rest of their life (Katz 1966, Andrews 1981).

Although most stroke patients regain independence many fail to regain functional use of the impaired upper limb. Despite different therapeutic concepts and an increase in treatment studies the best practice for the rehabilitation of the upper limb is still unclear (for review, see Barreca et al., 2003).

Standard rehabilitative therapies subacute and chronic phase

To improve motor function, intensive, focused physical therapy can be successful. Major therapies for motor rehabilitation training include traditional physiotherapy, neurodevelopmental training (Bobath-method), proprioceptive neuromuscular facilitation, the Rood-method, the Brunnstrom-method and the Vojta-method (for review see Hummelsheim et al., 1993). Neuropsychological therapy contributes to motor recovery mainly by reducing attention deficits (incl. neglect) which make rehabilitation of motor function more difficult. As adjuvant to physical treatment, peripheral nerve stimulation, cortical stimulation, and pharmacological strategies may be considered for motor rehabilitation.

Experimental rehabilitative therapies subacute and chronic phase

In the absence of universally accepted successful treatments for motor disabilities in chronic stroke (Barreca et al., 2003), improving motor function outcome remains a major task for basic and translational research. Thus, despite the above treatment options in rehabilitation, the knowledge about how the CNS responds to injury has been translated into new treatment strategies for motor rehabilitation (for review see Taub et al., 2002), including constrained-induced (CI-) therapy (for review see Taub 1999), stimulation of peripheral nerves, so-called “somatosensory stimulation” (Johansson 1993; Powell 1999; Wong 1999; Conforto 2002), pharmacological interventions (for review see Goldstein 1999), and transient deafferentation of body parts proximal to the injured (Muellbacher 2002).

Constraint induced therapy (CI-Therapy)

In some cases, stroke leaves patients with an apparently permanent loss of function in upper extremity even though the limb is not completely paralyzed. This observation is similar to the studied nonuse of deafferented forelimb in monkeys. Therefore Taub and colleagues (Taub et al., 1993; Taub et al., 1999) applied a protocol, previously used to force monkeys to

overcome nonuse to a population of chronic stroke patients. This method forces utilization of the plegic limb by constraining the unaffected limb and an additional training of the affected limb. In a number of clinical trials, there has been behavioral improvement even in patients with chronic and apparently stable deficits. In fact, Liepert and others have shown that TMS maps of the weakened muscles increase in size in this circumstance showing that the expected cortical changes appear to be occurring (Liepert et al., 1998; Liepert, Bauder, et al., 2000a; Liepert, Storch, et al., 2000b).

Somatosensory Stimulation

A further promising therapeutic tool for rehabilition of motor deficits is somatosensory stimulation. A prolonged period of peripheral nerve stimulation increases excitability of related muscle representations in the motor cortex, as assessed with TMS (Ridding et al., 2000); Additionally, the motor output maps can change (Ridding et al., 2001). Sensory stimulation can be given in a number of ways, from passive movement to cutaneous stimulation with electrical devices, or even needles as in acupuncture. Stimulation of the pharynx may improve swallowing function (Hamdy et al., 2001) a technique often applied in rehabilitation. Conforto et al., (2002) studied the effect of median nerve stimulation on pinch muscle strength and found an improvement in muscle strength after a 2-hour period of nerve stimulation. The effect was found without any motor training and outlasted the stimulation period.

Pharmacological interventions

Another method to enhance functional recovery after stroke is the administration of drugs affecting specific central neurotransmitters. This method for improving rehabilitation is often combined with physical therapy. Numerous studies have indicated that a combination of drug therapy with physical therapy is necessary, drugs alone do not seem to be efficacious (Hallett 2002). The best-documented influence is with amphetamine and related noradrenergic agents (Feeney et al., 1993; Feeney et al., 1997;

Gladstone and Black 2000). First demonstrated to be valuable in a rat model, there are now several clinical trials showing that the addition of amphetamine to physical therapy is better than physical therapy alone. The amphetamine-effect on motor recovery is blocked when rats are restrained rather than given motor practice after drug administration (Feeney et al., 1982). The mechanism for this drug action is not entirely understood. Although it is possible that it has effect by relieving diaschisis, amphetamine also enhances plastic changes in motor learning situations in both animals (Feeney et al., 1982) and humans (Buetefisch et al., 2002; Sawaki et al., 2002). Buetefisch et al., (2002) documented a facilitatory effect of d-amphetamine on use dependent plasticity. Sawaki et al., (2002) found that administration of d-amphetamine combined with motor training could elicit use dependent plasticity in individuals unresponsive to training alone.

Transient deafferentation

Due to the specific relevance for the present work, this procedure is introduced in detail below in section “Deafferentation”.

I.2 Mechanisms underlying recovery

The mechanisms underlying plastic changes and, in particular, recovery after stroke, are not entirely understood. During the first days and weeks after stroke, part of the recovery processes responsible for improvement are resolutions of reversible pathophysiological events that follow brain injury such as edema and recovery in tissues which were ischemic but not fatally destroyed (Hallett 2001). An impressive amount of studies provide evidence that the adult non-human and human brain maintains the capacity for plastic change following lesions (for reviews see Merzenich & Kaas 1982; Kaas et al., 1983; Kaas, 1991) or during learning processes (for review Sanes & Donoghue 2000). Cortical plasticity can be defined as any process that leads to enduring change in cortical properties.

The neuronal basis for plasticity are changes in efficiency of existing synapses as well as morphological changes at synaptical level that can lead to dynamic changes in cortical receptive fields (see below). Cortical reorganization can be beneficial by contributing to desirable behavioural developments or unwanted, in cases like phantom pain (Flor et al., 1995).

I.2.1 Evidence from animal experiments

Animal research at first provided evidence, that the adult mammalian central nervous system has the capacity to reorganize after injury. Dramatic changes in the organization map of the primary somatosensory cortex (S1) occur after amputation and peripheral lesions. Following peripheral nerve lesion or digit amputation in adult monkeys, parts of the S1 that previously responded to the deafferented body parts became responsive to inputs from neighboring body parts (Merzenich;, 1983). These changes can be reversed after nerve regeneration (Wall et al., 1983). Studies with flying fox and primates have shown that reduction of sensory input from one limb results in bilateral cortical reorganization. The authors saw rapid changes in both somatosensory cortices (Calford & Tweedale, 1990).

Although initial studies suggested that the upper limit of cortical expansion is 1-2 mm (Merzenich et al., 1983), it is now known that long-standing amputation may result in cortical reorganization over a distance of up to 14 mm (Pons et al., 1991). Fusion of the skin of two adjacent digits in adult monkeys also led to reorganization of somatosensory representation. The cortical representation of the fused fingers in S1 changed from the normal discontinuity between two fingers to a more continuous representation resembling one finger (Allard 1991). Similar changes in the S1 with amputation have also been demonstrated in other animals such as cats, raccoons, rodents, and bats (see Kaas, 1991 for review).

In the motor system, changes in cortical representation also occur after peripheral injury. Following amputation or peripheral nerve lesions, the area from which stimulation evoked movements of the adjacent body parts enlarged and the threshold for eliciting these movements was reduced

(Donoghue and Sanes, 1988; Sanes et al., 1990). These changes began within hours after the motor nerve lesion (Sanes et al., 1988, Donoghue et al., 1990).

I.2.2 Evidence from human experimental studies

For humans, an extensive amount of literature has described plastic changes following lesions of the central and peripheral nervous system such as blindness (Pascual-Leone et al., 1993; 1995; Cohen et al., 1997; 1999), or limb amputation (Cohen et al., 1991; 1991b; Flor et al., 1995; Chen et al., 1998).

Human experiments - evidence for synaptical changes

Some forms of neuroplasticity occur rapidly within minutes to hours. After peripheral nerve lesion or amputation the deafferented somatosensory cortex becomes responsive to sensory input from adjacent body parts (Merzenich et al., 1983; Flor et al., 1995; Silva et al., 1996). The representation in the motor cortex changes rapidly after nerve lesion (Sanes et al., 1988, Donoghue et al., 1990), after ischemic nerve block (Brasil-Neto et al., 1992,; Ziemann et al., 1998), or after motor practice (Ziemann et al., 2001).

Relatively fast processes of brain plasticity are modulations of synaptic efficacy due to strengthening or weakening of existing synapses such as long term potentiation (LTP) or long term depression (LTD) and the unmasking of existing but functionally irrelevant horizontal connections due to a removal of inhibition and a change in neuronal membrane excitability (for a review see Sanes & Donoghue 2000). These mechanisms rely on the concept that the motor cortex contains multiple overlapping motor representations. Although unmasking of horizontal connections provides means for rapid dynamic output modulations, processes like LTP and LTD provide more stable changes.

Human experiments - evidence for representational changes

Beyond this acute period of recovery, only functionally significant plasticity is likely to be responsible for further recovery. Slower processes then those described above, accompanied by changes in cortical representation are sprouting of fibers from undamaged neurons and the formation of new synapses (Chen et al., 2002). Reorganization of cortical representation occurs following a brain injury such as stroke (for review see Hallett, 2001; Frost, 2003) and there is growing evidence that the return of function is largely attributable to adaptive plasticity in the remaining cortical and subcortical motor apparatus (Chollet et al., 1991, Liepert et al., 2000).

Mechanisms underlying use dependent plasticity in human motor cortex have been investigated by using TMS and CNS active drugs that interfere with synaptic plasticity (Butefisch et al., 2000). TMS of the motor cortex has been used to evoke isolated and directionally consistent thumb movement followed by practicing voluntary thumb movement in opposite to baseline direction. The endpoint measure has been the magnitude of training induced directional changes in TMS evoked thumb movements. Use dependent plasticity has been substantially reduced by lorazepam (Butefisch et al., 2000), a drug that enhances $GABA_A$ receptor function and blocks the induction of LTP (Buetefisch, 2004). Therefore, it can be assumed that GABAergic inhibition is a mechanism active in use dependent plasticity in the intact human motor cortex. Other authors also have identified GABAergic inhibition as an important mechanism for plastic changes in human motor cortex. Brasil-Neto et al., (1993) have induced transient deafferentation of the forearm by inflating a blood pressure cuff above systolic blood pressure. This procedure resulted in a rapid increase of the motor cortical output to muscles proximal to the ischemic nerve block. The levels of GABA have been quickly reduced within minutes of deafferentation (Levy et al., 2002). In chronic stroke patients, deafferentation of the proximal arm and increased training has induced improvement of hand function and changed motor output of cortical representation of hand muscles involved in training movements (Muellbacher et al., 2002). The latter study gives evidence that GABAergic

inhibition as mechanism of plastic changes in human motor cortex is functionally relevant for motor recovery in chronic stroke.

However, it can be assumed that cortical reorganization may occur rapidly. Important mechanisms involve the unmasking of horizontal connections a modulation of GABAergic inhibition and changes in synaptic efficiency as well as anatomical alterations (axonal sprouting, recruitment of brain tissue surrounding lesion or in homotopic areas of the non-affected hemisphere).

I.3 Brain areas mediating recovery in stroke

Although recent neurological research has shed light on the brain's mechanisms of self-repair after stroke, the substrates mediating recovery of motor function after stroke are still incompletely understood (Frost, 2003; Werhahn et al., 2003; Ward et al., 2003).

1.3.1 Relevance of nonaffected (ipsilateral) hemisphere

Several studies have demonstrated an influence of ipsilateral motor areas (areas in the nonaffected hemisphere) for recovery of motor functions after stroke and the interpretation has been put forward that the intact hemisphere adaptively compensates for damaged regions (Fisher et al., 1992; Cao et al., 1998; Pineiro et al., 2001; Johansen-Berg et al., 2002).

Ipsilateral pathways are particularly important in recovery of functions with bilaterally representations. Hamdy et al., (1998b) found this bilateral representation for the process of swallowing. Swallowing problems are very common immediately after stroke but patients usually recover completely within weeks. This impressive capacity for recovery is likely to relate to how the area of the respective motor cortex is reorganized after stroke. In case of dysphagia the substrate for swallowing in the undamaged hemisphere increases the capacity for compensatory reorganization in the contralateral

hemisphere. This mechanism seems to be the reason for impressive recoveries (Hamdy et al., 1998a). Additionally, Muellbacher et al., (1999) found evidence for the important role of the intact hemisphere for recovery of lingual movements. They have used TMS of the motor cortex to study motor reorganization for control of the tongue after stroke. Based on their findings it has been postulated that activity in this region plays a crucial role in mediating functional recovery.

More important for the present experiments is the finding, that ipsilateral pathways are also relevant for recovery of functions without (primary) bilaterally representations. Functional imaging studies with mainly recovered patients following subcortical and cortical stroke have been reported. Chollet et al., (1991) have studied six patients with hemiplegic stroke from capsular infarction who had recovered full strength performing a thumb-to-finger opposition task with PET. Cao and collegues (1998) have studied eight hemiparetic patients suffering cortical stroke during a sequential finger opposition task with functional MRI. Cramer and collegues (1997) have analyzed ten well recovered stroke patients after cortical stroke during an index finger tapping task with functional MRI. All these brain imaging studies have demonstrated abnormal patterns of brain activation during movements of the affected hand including increased activation of ipsilateral motor areas and recruitment of additional sensory and secondary motor structures ususally not involved in the motor task. The authors have argued that the increased reliance on these motor areas represents an important component of motor recovery. Several case reports support the assumption of functional relevance of ipsilateral pathways for motor recovery after stroke (Ago et al., 2003; Song et al., 2005). Ago et al., (2003) described a case of a small lacunar infarct in the left corona radiata which caused deterioration in a pre-existing left hemiparesis that had resulted from an earlier right putaminal haemorrhage. Johansen-Berg et al., (2002) have provided evidence for the compensational function of ipsilateral activation for movement in stroke patients. They could slow simple reaction time finger movements with applying TMS over the ipsilateral primary motor and dorsal premotor cortex in stroke patients.

Taken together, the literature suggests that ipsilateral, i.e. intact, motor regions can - up to a limited degree and in certain circumstances - substitute for the function of the contralateral, damaged motor region.

I.3.2 Relevance of affected (contralateral) hemisphere

Several authors have argued that functionally significant recovery depends on reorganization within the affected (contralateral) hemisphere (Turton et al., 1996; Traversa et al., 1997; Weiller and Rijntjes, 1999; Hallett et al., 2001; Frost et al., 2003; Werhahn et al., 2003; Ward et al., 2003), with little functional relevance of ipsilateral activation (Meyer et al., 1995; Turton et al., 1996; Marshall et al., 2000). Several TMS-studies have shown that presence of contralateral MEPs early after stroke is a marker for good recovery (Turton et al., 1996). Rossini et al. demonstrated enlarged or relocated TMS maps of recovering muscles in the contralateral hemisphere. Indicating the importance of contralateral hemisphere plasticity for recovery after stroke (see Rossini et al., 2003 for review), Weiller et al., (1993) have analyzed the individual patterns of cerebral activation in eight patients with good stroke recovery compared with the pattern of a group of ten normal subjects. They have found additional activation of the ipsilateral sensorimotor cortex in patients with mirror movements of the unaffected hand, indicating that contralateral plasticity produces better recovery than ipsilateral plasticity. Studies with patients suffering congenital hemiparesis (Ragazzoni et al., 2002, Staudt et al., 2002) revealed severe impaired motor function in patients with ipsilateral cortico-motoneural output from the primary motor cortex of the unaffected hemisphere to the affected arm. These patients showed no MEPs in the paretic hand when TMS was applied over the affected hemisphere.

Although the precise substrate for recovery after stroke remains partly unknown, functional imaging provided important new information (for review see Calautti & Baron, 2003). A robust and coherent finding is an expansion and shift of SM1 activation after a motor system lesion, either cortical or subcortical. These findings may reflect the unmasking or disinhibition of preexisting but usually inactive representations or alternatively this

observation may reflect recruitments of neurons or connections in the affected hemisphere normally not devoted to motor functions.

I.3.3 Synopsis

Previously described neuroimaging and clinical studies (see I.3.1) led to the hypothesis that enhanced activity in the ipsilateral motor cortex plays an at least contributing role in the compensation of motor disabilities after chronic stroke.

However, several studies challenge this hypothesis. Werhahn et al., (2003a) have evaluated the role of the primary motor cortices on the recovered motor function after stroke. They have studied behavioral consequences of eliciting a transient reversible lesion using TMS. Twenty chronic stroke patients have been tested with single ischemic cerebral infarct which initially had caused complete paralysis. At the time of testing the patients had different degrees of motor recovery. The authors have shown that disruption of activity of ipsilateral M1 with TMS fails to delay simple reaction times in the paretic hand of chronic stroke patients. In another study, the magnitude of activation of the intact hemisphere with movements of the paretic hand did not correlate with functional recovery (Cao et al., 1998). For these reasons other studies have put forward the hypothesis: "… contralateral plasticity is better than ipsilateral plasticity in producing good improvement." (Hallett, 2001). Results from the above experiments (see I.3.2) support the hypothesis that recovery of motor function in well recovered chronic stroke patients relies predominantly on reorganized activity in the lesioned hemisphere, which is consistent with primate studies (Nudo, 2003).

The individual experimental characteristics of the respective studies may be a reason for the different findings described above. The studies used different techniques (PET, fMRI, TMS), the time from stroke ranged widely, so that patients in an acute stage and chronic stroke patients have been evaluated. In most studies the degree of recovery was variable between patients. Additionally, previous neuroimaging studies were contaminated,

since patients showed mirror movements in the intact hand when they intended to move only the paretic hand (Nelles et al., 1998).

Since the above studies found involvement of the ipsilateral, i.e. contralesional, hemisphere during movements of the affected hand in fMRI, Verleger and collegues (Verleger et al., 2003) have analyzed the functional relevance of this activation. Therefore, they have investigated the time course of ipsilateral and contralateral activation relative to the movement. Thirteen chronic stroke patients with subcortical lesion have been studied during a warned choice-response task with EEG. Following a normal contralateral activity 200 ms prior to the motor response, an additional ipsilateral activation has been found after response onset. This activation reached its maximum 200ms after response onset. This pattern did only occur in stroke patients and only during responses made with the affected hand. This time course of ipsilateral activation precludes its functional relevance for response initiation since it obviously occurred too late. Since the contralateral motor cortex was intact in these subcortically lesioned patients, the relevance of the demonstrated ipsilateral activity for maintaining, modifying or continuing the response is questionable. The authors argued that this activation might be prophylactic, in order that the unaffected hand may support the affected hand. They interpret this preparedness as a learned reflectory preactivation of the motor system opposite to lesioned one.

Some studies, especially those using TMS, provide evidence that ipsilateral corticomotoneuronal connections from the intact hemisphere to the paretic hand may contribute more to recovery in patients who experience poor motor recovery *(*Turton et al., 1996; Netz et al., 1997). Turton et al., (1996) investigated 21 patients in a 12 month longitudinal study. They examined the relationship between recovery and the presence of short-latency EMG-responses to TMS. The patients were divided into two groups according to their capability of performing a motor test (peg-test). The authors have found nine cases of ipsilateral responses in patients and none in healthy controls. The ipsilateral responses were more prevalent in patients with poorer recovery. Delveaux (Delvaux et al., 2003) have undertaken a 1 year follow up study of clinical and electrophysiological parameters of stroke patients with single ischemic lesion in the MCA. They found a good recovery

up to day 360 in patients whose affected motor cortex remained excitable at day one. Netz et al., (1997) have investigated motor evoked responses to focal TMS of 15 patients with hemiparesis after ischemic stroke. They described plastic changes in motor output organization in the unaffected hemisphere after a contralateral lesion but this changes did not correlate with clinical improvement. Neuroimaging studies also suggest that, in particular, poorly recovered patients show an increased activity in the nonaffected hemisphere. *(*Calautti et al., 2001)

It is now emerging that bihemispheric reorganization of motor networks during recovery is a dynamic process. It has been shown that recruitment (activation in areas not activated by movements of the healthy hand) persists in patients with lesions of M1 but decreases over time in patients with lesion sparing M1. In the latter patient group, an initial recruitment was followed by a more and more focused activation (Feydy et al., 2002). In those patients, no functional relevance of the different processes has been found; recruitment and focusing-processes have been found in cases of good and poor recovery. Marshall et al. (Marshall et al., 2000) have demonstrated an ipsilateral activation early after stroke but after regaining motor function ipsilateral activation disappeared and a contralateral pattern was found.

In summary, contribution of activity from the nonaffected hemisphere may be present in particular immediately after stroke (Tombari, 2004), in patients with poorer motor recovery (Turton et al., 1996; Netz et al., 1997; Johansen-Berg et al., 2002) or in bilaterally organized functions (Hamdy et al., 1998; Muellbacher et al., 1999). Plastic changes in the affected hemisphere are crucial and probably in general more efficient in producing the best recovery.

I.3.4 Role of Interhemispheric interaction - Concept of Hemispheric rivalry

Studies in primates have demonstrated anatomical connections between motor cortices of both hemispheres (Baumer et al., 2002). Interhemispheric interactions between hand areas of the primary motor cortex also have been documented in the intact (Ferbert et al., 1992; Gerloff et al., 1998; Meyer et al. 1998) and lesioned (Boroojerdi et al., 1996) human brain. The phenomenon seems to be transcallosally mediated since it is absent in patients with lesions of the corpus callosum (Meyer et al., 1998; Boroojerdi et al., 1998) although some subcortical mechanisms may also be involved (Gerloff 1998). The interhemispheric interaction between primary motor areas is strong and effective (Matsunami et al., 1984) although commissural fibers are relatively sparse (Rouiller et al., 1994). Additionally there is evidence for anatomical connections between premotor areas (Mochizuki et al., 2004a) and hemispheric interaction between dorsal pre motor cortex and the contralateral primary motor cortex (Mochizuki et al., 2004b). The possible interaction between the hemispheres could be either inhibitory or facilitory. An established method for measuring interhemispheric inhibition (IHI) is a TMS paradigm with a conditioning stimulus over the ipsilateral motor cortex reducing the contralateral motor evoked potentials generated by a test stimulus over the contralateral hemisphere. However, studies with TMS applied to the hand motor area in humans have revealed a predominantly inhibitory effect (Ferbert et al., 1992; Gerloff et al., 1998).

An emerging concept in neural plasticity is that of competition between the hemispheres (Boroojerdi et al., 1996; Traversa et al., 1998; Traversa et al., 2000; Liepert et al., 2000b; Shimizu et al., 2002; Plewnia et al., 2003; Schambra et al., 2003). It has been shown that each hemisphere exerts predominantly inhibitory influence on the homologous contralateral motor representations (M1) by its tight reciprocal connectivity (Plewnia et al., 2003; Schambra et al., 2003) resulting in a balanced interplay between both hemispheres. Electrophysiological studies with TMS show evidence that M1 stimulation of one hemisphere can lead to an inhibition of the contralateral motor cortex; (Di Lazzaro et al., 1999). In stroke patients, this inter-

hemispheric interplay is substantially disturbed (Boroojerdi et al., 1996; Traversa et al., 1998; Traversa et al., 2000; Liepert et al., 2000b) with (relatively) increased activity of the unaffected hemisphere (Weiller et al., 1993), resulting in a “hyperinhibition” of the affected hemisphere (Classen et al., 1997).

Murase et al., (2004) have measured the interhemispheric interactions serially at different time intervals, to evaluate interhemispheric inhibition (IHI) relative to the onset of voluntary movement in patients with subcortical stroke and healthy controls. Given the fact that interhemispheric interaction is disturbed in stroke patients and that balanced interhemispheric interactions are necessary for the generation of voluntary movements (Ferbert et al., 1992) differences in IHI between patients and healthy controls should be expected. Boroojerdi et al., (1996) have measured the IHI from the ipsilateral to the contralateral primary motor cortex at rest. They found no differences between chronic stroke patients and healthy controls. The experimental design allowed Murase et al., (2004) to show the dynamic nature of IHI from the contralateral hemisphere to the ipsilateral hemisphere in the process of generating a voluntary movement. They have found that the maximum IHI, short time after the GO-signal was comparable between patients and controls a finding consistent with Boroojerdi et al., (1996). Interestingly the IHI before movement onset was more pronounced in the paretic hand of patients compared to controls. Additionally Murase et al., (2004) have shown a time dependent modulation of IHI in healthy volunteers. The IHI decreased progressively as movement approached and turned into facilitation at movement onset. Stroke patients failed to show this modulation of IHI. The results of the above experiment show substantial differences in interhemispheric inhibition between healthy and stroke patients. This is a strong indicator for a maladaptive influence of this inhibition on motor function in stroke patients.

If there was indeed “hyperinhibition” from the healthy side onto the injured side that prevented the injured motor cortex from gaining more control, reducing excitability in the unaffected motor cortex and/or increasing excitability of the affected motor cortex would be beneficial for motor recovery.

I.4 Motor Tasks

In the present experiments motor performance and implicit motor learning in chronic stroke patients was evaluated.

I.4.1 Motor performance (experiment I) - Finger Tapping Task (FT)

The primary motor cortex (M1) is the principal unit for executing hand movements based on inputs provided by various other cortical, subcortical and cerebellar regions (Rizzolatti et al., 1998). In M1, neuronal populations that are active during individual movements of different fingers overlap extensively. The movement of a given finger appears to recruit a set of neurons distributed throughout the entire hand area (Schieber & Hibbard, 1993). Several experiments indicated that in addition to the contralateral primary motor cortex the ipsilateral primary motor cortex is involved in execution of unilateral finger movements (Gerloff et al., 1997). Finger sequence performance was disturbed when ipsilateral M1 was stimulated with repetitive TMS during the execution of especially more complex movement (Chen et al., 1997).

Several studies demonstrated increased regional cerebral blood flow (rCBF) in the ipsilateral primary motor cortex during unilateral finger movements (Rao et al., 1993; Sadato et al., 1996). Increases in rCBF are usually interpreted as enhanced excitatory neuronal activity but it could also indicate an inhibitory influence from the contralateral hemisphere. Studies with TMS demonstrated that that M1 stimulation of one hemisphere can induce an inhibition in the contralateral motor cortex (Ferbert et al., 1992). In addition to the activity of M1, somatosensory input is required for accurate motor performance (Pearson, 2000) and motor skill acquisition (Pavlides et al., 1993). Reduction of such input by local anesthesia impairs motor control (Aschersleben et al., 2001) as shown in patients with large-fiber sensory neuropathy who display characteristically abnormal motor behavior (Gordon et al., 1995). In patients with stroke, somatosensory deficits are associated with slower recovery of motor function (Reding & Potes, 1988). The major

source of somatosensory input is the primary sensory cortex with its direct connections to M1.

Finger tapping, as employed in the present study, can be described as a simple, repetitive, “open-loop” motor act. Rapid finger tapping is a task that relies predominantly on activity originating in the primary motor cortex (Rao et al., 1997; Jancke et al., 2004) and is conducted through fast corticospinal projections (Muller et al., 1992). Performance (“as fast and regularly as possible”) depends on the subjects’ intrinsically generated speed and rhythm. The number of taps within a given time interval and the velocity of key presses, represent the speed of simple movements at the finger joints (Ringendahl, 2002). Temporal regularity, as expressed by the coefficient of variation, reflects the integrity of the entire motor loop, including primary and supplementary motor areas, cerebellum (“internal timing system”), basal ganglia, and prefrontal cortex. The speed of simple movements at the hand level depends crucially on motor and premotor neuronal circuitry, and its fastest corticospinal efferents (Mueller, 1992). In children, the speed of simple repetitive movements depends on the maturation of the motor cortex and downstream corticospinal efferents, as assessed with TMS.

The finger tapping task is a well established motor task which is disturbed in hemiparetic patients (Shimoyama et al., 1990) it correlates well with the achievement of functional goals in patients with brain lesions undergoing rehabilitative treatments (Haaland et al., 1994; Prigatano et al., 1997) and is, therefore, especially suitable for this experiment.

I.4.2 Motor performance (experiment I) Control Task- Wrist Flexion (WF)

As control task to the finger tapping task an easy to perform motor task which predominantly engages forearm muscles (flexor carpi radialis) proximal to the anesthetic effect (wrist) was chosen.

I.4.3 Motor learning (experiment II) - Serial Reaction Time Task (SRTT)

Based on work in animals and humans, several brain structures, including the striatum, cerebellum, and motor cortical regions of the frontal lobe are involved in the acquisition of skilled motor behaviors (for review see Sanes & Donoghue, 2000). Muellbacher et al., (2001) have investigated learning related changes in M1 with TMS. They have found an increase in force and acceleration for a pinch task associated with an increase in motor evoked potentials (MEP) amplitudes in a muscle involved in the task. MEPs returned to baseline values after subjects had acquired the new skill. The changes in MEP have been observed only after TMS of M1 but not after direct stimulation of the corticospinal tract. These findings taken together with other studies (Nudo et al., 1996a; 1996b) demonstrate that some aspects of motor skill learning involve changes in M1, that these changes occur in the early acquisition phase of motor learning, and that they are task specific for rapid motor learning (Muellbacher, 2001).

The process of motor skill learning, which is of major interest for the present experiment, can be distinguished in explicit and implicit learning. In contrast to explicit learning, implicit learning is a form of behavioral improvement characterized as unintentional and non conscious. Implicit knowledge is expressed as a behavior that demonstrates performance improvement after previous exposure to a task. It seems that those two types of learning are independent (Willingham et al. 1989).

During a test for implicit learning, Grafton et al., (1992) have shown an increase in activity in the primary and supplementary motor area. Grafton et al., (1995) have studied implicit and explicit learning in healthy volunteers during a SRTT with PET. In one group, they investigated subjects performing the SRTT during the explicit learning phase in another group the impaired the explicit learning by implementing a distracting task. Thus, they were able to study implicit and explicit learning separately. In the implicit learning phase, the contralateral primary motor cortex (M1), the supplementary motor area (SMA) putamen and basal ganglia showed activity. In the explicit learning phase the ipsilateral dorsolateral prefrontal cortex, the premotor cortex and the parietal cortex bilaterally were active.

Now it is known that not only different cortical regions are involved in implicit and explicit motor learning; a growing body of literature showed evidence that learning processes involve various regions in a dynamical way. Grafton et al., (1995) showed an increased activity (increase in regional cerebral blood flow) in the primary motor cortex, the supplementary motor cortex and the thalamus during acquisition of implicit knowledge. After the task was explicitly learned the cortical motor outputs returned to baseline and other brain structures became more active during the execution of the task. Interestingly complete explicit knowledge was crucial for the change in cortical output. This is an indication that the different learning processes rely on different neuronal correlates in the brain. Pascual-Leone et al., (1994) have found - in a variation of the serial reaction time task (SRTT) - a correlation between improvement in reaction times (RT) during implicit learning and an enlargement in maps of cortical motor outputs to the muscles involved in the task as well as an increase in the intensity of signals within those maps. The maps of cortical outputs returned to baseline within three blocks after acquisition of explicit knowledge.

It has been shown that following stroke patients retain the ability to learn new motor skills. In most of these studies patients had explicit knowledge about the task and feedback about there performance. Boyd & Winstein, (2001) found implicit learning in stroke patients severely impaired without explicit knowledge. Even under conditions of extended practice they found no implicit learning in stroke patients, only providing explicit knowledge prior to task resulted in implicit motor sequence learning.

To study motor skill learning in animals or humans usually a reduction of reaction time or a change in movement kinematics is measured. Motor skill learning then can be defined as a change in the movement characteristic or a change in movement times (Hallett & Grafman, 1997). One part of the motor learning process for complex movement is to learn the order of a number of components with sequential elements. The serial reaction time task (SRTT) (Nissen & Bullemer, 1987), chosen for this experiment appears to be a good paradigm to study motor learning of sequences. The SRTT is a choice reaction time task with four possible responses. The response is made by key presses with four different fingers. A stimulus on a screen indicates

which response is the correct one. Thus this task requires smooth co-articulation of finger movements into a specific sequence and visual- motor integration. The completion of each response triggers the next stimulus. The stimuli are in a repeating sequence, one sequence usually consists of 12 or 10 stimuli. The subjects are naïve and perform finger movements repetitively without being aware of a sequential order. With practice at the task the responses became faster even if the subject has no conscious recognition of the repeating sequence. So far, the process reflects an implicit learning process. If the process continues with further practice the knowledge becomes explicit. The healthy subjects recognize that there is a sequence but are not able to specify the sequence. To a later stage the healthy subjects can even specify the sequence - the knowledge has become declarative. So the next stimulus can be anticipated by knowing the sequence. This task involves implicite as well as in the end explicit learning. To evaluate implicite learning, changes in reaction time between a random sequence and sequential patterns will be measured. For the task, as employed in the present experiment a 10-element sequence was randomly generated. The sequence consisted of key presses of 4 fingers in a complex nonconsecutive order (see Methods). During each experimental day the patients will learn different sequences of the same complexity.

I.5 Transient deafferentation

Transient deafferentation means the reversible depriving of cortical representation from their sensory inputs. This form of deafferentation can be induced by regional anaesthesia (Muellbacher et al., 2002) or, more commonly, ischemic nerve block (INB) by inflation of a blood pressure cuff above systolic pressure.

Transient deafferentation can induce rapid reorganization of the adult CNS and is a useful model to study short-term plasticity changes.

I.5.1 Ipsilateral deafferentation (deafferentation of adjacent body parts)

Merzenich et al., (1984) and Donoghue et al., (1990) have demonstrated that deafferentation of a limb was followed by reorganization of sensory as well as motor cortex. After experimental deafferentation of a digit of the hand, the representation of that digit was replaced by representation of adjacent digits (Merzenich et al., 1984). During epidural nerve block, neurons in the cat primary somatosensory cortex (S1) that originally respond to stimulation of the anesthetized area become responsive to stimulation of adjacent, unanesthetized areas. These changes reversed 2-4 hours after the nerve block. These findings suggest that cortical representation is dynamically modulated based on the pattern of afferent input and that the deafferented cortex area was taken over by adjacent cortex areas.

Work in the guest laboratory and elsewhere has indicated that deafferentation (with deefferentation) of a body part in a healthy human brain also can enhance cortical representation of adjacent body parts, an effect that is markedly increased by voluntary activity of that adjacent part (Ziemann et al., 1998).

Muellbacher et al., (2002) have applied the above principles of deafferentation to a population of stroke patients and investigated whether deafferentation of the upper arm helps improving hand function in the same limb. The patients suffered chronic stable weakness of their hand following stroke. The behavioral outcome of the study was peak pinch force and pinch acceleration in a finger-thumb-pinching task. With practice alone, patients rapidly improved in hand motor function as indicated by a significant increase in peak pinch force and pinch acceleration after the first practice episode. They showed both retention of this improvement and additional improvement during the second practice episode, but further practicing did not lead to additional improvement indicating that the behavioral gain had quickly reached a plateau by the second practice episode. Hand motor practice during regional anesthesia of the upper arm led to additional improvement in hand function as shown by a further significant increase in pinch force and pinch acceleration that had reached a plateau by the previous practice episodes. The lack of significant changes in pinch force in the intact

(contralateral) hand rules out nonspecific influences which possibly might bias behavioral test measurements.

The results of these study by Muellbacher et al., (2002) illustrates that principles of brain plasticity and especially the model of "competition among body parts for territory in the brain" have practical applications in stroke rehabilitation.

I.5.2 Contralateral deafferentation

Previous animal studies demonstrated that acute limb deafferentation results in reorganizational changes in the hemisphere contralateral to the deafferented one (Calford & Tweedale 1990).

Transient deafferentation in humans has been studied in a series of experiments (Brasil Neto, 1992; 1993; Sadato, 1995; Corwell 1997). Positron emission tomography (PET) studies have shown that during forearm ischemia, resting regional cerebral blood flow (rCBF) was increased in the sensorimotor cortex (SM1) bilaterally, suggesting that increased excitability of the motor cortex is associated with increased synaptic plasticity (Sadato, 1995).

Subsequent experiments in the guest lab demonstrated that changing the excitability of one motor cortex by either 1 Hz TMS stimulation (Schambra et al., 2002) or ischemic nerve block applied to the contralateral hand (Werhahn et al., 2002b) leads to lasting modulation of cortical excitability in the homonymous body part representation in the contralateral hemisphere. Werhahn et al (2002b) have evaluated the effect of ischemic nerve block (a method identical to the one used in the present experiments) on cortical excitability ipsilateral and contralateral to INB in healthy humans. In addition to changes in cortical excitability of muscles ipsilateral to INB they have found changes in cortical excitability of muscles contralateral to INB. The MEP amplitudes from the deafferented muscle (the muscle below the inflated tourniquet) decreased as a function of INB and MEP responses of the muscle proximal to the tourniquet increased during INB. In addition, the MEP

responses of the muscle contralateral to the deafferented also increased. The measured effect started about 15 minutes after cuff inflation at a time before complete motor block was achieved and began returning to baseline following tourniquet deflation.

A paired pulse stimulation with TMS revealed a significant decrease of interhemispheric inhibition during INB compared with pre-INB measurement. This reduction of interhemisperic inhibition could lead to a disinhibition of contralateral motor areas.

In an additional experiment Werhahn et al., (2002a) have demonstrated the behavioral relevance of the cortical changes during ischemic nerve block. In the somatosensory domain, ischemic nerve block applied to one hand leads to enhanced excitability in the somatosensory representation of the non-deafferented hand in the primary somatosensory cortex (Werhahn et al., 2002a). They measured tactile spatial acuity for the left hand during cutaneous anesthesia of the right hand in healthy volunteers. Limits of tactile spatial resolution were measured using Tactile Acuity Gratings in a grating orientation task (GOT) to assess the spatial accuracy. They demonstrated that right hand deafferentation resulted in better GOT performance in the left-hand index finger in 17 of 19 subjects. The performance returned to baseline after recovery from anesthesia. The anesthetic effect was specific since right foot anesthesia did not modify GOT thresholds at the left index finger. The deafferentation was required for the behavioral effect to occur since a sham condition (inflation of a tourniquet at the right forearm that was not sufficient enough to induce anesthesia at the hand) did not modify GOT thresholds at the left hand. Taken together this experiment provided evidence that deafferentation in one hand results in behavioral gains in tactile discriminative skills in the contralateral non-deafferented hand.

Taken together the above data suggest that deafferentation of a limb results in bilateral cortical reorganization. The most striking and interesting result, however, is that this well documented changes have behavioral consequences for healthy subjects as well as stroke patients (Werhahn et al., 2002a, Muellbacher et al., 2002). Overall, these data demonstrate that

deafferentation of one hand results in enhanced excitability and cortical processing in homonymous regions of the opposite hemisphere in healthy humans (Werhahn et al., 2002a). Additionally, Muellbacher et al., (2002) showed that the principles of brain plasticity induced by deafferentation are functionally relevant in rehabilitation of stroke patients. The basis for the present experiments is to combine these two ideas. The promising principle of boosting function of one hand due to decreasing of excitability of the cortical regions of the other hand was applied to patients with motor function deficits after stroke.

I.6 Ischemic nerve block

A promising tool for investigating influence of somatosensory input on motor function in patients is the method of ischemic nerve block. Short-term deprivation of sensory input leads to bilateral cortical reorganization and behavioral gains (see above). Plastic changes in human motor outputs occur also rapidly after disconnecting and reconnecting of the forearm with the CNS due to deafferentation (Brasil-Neto et al., 1992). Acute hand deafferentation can elicit a focal increase in excitability in the hand motor representation contralateral to the deafferented cortex. This excitability increase is supraspinal in origin, and most likely mediated by transcallosal interactions (direct interhemispheric connections linking primary motor and sensory cortices which exert inhibitory influences on homotopic sites in the contralateral hemisphere, or anatomical pathways mediating this effect include those linking the supplementary motor areas). The effect may be mediated by GABAergic transmission (Werhahn 2002b).

INB is accompanied by local discomfort beneath or distal to the tourniquet (Issberner et al., 1996). In the vast majority of cases this discomfort, which is proportional to the duration of INB, is described as bearable and subjects regard it as non-significant (Scott et al., 1998). Results of large studies (Derner et al., 1995; Michelson et al., 1996) using higher (300 mmHg and more) pressures of longer duration (1 hr and longer) than proposed in present experiments show that the procedure is safe and the incidence of

temporary side effects low (< 0.2 % or lower (Wakai et al., 2001)). These side effects include delay of recovery of muscle strength, post-ischemic swelling of the distal limb or skin discoloration due to subcutaneous microhematomas (petechias). With the conditions proposed for the present experiments (time period less than one hour and a cuff pressure of 20 mmHg suprasystolic), there have not been serious side (Pedowitz et al., 1991). Additionally, in the host research group, more than 100 subjects had been tested with this procedure in the past. Based on these reports, the extensive experience in the laboratory, and the fact that this procedure is used routinely in plastic surgery serious risk due to INB procedure was expected.

In the present experiments, the technique of ischemic nerve block, a noninvasive intervention, implemented by inflating a tourniquet around the forearm, was used to produce an acute, reversible deprivation of somatosensory input in the healthy forearm of chronic stroke patients, while they performed motor tasks with their paretic hand.

I.7 summary

It has been proposed that application of principles of neuroplasticity identified in animal models (Nudo et al., 1996) may improve chronic motor disability resulting from chronic stroke (Taub et al., 2002). In humans, hand anesthesia leads to bilateral cortical reorganization (Werhahn et al., 2002b) and, interestingly, to improvements in tactile discriminative skills in the non-anesthetized hand (Werhahn et al., 2002a), possibly through modulation of interhemispheric interactions (Werhahn et al., 2002b).

A crucial question for neurorehabilitation is whether cortical reorganization and behavioral gains due to ipsilateral deafferentation, demonstrated in animals (Calford and Tweedale 1990) and in healthy humans (Werhahn 2002a) can be translated into effective rehabilitative strategies geared to enhance functional recovery in patients with motor brain lesions. Given the existence of physiologically active interhemispheric interactions between motor and sensory cortices (Gerloff et al., 1998;

Werhahn et al., 2002b; Murase et al., 2004) it is not surprising that somatosensory input from one hand could influence motor function in the other hand in the healthy central nervous system (Werhahn et al., 2002a). Taken together the above data (see I.4.3) suggest that the potential for reorganization in the injured motor cortex may be diminished by hyperinhibition from the healthy side. Thus, activity in the healthy hemisphere might prevent the injured hemisphere from gaining more control. It is conceivable, then, that anesthetizing the healthy hand of chronic stroke patients may influence motor function in the paretic hand.

Following the concept of hemispheric rivalry, the following experiments were conducted to assess whether deafferentation of the healthy hand, known to increase excitability of the injured motor cortex, leads to improved motor performance and motor learning in the affected hand in chronic stroke patients. Therefore, the effects of cutaneous anesthesia of the healthy hand and healthy foot (control condition) on performance of a finger-tapping task and a forearm motor task (control task) implemented by the paretic arm in patients with chronic stroke were evaluated. Additionally a motor learning task under cutaneous anesthesia of the healthy hand and healthy foot (control condition) were evaluated. It is hypothesized that the enhanced excitability in homonymous representations of the ipsilateral side would lead to enhanced performance in simple motor tasks (speed in a finger tapping task) in the affected hand of chronic stroke patients, as compared to a control intervention (leg-INB), and control tasks (wrist flexion for experiment 1) and in motor learning in the affected hand of chronic stroke patients, as compared to a control condition.

I.8 Hypotheses

<u>Hypothesis 1:</u> Anesthesia of the intact hand by INB in chronic stroke patients will improve motor function as determined by finger tapping in the paretic hand.

<u>Hypothesis 2:</u> Anesthesia of the intact hand by INB in chronic stroke patients will improve implicit motor learning as determined by simple reaction time task (SRTT) in the paretic hand.

II. Patients and Methods

II.1 Patients

Patients were recruited from a volunteer patient list available at the NINDS, NIH. All patients on this list were recruited in the NINDS out-patient clinic where they had been tested for general eligibility for participating in scientific studies and were they received an MRI-scan. Patients were contacted and ask for participation. If the respective patient was interested in participating in the study, the protocol was sent to her/him. In case she/he was interested the patient signed the protocol, sent it back to the institution and received an appointment. All participants had to give their written informed consent to each experiment according to the declaration of Helsinki (http://www.wma.net/e/policy/17-c_e.html). The NINDS Institutional Review Board approved the study protocol (03-N-0135). Please see also Patient Information Form in supplement. Participation was voluntarily and consent could have been withdrawn at any time of the study. Traveling to the NIH and accommodation was paid for by the NIH. Patient inclusion was performed according to study protocol 03-N-0135 (see supplement). Inclusion- and exclusion criteria were as followed:

Inclusion criteria

- Chronic stroke patients (at least 12 month after the stroke)
- Single ischemic lesion
- Cortical or subcortical lesion
- Unilateral motor impairment
- Initially severe impaired motor function of the arm (MRC<2)
- At this time able to perform the task
- Without serious cognitive deficits (MMSE ≥ 21)

Exclusion criteria

- brainstem or cerebellar lesion
- a history of severe alcohol or drug abuse,
- psychiatric illness or severe language disturbances
- severe uncontrolled medical problems
- increased intracranial pressure as evaluated by clinical means
- history of loss of consciousness or epilepsy
- unstable cardiac dysrhythmia
- patients or subjects with h/o hyperthyroidism
- individuals receiving drugs acting primarily on the central nervous system
- pregnant patients

II.2 Methods Experiment I (Motor Performance Experiment)

II.2.1 Experimental design

All patients were asked to participate in three sessions, a NO-Intervention session (always first), an intervention session with the intervention arm-INB, and an intervention session with the intervention leg-INB. The latter two were randomized between patients. Each of the sessions was conducted on a separate day within one week. During the NO-Intervention session, patients were familiarized with the study conditions, and practiced the experimental tasks (finger tapping, wrist flexion, see below) three times. All conditions, in particular instructions and order of tasks, were identical to the intervention sessions except for the lack of INB. On the intervention sessions, subjects first completed a baseline measurement for each of the tasks. Then, the cuff was applied around the forearm or the calf (see below), and patients underwent two anesthetic measurements of the experimental tasks. Subsequently, the cuff was released, and after 20 minutes, a post anesthetic measurement was conducted. The order of the

study days for the intervention session leg-INB and intervention session arm-INB was randomized across subjects. During the experiments, additionally, several psychophysical measurements were taken. After the last session, patients were given a questionnaire about their expectations of their performance during the interventions. To assure standardized instructions for experimental and control interventions, instructions were given by a native speaker from tape before each task, and no additional encouragement was provided by the experimenter during the measurement.

Figure II.1 Experimental design

Figure A

No-Intervention session	**Intervention session arm anesthesia**	**Intervention session leg anesthesia**
Introduction & study outline	1. Baseline (psychophysical measurement and motor tasks)	1. Baseline (psychophysical measurement and motor tasks)
Practice motor task	**Arm anesthesia (INB)** (psychophysical measurement)	**Leg anesthesia (INB)** (psychophysical measurement)
Practice motor task	2. INB I (psychophysical measurement and motor tasks)	2. INB I (psychophysical measurement and motor tasks)
Practice motor task	3. INB II (psychophysical measurement and motor tasks)	3. INB II (psychophysical measurement and motor tasks)
	Anesthesia off (psychophysical measurement)	**Anesthesia off** (psychophysical measurement)
	4. Post INB (psychophysical measurement and motor tasks)	4. Post INB (psychophysical measurement and motor tasks)

Figure B

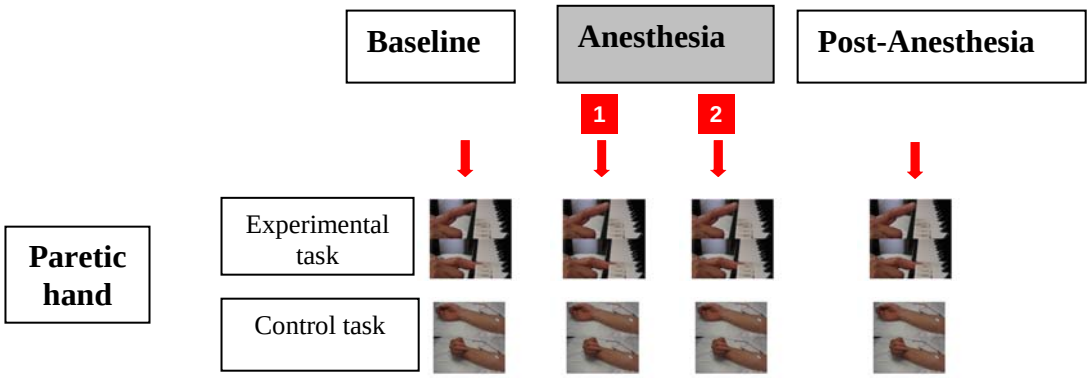


Fig. II.1: Experimental design, Figure A: summary of the experimental procedure for all three sessions (intervention sessions are randomized between patients), Figure B: design for a separate intervention session

II.2.2 Anesthetic procedure – repeated measure

Anesthesia was achieved by inducing an ischemic nerve block at the healthy wrist and calf, respectively in separate sessions. The experimenter elevated the patient's arm or leg for 3 min to drain venous blood. A conventional sphygmomanometer, 7.5 cm wide, was placed at the wrist (Intervention session arm-anesthesia) or the ankle (Intervention session leg anesthesia) and inflated to 40 mm Hg above systolic blood pressure (see figure II.2). The arm or leg was then returned to the horizontal position. Low-threshold mechanoreceptive function (perception thresholds to light touch) at the distal pad of the second finger or toe was assessed using von Frey filaments (Aesthesiometer, Stoelting Co, Wood Dale, IL, USA). Complete anesthesia was defined at the time when light-touch perception tested with a 4.56-mm diameter von Frey filament was abolished in5 out of 5 trials (for more detail see II.2.4.2). Measurement of motor tasks started immediately after cuff inflation. In both Intervention sessions, subjects rated the intensity and affective reaction to the tourniquet-induced discomfort on a questionnaire with a verbal numeric scale (VNS) ranging from 'no pain' to 'worst pain of life' on a scale from 1-6. Additionally, the level of fatigue and attention was assessed with a questionnaire. Psychophysical measurements (light touch perception, pulse, questionnaires) were taken six times in each Intervention

session before and after each of the four motor task measurements, and immediately after cuff release (See Figure II.1).

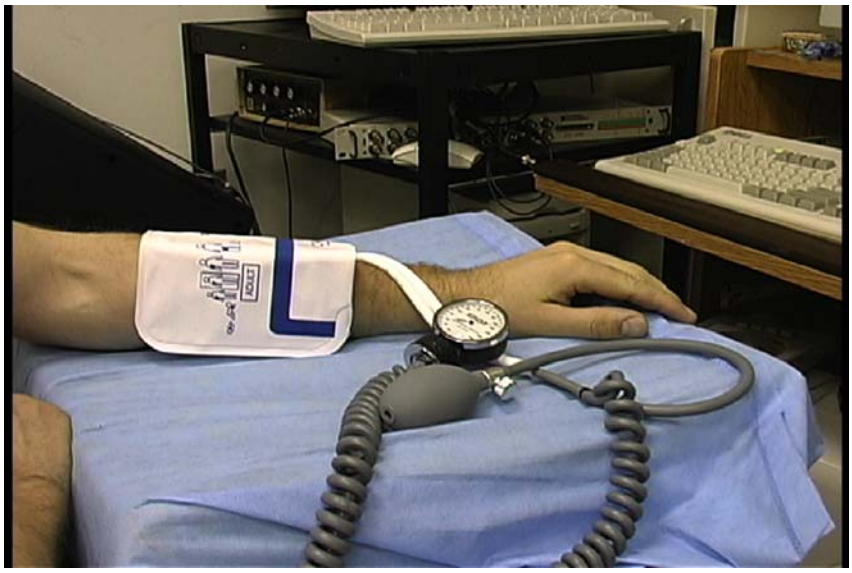


Figure II.2 A conventional sphygmomanometer, 7.5 cm wide, placed at the wrist and inflated to 40 mm Hg above individual systolic blood pressure.

II.2.3 Evaluated variables - Motor tasks

Two motor tasks were used. Finger tapping – a motor function – involving body parts distal to the deafferentation – served as experimental task. Wrist flexion - a motor function involving body parts proximal to the deafferentation - was used as control task.

II 2.3.1 Experimental task - Finger tapping

Patients were seated in front of an electronic keyboard (Yamaha pf85, Yamaha Inc.) in an upright position with the forearm supported by a cushion. Via MIDI-interface the keyboard was connected to a laboratory computer that recorded the outcome measures using Vision 1.4 (Opcode Systems Inc.).

Patients were instructed to press a specific key with the paretic index finger as fast and as regularly as possible for a total of 10 seconds (see Fig. II.3) (for detailed instruction see supplement). A break of fifty seconds separated the three repetitions.

The **outcome measures** of the finger tapping are:

- **tapping interval** [ms],
- **tapping force** exerted on the piano key [expressed on an arbitrary, ordinal scale with values ranging from 1-127], and
- **variability of tapping intervals** [expressed as coefficient of variance (standard deviation/ mean) of the tapping interval]

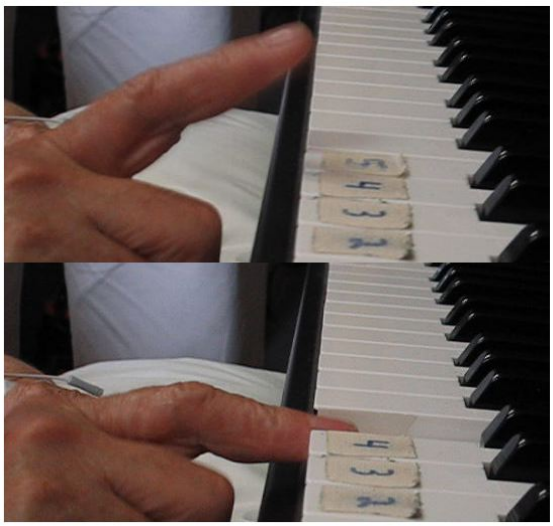


Fig. II.3: Motor task “finger tapping” was performed using an electronic keyboard connected to a laboratory computer.

II.2.3.2 Control task - Wrist flexion

Patients were seated 60 cm in front of a 20 inch-monitor with both arms supported by a cushion, and the paretic arm stabilized with a cast (Fig. II.4). Patients were instructed to focus on a cross in the center of the screen, and to bend their wrist as quickly as possible in response to a GO-signal presented on the monitor (for detailed instruction see supplement). Each trial

started with a visual warning signal (‘Get ready…’), followed at random intervals (2-6 seconds) by a GO-signal. Each measurement consisted of 23 wrist flexion trials (first three were practice-trials).

The **outcome measure** of the wrist flexion task is:

- The **reaction time** (RT in ms) defined as the time interval between the GO-signal and the onset of the electromyogram (EMG)-burst in the flexor carpi radialis muscle.

Fig. II.4: Wrist flexion was performed after a GO signal on the screen. Reaction time was measured using an electromyogram.

The EMG was recorded from silver-silver chloride electrodes positioned in a belly tendon montage on the skin overlying the flexor carpi radialis (50Hz-2khz, sampling rate 5KHz) from a Counterpoint Electromyograph (Dantec Electronics Sklovlunde, Denmark). See figure II.5.

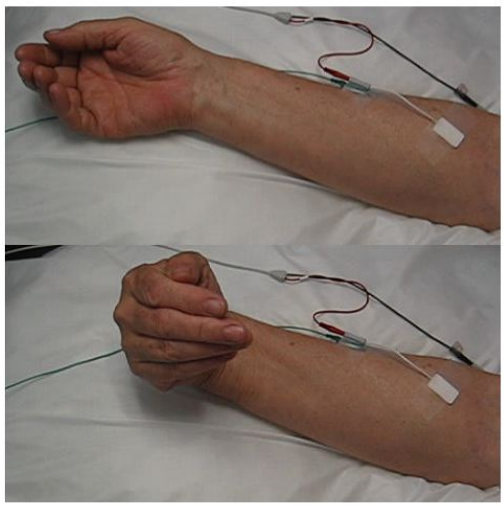


Fig. II.5: The EMG was recorded from electrodes positioned in on the skin overlying the flexor carpi radialis.

II.2.4 Additional measurements

Original forms for psychometric and psychophysical measurements as well as all questionnaires are attached in the supplements

II.2.4.1 Independent variables

Attention-fatigue-pain-questionnaire

Subjects were asked to rate their attention, fatigue, and pain level on visual analogue scales several times before, during and after anesthesia procedure to control the influence of alertness and attention to the task and the discomfort of the anesthetic procedure. Pain was assessed with a 6-point visual numeric scale ranging from 1 = no pain to 6 = worst pain of live. Fatigue was assessed with a 7-point visual analog scale ranging from 1 = falling asleep to 7 = can not sit still. Attention was assessed with a 7-point

visual analog scale ranging from 1 = inattentive to 7 = engrossed in task (for details see supplement).

II.2.4.2 Questionnaires and Physiological measurements

Mental state

Mini-mental state-examination (MMSE) (Folstein et al., 1974)

The MMSE is a brief, quantitative test of cognitive status in adults. It can be used to screen for cognitive impairment and to estimate the severity of cognitive impairment.

Handedness

Edinburgh Handedness Inventory (EHI) (Oldfield RC.; 1971)

Handedness was assessed using a 10-item qualitative questionnaire based on the EHI.

Motor function and spasticity

Fugl-Meyer-Score (FMS) (Fugl-Meyer AR et al.; 1975)

The Fugl-Meyer score is an established method for evaluation of physical performance in hemiplegic patients. For the described experiments only the upper extremity part of the test was performed to test shoulder, elbow and forearm function.

Modified Ashworth Scale (MAS) (Ashworth B. 1964)

The MAS is a formally evaluated ordinal Scale for grading spasticity. Spasticity is measured by grading the resistance encountered while passively moving a limb segment through its full range of movement briskly. The 6-point scale ranges from 0= no increase in muscle tone to 4= affected part rigid in flexion or extension.

Medical Research Council (MRC) grading system (HMSO. 1976)

The MRC scale is a 7-point ordinal scale for grading muscle strength with 0= no movement to 5= normal movement.

somatosensory perception

NIH-Stroke Scale/ part sensory function

The scale ranges from 0-2 to describe sensory function in stroke patients with 0= anaesthesia, 1= hypaesthesia, 2= full sensory function

Additional questionnaires

Questionnaire concerning patient data and medical history

A questionnaire with question concerning the patient's medical and social history was performed to control exclusion and inclusion criteria.

After-Questionnaire

Since every patient read an extensive consent form about the experiment (including scope), an after-questionnaire was performed to control effects of the patient's expectation concerning the experimental outcome. Therefore patients were ask to rate their expectations regarding the experimental outcome and their actual performance during the experiment for both experimental conditions at the end of the experiment.

Physiological measurements

Blood pressure

Blood pressure was measured at arm and leg at the beginning of the first experiment. Blood pressure needed to achieve anesthesia was determined (40 mmHG suprasystolic).

Pulse

Pulse (heart frequency) was checked manually before, during and after the anesthetic procedure to control the hydrostatic status of the patients.

Light touch perception

To test the anesthetic effect, light touch perception was analyzed using a 4.56-mm diameter von Frey Monofilament (Aesthesiometer, Stoelting Co, Wood Dale, IL, USA). The 4.56-mm diameter von Frey Monofilament cause a visible skin indentation has a target force of 4 N. Complete anesthesia was defined when light-touch perception was abolished in 5 out of 5 successive trials.

II.2.5 Detailed experimental procedure

The experiment included 3 sessions for each patient, one No-Intervention session, and 2 intervention sessions: the arm (target) anesthesia session, and the leg (control) anesthesia session. The order of anesthesia sessions was counterbalanced between subjects. Instructions and order of presentation of the tasks within each session were identical on each of the three days

<u>No Intervention session</u>

In the No-Intervention session, always the first day, patients were accustomed to experimental procedure and the experimental tasks. Patients were again informed about the experimental design and examined. Patients were asked to fill in all necessary forms and questionnaires. The experimental laboratory room was shown and open questions were answered. After the patient had given her/his written consent, medical history was evaluated to confirm and up-date data in the patient's neurological chart. Then MMS and EHI were performed to evaluate the patient's cognitive status and her/his handedness. Subsequently Examination of spasticity and motor function was performed, Fugl-Meyer-Score, Modified Ashworth Scale, and Medical research Council grading were assessed. Then detailed information about the experimental procedures was given. The patient was seated in front of a computer screen (see Methods Wrist Flexion). EMG electrodes were fixed and a convenient position in the chair was found. The wrist flexion

task was practiced. Special attention was paid to accurate performance according to the instructions and to the fact that EMG data documentation was not disturbed by movement/positioning artefacts. After removing the EMG connections, the patient was moved so that she/he reached the keyboard for the finger tapping task. After a detailed task description, the patient performed the finger tapping. Accurate performance was controlled. Then both wrist flexion task and finger tapping task were practiced again. Patients were informed that the next (third) motor task performance is performed under the same conditions as in the following intervention sessions. Instructions for the tasks were played from tape and no feedback was given to the patient.

Intervention session arm anesthesia

At the intervention session arm anesthesia, motor tasks of the paretic hand were measured 4 times: once as baseline measurement before cuff inflation, twice during anesthesia and, finally, 20 minutes after cuff release (post measurement). Anesthesia was achieved by inducing ischemic nerve block at the healthy wrist. Before each following measurement the perception thresholds to light touch at the distal pad of the second finger was assessed using von Frey Monofilaments. After cuff inflation the arm was covered with a blanket. The anesthetic task measurements were taken at the beginning of anesthesia, usually 10 minutes after cuff inflation, and before finishing the anesthesia usually 30 minutes after cuff inflation. The fourth measurement was obtained 20 minutes after cuff release, at a time when sensation from the hand had been recovered.

Before baseline task performance, psychophysical measurements concerning pain, attention and fatigue were assessed. Pulse, blood pressure and light-touch-perception were measured. Standardized instructions were given from tape. The Intervention arm-anesthesia session started with a baseline measurement without anesthesia for each motor task, always with the paretic hand. Identically to the NO-Intervention session the wrist flexion task was performed first and the finger-tapping-task was performed second. After baseline measurement, a blood pressure cuff was inflated around the

healthy wrist. The experimenter elevated the patient's arm for 3 min to drain venous blood. A conventional blood pressure cuff was placed around the wrist and inflated to 40 mm Hg above systolic blood pressure. Arm was then returned to a horizontal position and covered with a blanket. The patient answered the pain, attention & fatigue questionnaire again. Pulse and perception thresholds to light touch were assessed. About ten minutes after inflating the blood cuff, the patient started performing wrist flexion task and finger tapping task according to the known instruction from tape. After this first anesthetic measurement the patient – still under ongoing anesthetic condition - again answered pain, attention and fatigue questionnaires; and pulse and perception thresholds to light touch were measured. Then the second anesthetic measurement for both tasks was performed. Subsequently, the psychophysical questionnaires were answered again; and another physiological measurement for pulse and perception thresholds was undertaken. The air was then slowly released from the cuff. At this point and 20 minutes later another round of pain, attention & fatigue questionnaires and physiological measurements were performed. Finally the motor tasks were performed fort he fourth time (post measurement).

Intervention session leg anesthesia

Besides the anesthesia location the experimental procedure was identical to the arm anesthesia session. Patients received an anesthesia of the leg. After baseline measurement, a blood pressure cuff was inflated around the healthy calf. The experimenter elevated the patient's leg for 3 min to drain venous blood. A conventional blood pressure cuff was placed around the calf and inflated to 40 mm Hg above systolic blood pressure. Leg was then returned to a normal sitting position and covered with a blanket. The perception thresholds to light touch was assessed at the toe using von Frey Monofilaments. Motor tasks of the paretic hand were measured 4 times: once as baseline measurement before cuff inflation, twice during anesthesia and, finally, 20 minutes after cuff release (for details see above).

At the end of the third day patients were ask to rate their expectations concerning the experimental outcome and their actual performance (after-

questionnaire) during the experiment for both experimental conditions. Finally, the experimenter thanked the patient for participation.

II.2.6 Statistical data analysis

Before statistical analysis, data were blinded concerning experimental and control condition. Hereby, data analysis was performed blind to the intervention type. Normal distribution (Shapiro-Wilk test of normality) and homogeneity of variance (Bartlett's Chi-Square) was assessed for all data. To compare the effects of TIME (6 PA measurements, Fig II.2.B) and SITE of anesthesia (hand, leg) on the psychophysical measurements of fatigue, attention, and pain a separate $ANOVA_{RM,}$ with TIME as repeated measure, and SITE as between-subject factor was used. Similarly, separate $ANOVA_{RM}$ with TIME as repeated measures, and SITE as between-subject factor was used to compare the effects of TIME (4 motor task measurements, arrows in Fig II.2. B), and SITE of anesthesia (hand, foot) on tapping interval, tapping force, and variability of tapping intervals in the finger tapping task, and reaction time (RT) in the wrist flexion task. Practice effects were evaluated using one-way $ANOVA_{RM}$ with repeated measures TIME (5 determinations in the absence of anesthesia). Conditioned on significant F-values ($p < 0.05$), post hoc analyses were conducted using paired t-tests with Bonferroni correction.

According to degree of motor function (as assessed by Fugl- Meyer scale), patients were divided by median split into a group with good (n = 7) and a group with poor (n = 6) motor function. Correlation between Fugl-Meyer score and improvement in finger tapping during hand anesthesia was assessed with Spearman’s Rank Correlation. All data are expressed as mean $\pm$ SEM.

II.3 Methods experiment II (Motor learning Experiment)

After successful realization of experiment I, the second experiment was designed as a pilot study. Chronic stroke patients were asked to perform the implicit motor learning task “Serial Reaction Time Task” (Nissen and Bullemer, 1987) with their paretic hand during anesthesia of the healthy arm (target) and leg (control) and without anesthesia. Due to the more complex finger movement required in the motor learning task only seven patients fullfiled the inclusion criteria (especially, being able to perform the task).

II.3.1 Experimental design

All patients were asked to participate in three sessions, a NO-Intervention session (always last), and two intervention session with the intervention arm anesthesia, and the intervention leg anesthesia. The latter two were randomized between patients. Each of the sessions was conducted on a separate day within one week. The order of study days for the intervention sessions was randomized between patients. During each session 8 stimuli blocks were presented (see II.3.3). Psychophysical measurements were taken before each block of the serial reaction time task, and additionally immediately after cuff release for the intervention sessions. For the No intervention session only questionnaires were answered and no pulse or light touch-perception was measured.

Figure II.7A

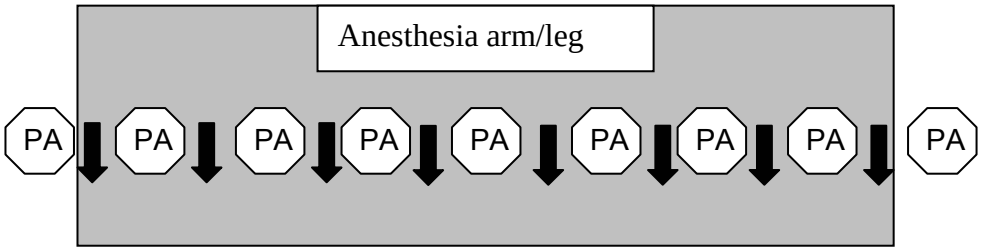


Figure II.7B

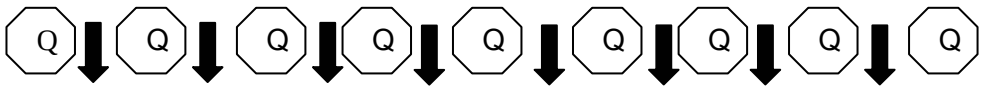
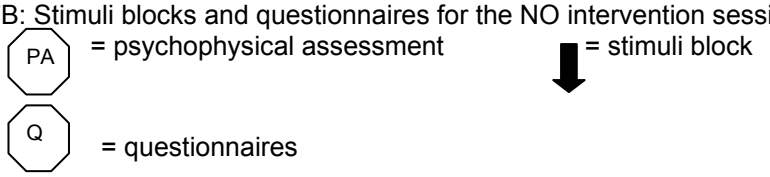


Fig. II.7A: Stimuli blocks and psychophysical measurements for the intervention sessions
Fig. II.7B: Stimuli blocks and questionnaires for the NO intervention sessions



II.3.2 Anesthetic procedure – repeated measure

Anesthesia was achieved by inducing ischemic nerve block using a conventional sphygmomanometer at the healthy wrist or ankle in separate sessions. This procedure was identical to experiment I (for details see II.2.2)

II.3.3 Experimental task - Serial Reaction Time Task (SRTT)

The patient performed a serial reaction time task with their paretic hand. For the task a speed pad for ambidextrous use (Belkin Nostromo n50 Speed pad, see figure II.8) was connected via USB-port to a laboratory computer that recorded the outcome measures using Superlab (Cedrus Corporation, Palo Alto, California, USA). A total of 800 stimuli per session and subject were presented via a computer screen in eight blocks of 100 stimuli with an inter stimulus interval (ISI) of 500ms. The blocks were divided by a 90 second break. The stimuli in blocks 1 and 6 were presented in random order, and the remaining blocks repeated a particular 10-element sequence ten times. The beginning and end of sequences were not marked. The repeated 10-element sequences were different for the three sessions but with the same complexity for each session (see sequences below). The complexity was accessed using the Kolmogoroff index (Lempel and Ziv, 1976). The reaction time differences between blocks 5 and 6 are indicative of

the amount of implicit knowledge the subject has acquired. To control for shifts in speed-accuracy-trade-off, the error rate differences between block 5 and 6 were measured. Patients were seated 60 cm in front of a 20 inch-monitor with both arms supported by a cushion. The speed pad was fixed at the surface of the table in a way that the patient could reach the pad with the paretic hand in a comfortable way. The patients were instructed to concentrate on the task and to press the key corresponding to the position of the asterisk on the screen. Instructions for the task were played from tape and no feedback was given to the patient.

Sequences	Day 1	1324324113
	Day2	3114234231
	Day3	2112412343

The **outcome measures** of the SRTT are:

- The **reaction time differences** between blocks 5 and 6
- The **error rate differences** between blocks 5 and 6

Fig. II.8 Speed pad and screen, the subject was instructed to press that key on his pad corresponding to the stimulus (asterisk) on the screen (in the given example “2”).

II.3.4 Additional measurements (questionnaires and physiological measurements)

The following questionnaires and measurements were identical to the ones in Experiment I: MMSE, Edinburgh handedness inventory (EHI), Fugl-Meyer-Score (FMS), Modified Ashworth Scale (MAS), Medical Research Council (MRC) grading system, blood pressure (arm, leg), pulse, anesthetic effect-light touch perception, pain, fatigue, attention, and questionnaire concerning patient data and medical history. For detailed information please see II.2.4 and supplement.

A specified After-Questionnaire was answered after completing the experiment to control the amount of explicit knowledge acquired, the patient answered a questionnaire which assessed successively the explicit knowledge. The questionnaires started with the question if the patients noticed anything and ended with playing the recognized sequence (see supplement).

II.3.5. Detailed experimental procedure

The experiment included three sessions a NO-intervention session, and 2 intervention sessions: the arm (target) anesthesia session, and the leg (control) anesthesia session. The order of anesthesia sessions was counterbalanced between subjects. Instructions and order of presentation of the tasks within each session were identical for the three sessions (see figure II.7).

On day 1, patients were examined and informed about the experiments. Patients were asked to fill in all necessary forms and questionnaires. The experimental laboratory was shown; and open questions were answered. After the patient had given her/his written consent, medical history was evaluated to confirm and up-date data in the patient's neurological chart. If necessary, MMS and EHI were performed to evaluate the patient's cognitive status and her/his handedness. Examination of

spasticity and motor function was performed. Then, detailed information about the forthcoming experimental procedures was given.

Intervention session arm anesthesia

The patient was seated in front of a computer screen (see Methods SRTT). Subsequently, a position convenient to the patient was found; and the experimenter gave detailed instruction concerning the SRTT. Afterwards anesthesia was achieved by inducing ischemic nerve block (see Methods INB) at the healthy wrist. After cuff inflation the arm was covered with a blanket. Then the task instruction (see II.3.3 and supplement) was given; and the first stimuli block was started. After first block, during a 90 second break, the perception thresholds to light touch at the distal pad of the second finger were assessed using von Frey Monofilaments. Psychophysical measurements concerning pain, attention, fatigue and pulse were assessed. Then the second stimuli block were started. During each subsequent break, before each stimuli block, the perception thresholds to light touch and the psychophysical measurements concerning pain, attention, fatigue and pulse were performed (see Fig. II.8). After experiments termination, patients were supervised for 20 more minutes and then the perception thresholds to light touch and the pulse were assessed.

Intervention session leg anesthesia

Besides the anesthesia location, the experimental procedure for the intervention session leg anesthesia was identical to the intervention session arm anesthesia. The perception thresholds to light touch was assessed at the toe using von Frey Monofilaments.

NO-Intervention session

Besides the anesthetic procedure the experimental procedure on day 3 was identical to those on day 1 and day 2. The patients performed the SRTT without anesthesia.

At the end of the day 3, patients were ask to answer a questionnaire to assess the amount of explicit knowledge about the repeating sequence the patients acquired (see supplement). Finally, the experimenter thanked the patient for participation.

II.3.6 Statistical data analysis

Before statistical analysis, data were blinded concerning experimental and control condition. Hereby, data analysis was performed blind to the intervention type. To compare effects of TIME (7 PA measurements, Fig II.8.) and SITE of anesthesia (arm, leg) on the measurements of pain, separate $ANOVA_{RM,}$ with TIME as repeated measure, and SITE as between-subject factor was used. Similarly, separate $ANOVA_{RM}$ with SITE as between-subject factor was used to evaluate the effect of SITE of anesthesia (arm, leg) on reaction time differences and error rate differences. Conditioned on significant F-values ($p<0.05$), post hoc testing was performed using paired t-test with Bonferroni correction**.**

Practice effects were evaluated using one-way $ANOVA_{RM}$ with repeated measures TIME (5 determinations in the absence of anesthesia). All data are expressed as mean $\pm$ SEM.

III. Results

III.1 Results Experiment I (Motor Performance Experiment)

III.1.1 Patients' characteristics

Thirteen patients with cerebral infarcts aged 63.8 ± 4.6 (range 23-83) years participated in the present study. Six patients were female, seven male. Eleven patients were right-handed, two patients left-handed. Patients had a single ischemic cerebral infarct, as documented by MRI: seven right hemispheric and six left hemispheric. Experiments were performed at least one year after the stroke (M= 6.5 years ± 1 year, range 2.7-13.3 years). All patients had initially a severe motor paresis after their stroke (below MRC grade 2). At the time of study, all patients had a residual motor deficit but were able to perform required movements with respect to the performed tasks. The only exception is patient I 11, who was motorically not able to perform the finger tapping task. Spasticity, as assessed by the Modified Ashworth Scale for Grading Spasticity, ranged from 0-3 (M = 2.0 ± 0.2)

At the time of the study the average muscle strength in hand and forearm muscles on the paretic side was 4.1 ± 0.8, as assessed by the MRC scale (range 2.3 to 4.8), and 83 ± 11 %, as assessed by the Fugl-Meyer scale (upper extremity section), see table III.1 for details. Somatosensory perception, which was impaired initially after the stroke in nine out of thirteen patients, had returned to normal in all but two subjects (no. I 2 and I 5), as assessed by NIH-SS scale. All patients had visual perception within normal limits and a normal Mini- Mental- State- Examination (M= 28.5 ± 1.8; range 26-30).

Ten patients out of thirteen initially recruited were able to complete the entire experimental procedure. One patient could not perform the finger tapping task (no. 11). One measurement arm-INB could not be acquired due to local discomfort beneath the tourniquet, a known phenomenon during ischemic nerve block (Issberner, Reh et al. 1996; Scott JN 1998). One measurement leg-INB was not conducted due to an adverse event during the

arm-INB session (mild petechial bleeding below the arm cuff, patient no. 6; although the petechia resolved completely within 4 days, the patient was excluded from further participation as a precaution). The final analysis for the finger tapping task was therefore conducted on 11 patients (finger tapping) and 12 patients (wrist flexion), respectively.

Table III 1. Clinical characteristics of stroke patients

Pat.	Age	Sex	Years post stroke	Day of arm anes-thesia	Lesion site	Motor function		
						MRC	FMS	MAS
I 1	79	M	5	2	**R**-centum semiovale	4.4	94%	1+
I 2	60	F	3	3	**L**-fronto-parietal cortex, corona radiata	3.8	82%	3
I 3	66	M	8.6	2	**L**- internal capsule, centrum semiovale	4.4	83%	1+
I 4	74	M	8.7	3	**R**-parietal and temporal cortex, corona radiata, centrum semiovale, thalamus	4.7	88%	2 to 3
I 5	54	F	5.4	2	**R**-basal ganglia	3.0	76%	2
I 6	75	F	2.7	2	**R**-lacunar infarct, putamen, corona radiata	4.7	89%	2
I 7	60	M	3.3	3	**L**-basal ganglia	4.5	79%	3

Continuation table III.1. Clinical characteristics of stroke patients

Pat.	Age	Sex	Years post stroke	Day of arm anes-thesia	Lesion site	Motor function		
						MRC	FMS	MAS
I 8	35	M	3.6	2	**R**-frontal operculum, putamen, corona radiata and insula	4.8	95%	2
I 9	76	F	13.3	3	**L**-internal capsule to centrum semiovale	4.0	85%	1+
I 10	23	M	4.3	2	**R**- medial temporal lobe, basal ganglia, corona radiata	3.5	76%	2
I 11	71	F	6.5	3	**L**-corona radiata	2.3	53%	3
I 12	83	M	7.5	2	**L**-basal ganglia	4.8	96%	0
I 13	65	F	12.5	3	**R**-basal ganglia, centrum semiovale, corona radiata	4.5	83%	1+ to 2
X ± SEM	**63.8 ± 4.6**	**6xF 7xM**	**6.5 ± 1**	**7x day2 6x day3**	**6x left hemisphere 7x right hemisphere**	**4.1 ± 0.2**	**83% ± 3.1**	**1.96 ± 0.2**

Abbr.: MRC: Medical Research Council grading system; MAS: Modified Ashworth Scale for Grading Spasticity; FMS: Fugl-Meyer-Score, F: Female; M: Male; L: left hemisphere; R: right hemisphere

III.1.2 Independent variables

Fatigue and attention

According to the psychophysical measurement, there was no significant difference between arm-INB days and leg-INB days (attention: F= 0.54; n. s.: fatigue: F= 0.38; n. s.), and no significant change in attention and fatigue levels over the course of one study day (fatigue arm: F = 0.95; n. s.; fatigue leg : F=0.67; n. s.: attention arm: F= 0.96; n. s.; attention leg: F= 0.17; n. s.).

Pain

$ANOVA_{RM}$ for pain showed significant effects of TIME (F = 24.6; p < 0.01**) but not SITE of anesthesia (F= 1.5; ns) or TIME x SITE of anesthesia interaction (F= 1.5; ns), reflecting a comparable significant increment in discomfort with hand and leg anesthesia (hand anesthesia: F= 24.64; p<0.01**; leg-anesthesia: F= 28.85; p<0.01**) that remitted completely after cuff deflation (Table III.3).

Measurement		Baseline	Anesthesia 1	Anesthesia 2	Anesthesia 3	Post-Anesthesia 1	Post-Anesthesia 2
hand anesthesia	fatigue	4.3 ± .0	4.3 ± .5	4.2±.72	4.3±.50	4.3±.72	4.5±.88
	attention	4.8 ± .6	4.5 ± .5	4.2±.84	4.3±.71	4.4±.71	4.7±.63
	pain	1.0 ± 0	2.1 ± 1.2	3.7±1.1	4.0±1.3	2.3±1.0	1.0±.00
leg anesthesia	fatigue	4.5 ± .1	4.3 ± .7	4.2±1.1	4.3±.75	4.3±.79	4.3±.69
	attention	4.8 ± .6	4.6 ± .7	4.6±1.2	4.6±.77	4.5±.79	4.6±.71
	pain	1.0 ± 0	2.4 ± 1.0	3.0±.87	3.3±1.1	1.9±1.0	1.0±.00

Table III.3: Fatigue, attention to task, and pain ratings, Abbr.: Baseline: baseline measurement; 1: first measurement during anesthesia; 2: second measurement during anesthesia: 3: third measurement during anesthesia, before cuff release; post anesthesia 1: measurement 5 min. after cuff release, post anesthesia 2: measurement 20 min. after cuff release

III.1.3 Repeated measure – Anesthesia

Seven of the 13 patients reached complete anesthesia by the time of their second measurement, and in five patient's perception was reduced to < 25% of pre- anesthesia levels. The mean duration (range) of tourniquet inflation was similar between sessions being 35.3 $\pm$ 4.3 min for the hand and 38.3 $\pm$ 4.1 min for the leg.

III.1.4 Expectations and self-evaluation of motor performance

Four patients expected that the anesthesia procedure could result in performance improvements; two expected a performance decline and 7 predicted no changes. None of the patients predicted differences between hand and leg anesthesia. After the experiments, three patients felt that their motor performance improved during hand anesthesia while three felt that it declined, and 7 did not report differences. Only four out of thirteen patients had correct hypothesis concerning the expected outcome of the experiment.

III.1.5 Results motor performance tasks

III.1.5.1 Effect of anesthesia on Finger Tapping Task

Tapping interval (TI)

Practice effect for TI

The repeated-measures ANOVA, with repeated measures TIME (practice1-day1/ practice2-day1/ practice3-day1/ Baseline day2/ Baseline-day3), showed no significant practice effect and no baseline differences between study days for tapping interval (F= 2.318; n. s.) (See Fig. III. 2).

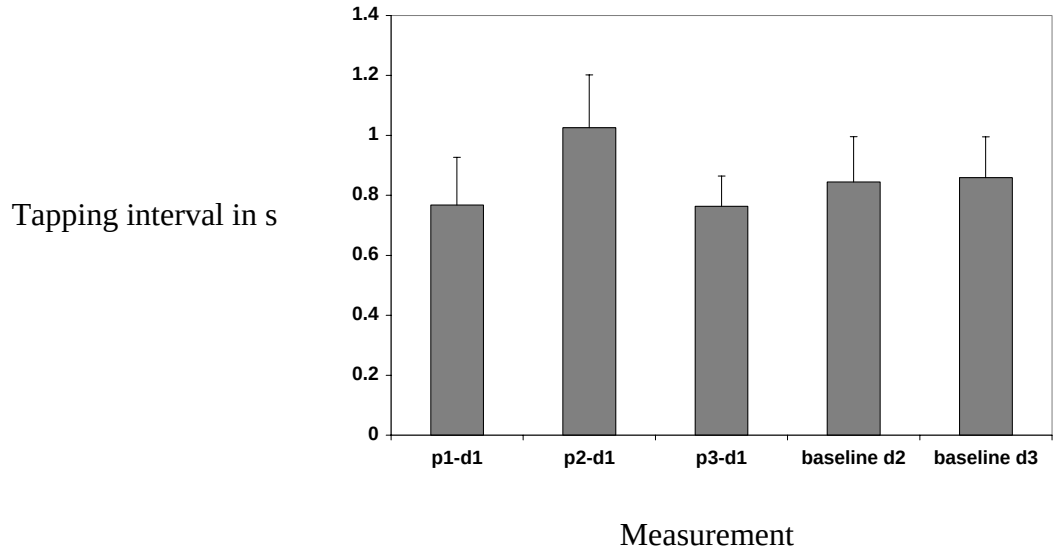


Fig.III.2: Practice effect for three practice measurements on day 1(d1-p1, d1-p2, d1-p3), and Baseline-measurements for day 2 and day 3 for TI.

Effect of anesthesia on motor performance for TI

$ANOVA_{RM}$ showed a significant TIME x SITE of anesthesia interaction on finger tapping intervals expressed in ms ($F = 2.8$; $p < 0.05$*, see supplement) and also expressed as % of baseline values ($F = 3.6$; $p < 0.05$*). Post-hoc testing revealed a significant reduction of finger tapping intervals in the paretic hand during anesthesia of the intact hand (first measurement, $p < .05$* and second measurement, $p < .01$**) but not during anesthesia of the intact leg (see Figure III.3).

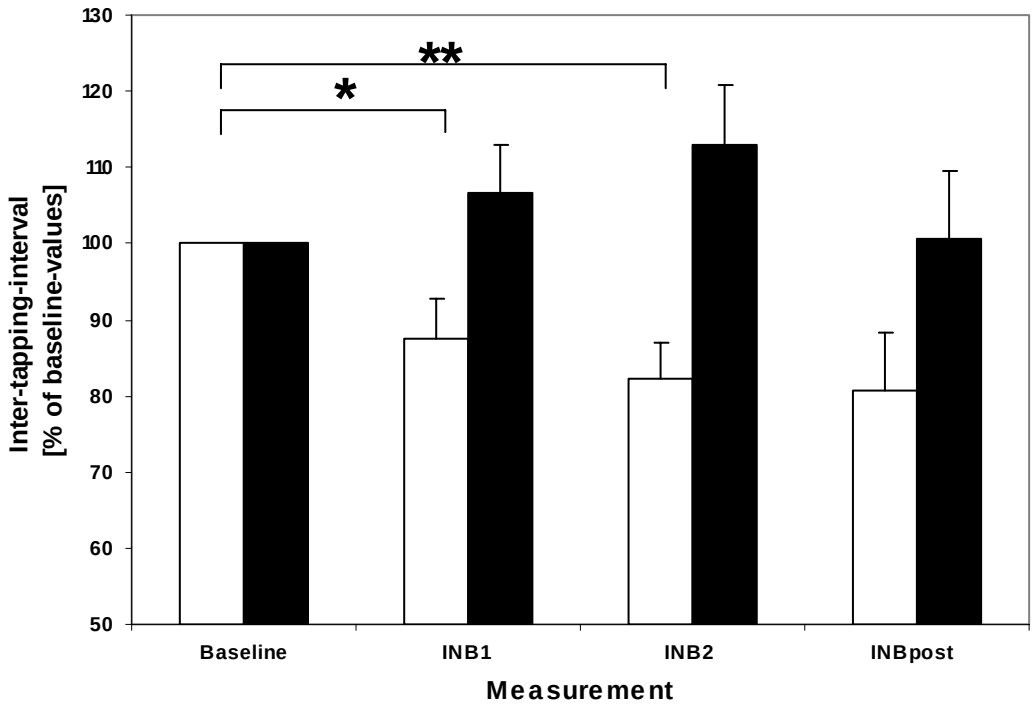


Fig. III.3: Improvement of finger tapping interval during hand anesthesia, Tapping interval during hand (white bars) and leg (black bars) anesthesia expressed in percent of baseline values , *: $p < 0.05$; **: $p < 0.01$; Baseline: measurement before anesthesia; INB1: 1st measurement during anesthesia; INB2: 2nd measurement during anesthesia; INBpost: measurement 20 minutes after release of cuff; (error bars indicate standard error of the mean), of note, the difference between baseline and INB2 leg was not significant

Time course of anesthetic effect for TI

The time course of the anesthetic effect after cuff release was formally only addressed 20 minutes after the end of the anesthetic procedure. Interestingly, the shortening in tapping intervals remained present for at least 20 minutes ($p < .05$*), but returned to about 89% of baseline values (ns) 24-48 hours later. Only patients with arm INB on day 2 could be considered for this analysis.

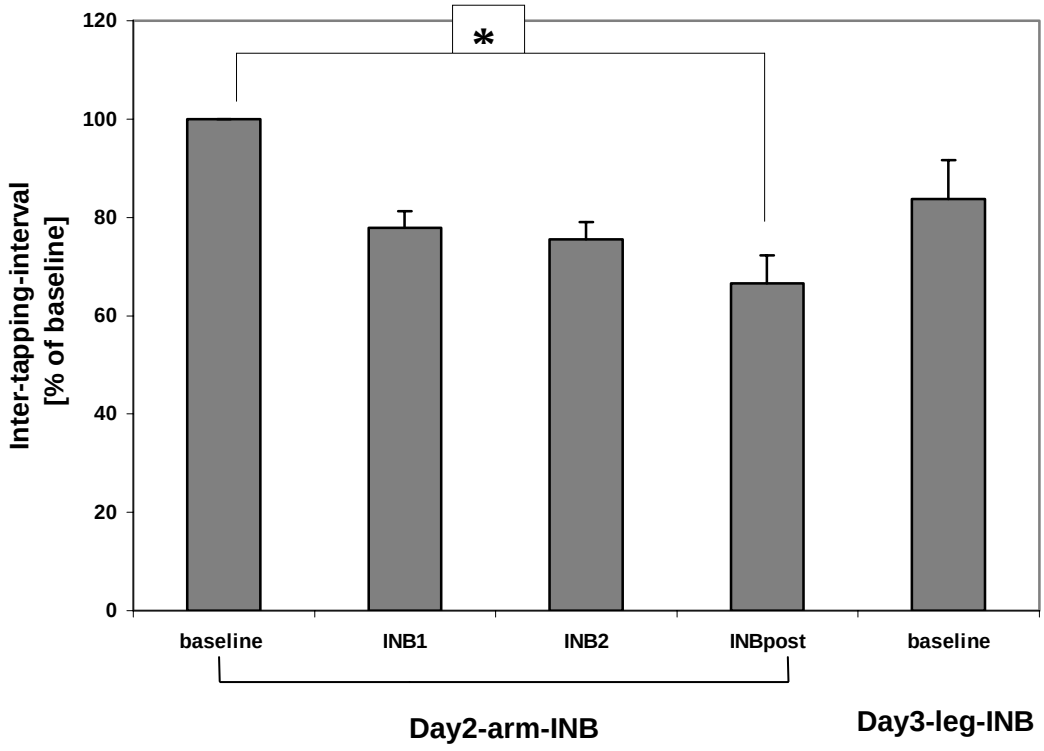


Fig. III.4: Time course of anesthetic effect for patients with arm anesthesia on day 2 and leg anesthesia on day 3.

Relations between improvements in TI and motor function

The TI was significantly longer for poorly recovered patients compared to well recovered patients (F= 10.2; p< 0.01**). Improvements in finger tapping intervals during hand anesthesia correlated well with performance in the Fugl-Meyer score only in the group with good motor function (r = .92; z = 2.78; p < .01** see Fig. III.5) and not in the group with poor motor function (r = .62; z = .73; p = .47).

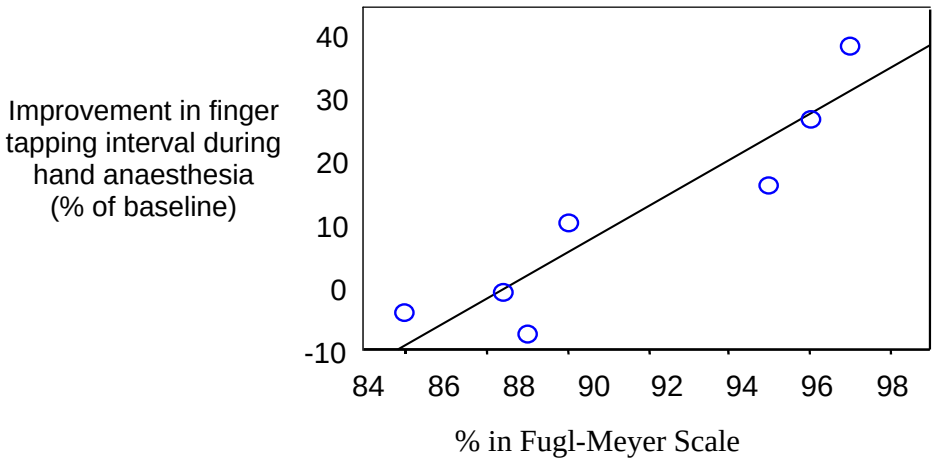


Fig.III.5: Relation between improvement in finger tapping interval and Fugl-Meyer score for patients with good motor function

Tapping Force (TF)

Practice effect for TF

The repeated-measures ANOVA, with repeated measures TIME (practice1-day1/ practice2-day1/ practice3-day1/ Baseline day2/ Baseline-day3), showed no significant practice effect and no baseline difference between study days for tapping force (F= .54; n. s.).

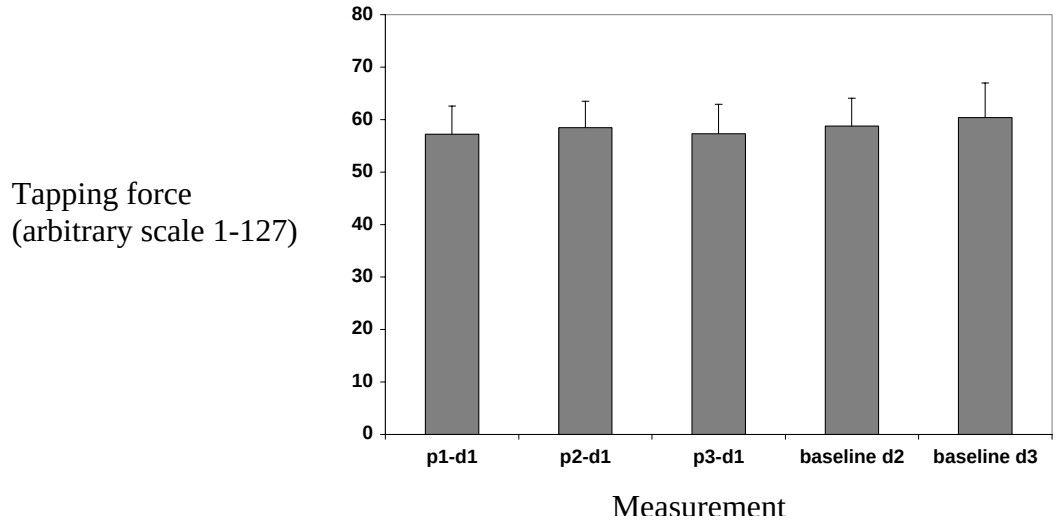


Fig. III.6: Practice effect for three practice measurements on day 1(d1-p1, d1-p2, d1-p3), and Baseline-measurements for day 2 and day 3 for TF.

Effect of anesthesia on motor performance for TF

The overall $ANOVA_{RM}$ showed no significant TIME x SITE of anesthesia interaction on finger tapping force (F= 1.8; n. s.).

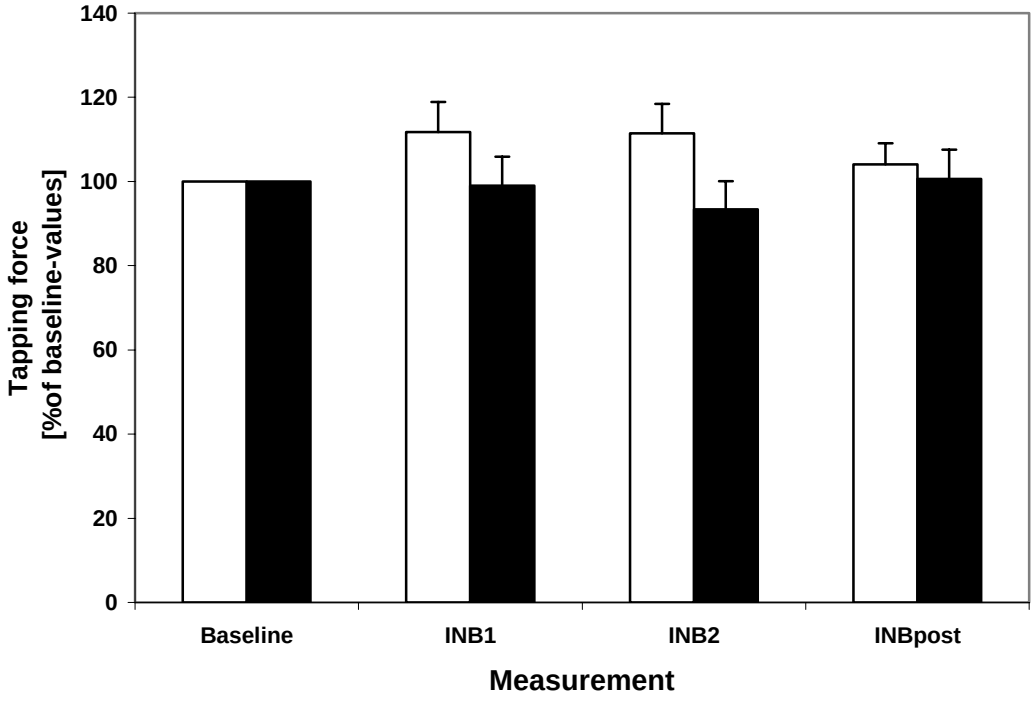


Fig. III. 7: Improvement of finger tapping force during hand anesthesia, Tapping force during hand (white bars) and leg (black bars) anesthesia expressed in percent of baseline values; Baseline: measurement before anesthesia; INB1: 1st measurement during anesthesia; INB2: 2nd measurement during anesthesia; INBpost: measurement 20 minutes after release of cuff; (error bars indicate standard error of the mean)

Tapping variability (TV)

Practice effect for TV

The repeated-measures ANOVA, with repeated measures TIME (practice1-day1/ practice2-day1/ practice3-day1/ Baseline day2/ Baseline-day3), showed no significant practice effect and no baseline difference between study days for tapping variability (F= .199; n. s.).

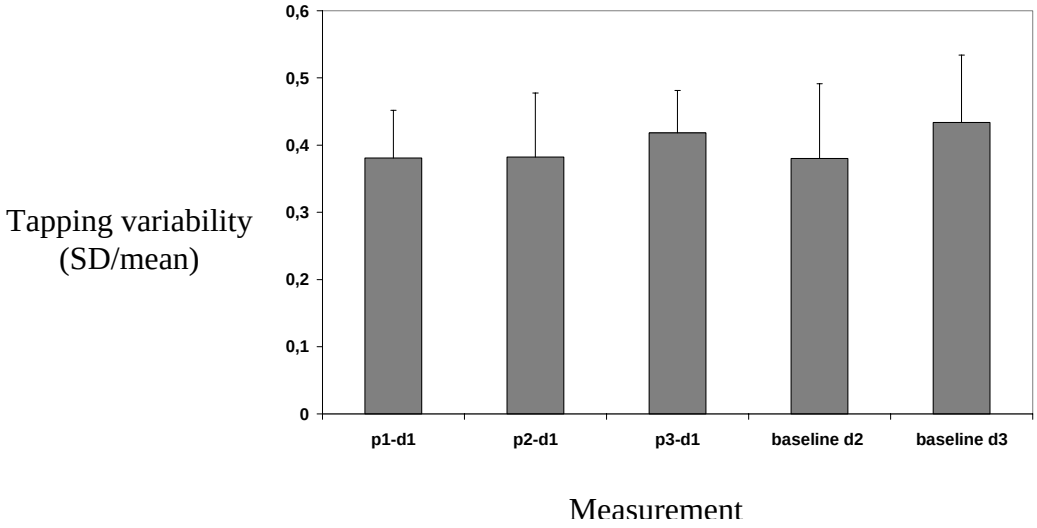


Fig. III.8: Practice effect for three practice measurements on day 1(d1-p1, d1-p2, d1-p3), and Baseline-measurements for day 2 and day 3 for TV.

Effect of anesthesia on motor performance for TV

The overall $ANOVA_{RM}$, showed no significant TIME x SITE of anesthesia interaction on finger tapping variability ($ANOVA_{RM}$: F= 1.9; n. s.).

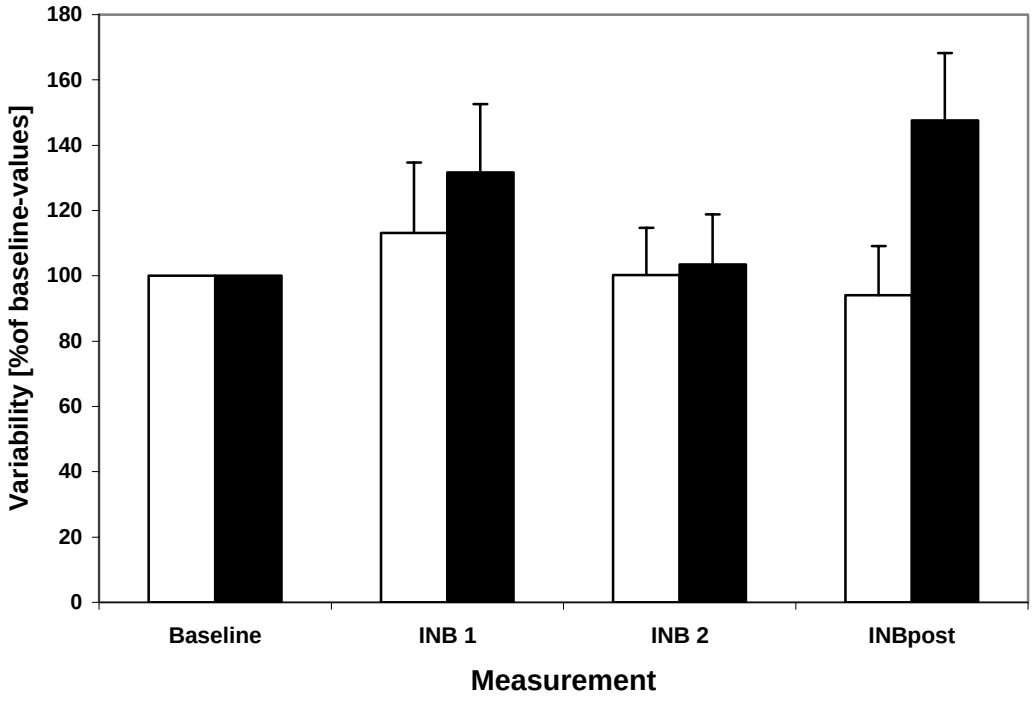


Fig. III.9: Improvement of finger tapping variability during hand anesthesia, Tapping variability during hand (white bars) and leg (black bars) anesthesia expressed in percent of baseline values, Baseline: measurement before anesthesia; INB1: 1st measurement during anesthesia; INB2: 2nd measurement during anesthesia; INBpost: measurement 20 minutes after release of cuff; (error bars indicate standard error of the mean)

III.1.5.2 Effect of anesthesia on Wrist Flexion Task (WF)

Practice effect for WF

The repeated-measures ANOVA, with repeated measures TIME (practice1-day1/ practice2-day1/ practice3-day1/ Baseline day2/ Baseline-day3), showed no significant practice effect and no baseline difference between study days for wrist flexion (F= .45; n. s.).

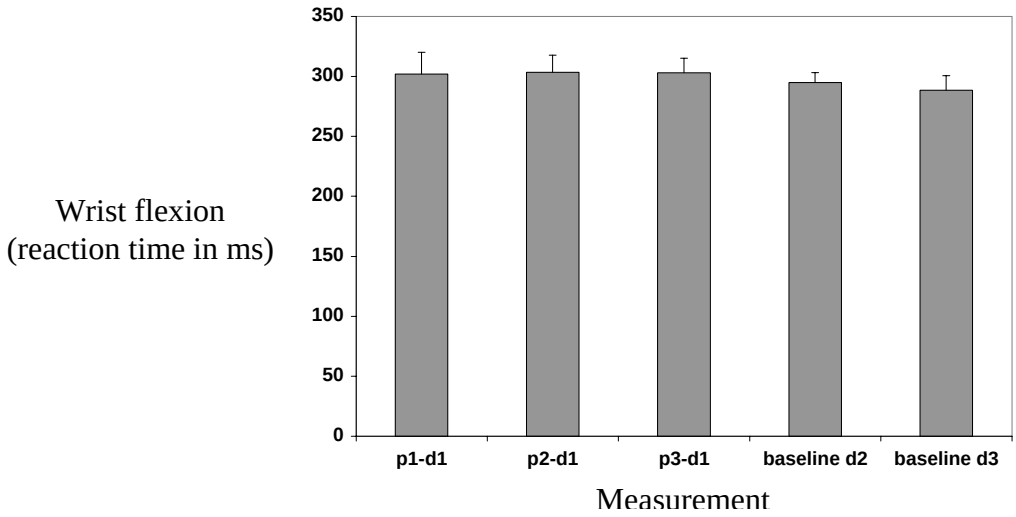


Fig. III.10: Practice effect for three practice measurements on day 1(d1-p1, d1-p2, d1-p3), and Baseline-measurements for day 2 and day 3 for WF.

Effect of anesthesia on motor performance for WF

The overall $ANOVA_{RM}$, showed no significant TIME x SITE of anesthesia interaction on wrist flexion reaction times ($ANOVA_{RM}$: F= 1.9; n. s.).

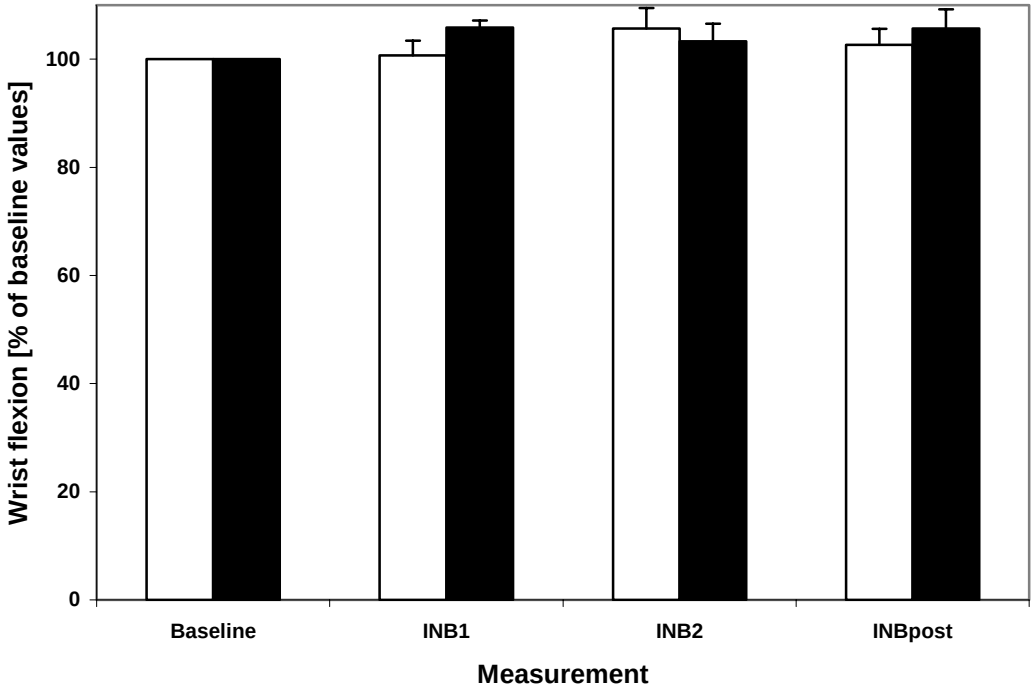


Fig. III.11: Improvement of wrist flexion-reaction time during hand anesthesia, reaction time during hand (white bars) and leg (black bars) anesthesia expressed in percent of baseline values, Baseline: measurement before anesthesia; INB1: 1st measurement during anesthesia; INB2: 2nd measurement during anesthesia; INBpost: measurement 20 minutes after release of cuff; (error bars indicate standard error of the mean)

III.2 Results Experiment II (Motor learning Experiment)

III.2.1 Patients' characteristics

Seven patients with cerebral infarcts aged 68 years ± 9.1 (SE) years (one of them female, all but one of them right handed) participated in the study. Patients had a single ischemic cerebral infarct, as documented by MRI (four right and three left hemispheric), and were tested at least 1 year after the stroke (M= 4.7; ± 2.3 SE). All patients initially had a severe motor paresis (below MRC grade 2). At the time of the study, they had a residual motor deficit but could perform movements with respect to the required tasks. Spasticity, as assessed by the Modified Ashworth Scale for Grading Spasticity, ranged from 0-2, (M= 0.7 ± 0.6 SE).
At the time of the study the average muscle strength in hand and forearm muscles on the paretic side, as assessed by the MRC scale ranged from 4.4 to 4.9 (M: 4.7 ± 0.2 SE), and from 83-96 % (M: 92.7 ± 3.3 SE), as assessed by the Fugl-Meyer scale (upper extremity section), see table III.4 for details. All patients had visual perception within normal limits and a normal Mini-Mental-State-Examination (M= 28.5 ± 1.8 SE)

There was an overlap of 4 patients between patient population of experiment I and experiment II (patients No 1, 3, 8, 12 of experiment I).

None of the seven patients recruited, was able to complete the entire experimental procedure. Due to local discomfort beneath the tourniquet during ischemic nerve block only seven stimuli blocks where presented to shorten the time of anesthetic procedure.

Table III.4 Clinical characteristics of stroke patients

Pat.	Age	Sex	Years post stroke	Day of arm anes-thesia	Lesion side and site	Motor function		
						MRC	FMS	MAS
II 1	79	M	5	1	**R**-centum semiovale	4.4	94%	1+
II 2	66	M	8.6	2	**L**- internal capsule, centrum semiovale	4.4	83%	1+
II 3	41	M	3.6	2	**R**-frontal operculum, putamen, corona radiata and insula	4.8	95%	2
II 4	83	M	7.5	1	**L**-basal ganglia	4.8	96%	0
II 5	70	M	2	1	**L-**occipito-posterior junction, centrum semiovale	4.7	91%	1+
II 6	72	F	1,5	1	**R**-internal capsule	4.9	95%	0
II 7	65	M	5	2	**R**-thalamus	4.9	95%	0
X ± SEM	**68± 9,1**	**6M/ 1F**	**4,7±2,3**	**4x day1 3x day2**	**4 R/ 3L**	**4,7±0,17**	**92,7±3,3**	**0,71±0,61**

Abbr.: MRC: Medical Research Council grading system; MAS: Modified Ashworth Scale for Grading Spasticity; FMS: Fugl-Meyer-Score, F: Female; M: Male; L: left hemisphere; R: right hemisphere

III.2.2 Independent variables

Fatigue and attention

Due to the discomfort and the high pain ratings (see below) the fatigue and attention ratings had to be canceled to shorten the time of anesthesia.

Pain

$ANOVA_{RM}$ for pain showed significant effects of TIME ($F = 14.8$, $p < 0.01$**) and SITE of anesthesia ($F= 10.8$; $p < 0.05$*) but no significant TIME x SITE of anesthesia interaction ($F= 1.7$; ns), reflecting a comparable significant increment in discomfort with hand and leg anesthesia, starting at a lower pain level for leg anesthesia. The pain remitted completely after cuff deflation.

			Anesthesia							
		Base-line	1	2	3	4	5	6	7	Post-anesthesia
Hand anesthesia	pain	1,0 ±0	3,1 ±0,6	3,3 ±0,6	3,4 ±0,8	3,6 ±0,9	4,1 ±0,8	4,2±0,7	4,4 ±0,7	1,0 ±0
Leg anesthesia	pain	1,0 ±0	2,6 ±1,3	2,7 ±1,0	3,1 ±1,1	3,1 ±0,9	3,1 ±0,9	3,5±0,8	4,0 ±0,8	1,0 ±0

Table III.6: Pain ratings before each block.

III.2.3 Repeated measure – anesthesia

Three of the seven patients reached complete anesthesia by the time after the seventh block and in four patient's perception was reduced to < 25% of pre- anesthesia levels. The mean duration (range) of tourniquet inflation was similar between sessions being 34.0 $\pm$ 2.7 min for the arm and 35.0 $\pm$ 3.3 min for the leg.

III.2.4 Questionnaire

None of the patients recognized a repeating sequence, so that no one could replicate the repeating sequence by writing it down or playing it on the speed pad. It can be assumed that no patient gained explicit knowledge about a repeating pattern in the task.

III.2.5 Results motor learning task

III.2.5.1 Effect of anesthesia on Serial Reaction Time Task (SRTT)

SRTT-error rate differences

The overall $ANOVA_{RM}$, showed no significant SITE of anesthesia effect on error rate differences (see supplement for error rate data), indicating no effect on the accuracy that might have account for reaction time differences.

SRTT-reaction time differences

The overall $ANOVA_{RM}$, showed a significant SITE of anesthesia effect on implicit motor learning ($ANOVA_{RM}$: $F= 4.4$; $p < .05$*; see Figure III.13).
Post hoc testing revealed a increased motor learning with the paretic hand at arm anesthesia measurement compared to the NO-Intervention condition ($p= .042$*) and a trend towards worsened motor learning at leg anesthesia measurement compared to the NO-Intervention condition ($p= .07$).

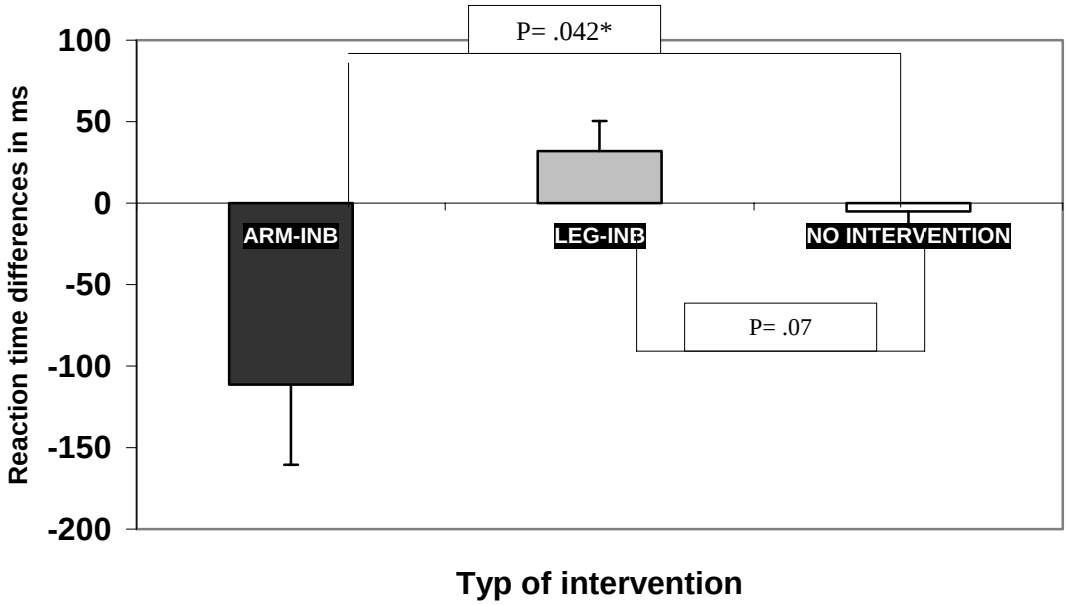


Fig.III.13: Average reaction time differences for reaction time of block 6 minus reaction time of block 5, negative values indicate implicit learning.

IV Discussion

Main results

The present data demonstrate that cutaneous anesthesia of the intact hand of chronic stroke patient's results in improvements in performance of the dynamic finger motor task as well as in improvements in implicit motor learning with the paretic hand.

In experiment I it was found that cutaneous anesthesia of the healthy hand led to a significant improvement in tapping speed (quantified by the tapping interval) in the paretic hand. The ANOVA-RM yielded a significant interaction TIME x SITE, demonstrating improved motor performance in the paretic hand with intact arm anesthesia relative to pre-anesthesia levels. Paired t-tests (arm-pre versus arm-anesthesia 2-measurement) revealed an even more significant effect in the absence of changes with leg anesthesia.

The results of the second experiment are in line with the first one. The analysis of the reaction time differences revealed significant better implicit learning for the paretic hand during anesthesia of the unaffected hand compared to a No-Intervention condition. As well as in experiment I a tendency for decreased performance during leg INB procedure compared to the No-Intervention condition was found. In fact in case of No-Intervention patient showed no implicit learning.

Methodological considerations - patients

Although most often the elderly are affected by condition such as stroke, ischemic infarcts are not uncommon in younger patients, in particular when suffering from predisposing conditions (see also introduction).

Here the patient group represents a typical cohort with mainly patients at least 60 years old. Recruited patients were well balanced with regard in gender and side of lesion. However, due to the nature of small experimental trials and to ensure a homonymous study group strict inclusion and exclusion

criteria were defined. Only patients with a single cerebral lesion (no brain stem or cerebellar lesion) participated. Patients at least one year after stroke participated in this study, thus, the patients tested were considered as suffering from chronic stroke. Furthermore all chronic stroke patients participating in this experiments were initially severely affected (MRC below 2) but, over time, recovered to the point that they were able to sufficiently perform the motor tasks. These inclusion criteria were necessary to exclude biases and, thus, to allow a meaningful experimental analysis.

Methodological considerations - placebo effect

The possibility of placebo effects was carefully considered at the design, experimental and analytical stages of the experiments. To control the effects of possible increased fatigue and decreased attentional load during the experimental procedure the patients in experiment I rated their fatigue and attention several times during the experiments. According to the ratings of experiment I there never was a significant change in attention and fatigue levels over one study day or a significant difference between days. Anesthesia of healthy arm healthy leg scored similarly in terms of fatigue, discomfort and attentional load. Thus, for experiment I it can be excluded that the above independent variables bias the results. For experiment II the fatigue and attention level could not be followed as often as planed during the experiment. The pain was rated so high that the experimental design had to be changed to minimize the time of INB and thereby to lower the discomfort for the patients. This fact and the fact that patients rated their pain level for arm anesthesia higher compared to leg anesthesia makes an interpretation more difficult.

All patients were naïve to the experimental hypothesis when entering and exiting the study. They were told that the effects of two interventions involving the healthy side, arm and leg anesthesia on their motor function are to evaluate. Instructions, played by a tape recorder, were identical for both interventions, and at the end of the study, patients were asked about their perception of changes in motor performance with both interventions: 7/13 felt

no change, 4/13 felt improvement, and 1/13 thought motor function declined during both arm and leg tourniquet inflation. None of the patients reported feeling performance differences between hand and leg anaesthesia. Given these results, it is unlikely that differences in motor performance detected in the experiment resulted from placebo effects.

Methodological considerations - anesthesia

Transient deafferentation in humans has been studied in several experiments (Brasil-Neto et al., 1993, Levy et al., 1998; Werhahn et al., 2002b). Deafferentation can be induced by regional anesthesia or ischemic nerve block (INB) with inflation of a blood pressure cuff above systolic pressure. An easy-to-perform procedure with only mild side effects was chosen to induce anesthesia, This INB procedure is known to elicit acute reversible deprivation of somatosensory input and functional changes in the contralateral (Brasil-Neto et al., 1992) as well as in the ipsilateral motor cortex (Werhahn et al., 2002b).

Although the pain during INB is described as bearable; and subjects have regarded it as non-significant (Scott et al., 1998) patients in the present experiments described the procedure as painful. Patients rated the pain intensity on a visual analogue scale (VAS) ranging from 1 to 7. This measurement has been shown to have good internal consistency, reliability, and objectivity (Chibnall JT 2001, Pain). The pain increased proportionally to the duration of INB. Pressure secondary to tourniquet inflation was a feature of both healthy arm (target) and healthy leg (control) anesthesia. In the first experiment both conditions, experimental (arm anaesthesia) as well as control condition (leg anaesthesia) scored similarly in terms of pain, both conditions are so far comparable; and thus, it can be excluded that the pain level explains the results. For the second experiment the pain also increased proportionally to the duration of INB. Here, in contrast to experiment I, the pain level for the experimental condition (hand anesthesia) scored significant higher compared to the pain level of the control condition (leg anesthesia). The pain during hand anesthesia in experiment II was so high that the light

touch perception was measured only at the end of the experiment to shorten the duration of tourniquet inflation. Since the experimental procedure for anesthesia was exactly the same in both experiments it can be assumed that the course of anesthesia was similar in both experiments.

It is possible that ischemic nerve block is less suitable for difficult motor task such as the motor learning task (playing a sequence in experiment II in contrast to finger tapping in experiment I). The patient showed muscle activity in the healthy arm during the task. This might be a reason for the higher pain level during arm anesthesia compared to leg anesthesia in experiment II. Voller et al., (in press) also utilized the ischemic nerve block to induce anesthesia, the found no differences in pain-levels between arm and leg anesthesia in an easy to perform grating orientation task. It is of note that without the interhemispheric mechanism which seems to promote improvement during INB, patients in both experiments even tended to worsen in their performance during the INB procedure (during leg INB), most likely due to the pain involved in the task. The unspecific behavioral effects in the opposite direction underline the magnitude of the proposed mechanism for arm INB.

Taken together, it can be assumed that for experiment I potential biases were controlled and kept constant, that a basically representative group of chronic stroke patients with specified brain lesions was analyzed, that patients were blinded to the hypothesis and, thus, the experimental setting was as free of biases as possible. For experiment II these conclusions can only bee drawn up to a limited degree. Differences in pain levels for arm and leg anesthesia made it more difficult for experiment II to control and compare fatigue and attention levels between conditions.

Discussion results

In experiment I the anesthetic effect started rapidly after onset of anesthesia, peaked at the end of the anesthetic procedure, and outlasted the anesthesia period by at least 20 minutes. Performance improvements in the paretic hand, measured serially in experiment I, started shortly after tourniquet inflation and became maximal once perception of von Frey filaments (4.56 mm diameter) in the intact hand was abolished in 5/5 trials below the anesthetic tourniquet (i.e., at second measurement during anesthesia), hence documenting advanced cutaneous anesthesia. This time line was well established in previous experiments measuring light-touch perception, SSEPs, and MEPs (Brasil Neto et al., 1992; 1993; Ziemann et al., 1998; Werhahn et al., 2002b). Within minutes after the onset of deafferentation the MEP amplitude elicited by TMS in the muscle immediately proximal to deafferentation increased and returned to baseline values within 20 minutes after termination of ischemia.

The anesthetic effect found in the motor performance experiment was topographically specific because anesthesia of the intact hand led to improved performance in the distal-finger motor task but not in the wrist-flexion task, which predominantly engages forearm muscles proximal to the anesthetic effect (wrist). Additionally, no improved motor performance was found with anesthesia of the intact leg.

A potential concern regarding the design of the motor performance experiments is the possible effect of motor practice for the utilized relatively simple finger tapping task. This led to the assumption that under the used conditions a motor practice might occur. Therefore, baseline values of all experimental sessions were compared. The patients showed no learning effects over the period of the three days, i.e. no changes in baseline values over three days.

The magnitude of the improvements in finger tapping in experiment I was very similar to improvements in performance reported in a previous study in healthy humans (Werhahn et al., 2002). Werhahn et al. have demonstrated that hand anesthesia results in improvements in performance of a tactile discriminative task by the other, non-anesthetized hand (Werhahn

et al., 2002) of healthy volunteers (18% in the present study and 19% in Werhahn et al., 2002). The improvement in motor performance was on average 18% but the individual responses varied (see supplement for individual data). Given this variability, it was evaluated which patients benefit most from this approach. It was found that tapping intervals were significantly shorter in well-recovered patients compared to poorly recovered patients. In patients with good pre-experimental motor function, a decrease in finger tapping intervals during hand anesthesia correlated well with performance in the Fugl-Meyer score, an established method for evaluation of physical performance (Fugl-Meyer et al., 1975).

Patients in experiment II showed no implicit learning in the No-intervention condition. This result is in line with the finding of Boyd & Winstein, (2001) who demonstrated an impaired implicit motor learning in patients after unilateral stroke. It is known that explicit knowledge prior to task can augment implicit learning in stroke patients (Boyd & Winstein, 2001). With the repeated measure design in experiment II only one naïve learning session was possible. The subjects could have acquired explicit knowledge about the task and on day 2 or 3 being aware of a sequence so that gained explicit knowledge interferes with the issue to test implicit learning. Patients did not required any explicit knowledge as assessed by a questionnaire (see supplement). Thus, it can be assumed that patients where naïve about the task design for both experimental sessions and that it was possible to choose a repeated measure design for a learning task. Additionally the experimental (arm INB) and control (leg INB) condition were randomized within subjects and for each day different sequences were presented.

The present analysis suggests that anesthesia of the intact hand leads to improvements in motor function and motor learning in the impaired hand of chronic stroke patients. Additionally, the data suggest that a “minimum” degree of function may be required for the improvement effects during healthy arm-anesthesia to occur. Future investigations, including additional testing of SSEP, MEP, sensory and motor nerve action potentials, could provide information on the input modalities which contribute most to the

improvements in the paretic hand, an issue that could not be addressed within the scope of this design.

Scientific and clinical implications

In the present experiments, the principles of neuroplasticity as previously tested in animals (Calford and Tweedale, 1990) and healthy volunteers (Werhahn et al., 2002) were applied to a group of chronic stroke patients. It is known from animal and human studies that there are inhibitory interactions between M1 hand representations (Ferbert et al., 1992; Gerloff et al., 1998). The relationship between improvement of motor function and interhemispheric inhibitory processes seems to be less clear. Some studies show an association between motor function improvement and increase in activation of ipsilateral motor areas when moving the affected hand (Bütefisch et al., 2003) whereas other found a negative correlation between the amount of motor related activation and improvement of motor function (Ward et al., 2003; see Baron & Calautti, 2003 for review). Johansen & Berg, (2002) could disrupt motor performance of the paretic hand with TMS of the ipsilateral motor area. In contrast, Werhahn et al., (2002) failed to delay reaction times in the paretic hand after TMS of the ipsilateral hand motor area.

The data of experiment I and experiment II suggest that anesthesia of the intact hand in chronic stroke patients can lead to improvement in a motor performance task and in an implicit motor learning task performed by the paretic hand. Although the specific mechanisms underlying this effect remain to be determined, they could involve modulation of abnormal intracortical inhibition in the affected hemisphere (Classen et al., 1997) and/or a correction of abnormal interhemispheric interactions documented in patients with chronic stroke (Murase et al., 2004). Anesthesia suppresses interhemispheric inhibitory interactions resulting in a disinhibition of the contralateral (affected) hemisphere and thereby allowing the affected hemisphere to improve in performance, a process possibly mediated through regulation of the neurotransmitter GABA (Ziemann et al., 1998). In this

interpretation the data provide another rationale why treatments like constraint induced therapy might be effective (Taub et al., 1998). The activation of the healthy hand must be suppressed in order that the affected motor system can become more self reliant and can improve more efficiently.

This mechanism seems to apply in particular to better recovered patients. It seems that these patients have, up to a limited degree, the possibility for reorganization within the injured hemisphere which is suppressed by inhibitory activity of the healthy hemisphere. Severely affected patients seem to depend on mechanisms such as activity in the healthy hemisphere to compensate for loss of motor function. If this is the case techniques such as down regulation of adjacent or contralateral healthy body parts may be helpful for good recovering patient.

These results may influence future strategies of neurorehabilitation of stroke patients. Furthermore they provide an additional rationale behind existing rehabilitation procedures, such as constraint induced therapy.

V. Outlook

Based on the results of above experiments and other studies, the following model can be formulated: Motor performance of the paretic hand may be influenced by different operational strategies (Figure 4.1), including: (a) Reduction of somatosensory input from the intact hand, as in cutaneous anesthesia, leads to performance improvements in the other hand in healthy volunteers (Werhahn et al., 2002) and in patients with chronic stroke (present experiments). These findings are consistent with the proposed beneficial influence of immobilization of the intact hand (which also reduces somatosensory input from the immobilized limb) on training-dependent motor improvements in the weak hand of chronic stroke patients undergoing constraint induced-therapy (Nudo et al., 1996; Nudo & Milliken 1996; Taub et al., 1999). (b) Increased somatosensory input from the paretic hand may improve motor function (Johannson et al., 1993; Powell et al., 1999; Wong et al., 1999; Conforto et al., 2002), a finding consistent with the documented beneficial effect of massed motor training (which, in addition to the pure motor effects, increases somatosensory input from the paretic hand) (Nudo et al., 1996; Nudo & Milliken, 1996; Taub et al., 1999). (c) Anesthesia of a body part proximal to the paretic hand (upper arm) may constitute another beneficial option to influence hand motor function (Muellbacher et al., 2002). In this case, anesthesia of the affected upper limb in patients with chronic stroke leads to training-dependent improvements in motor function of the paretic hand, consistent with the view that the cortical representation of the paretic hand extended over the nearby deafferented upper-arm representation (Merzenich et al., 1998).

In summary, the present results indicate that somatosensory input originating in the intact hand influences motor function in the paretic hand of patients with chronic stroke and could possibly modulate the beneficial effects of motor training. These findings may be relevant for design and optimization of neurorehabilitative strategies after stroke.

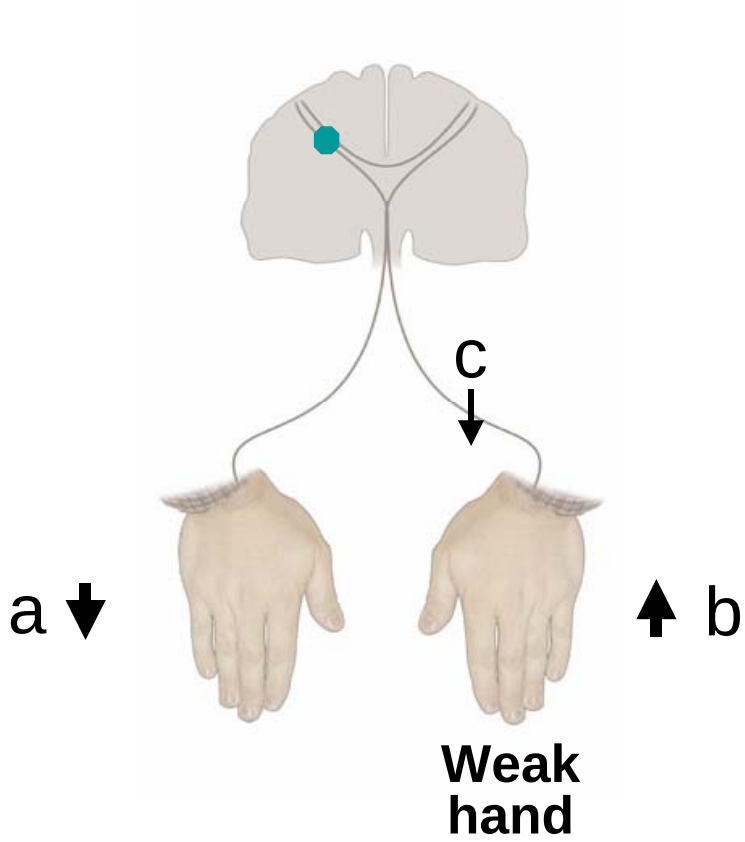


Figure 4.1

Motor performance of the paretic hand could be influenced by different operational strategies, including reduction of somatosensory input from the intact hand, as determined in this study (a); increased somatosensory input from the paretic hand (b); and anesthesia of a body part proximal to the paretic hand (c).

VI. Summary

VI.1 Summary

Stroke is a leading cause of long term disability in the western world. Two thirds of those surviving stroke suffer from residual neurological deficits, and at least 50% of stroke survivors are left with residual motor deficits, in particular affecting the hand. Besides intensive training there are few therapeutic options and no universally accepted treatment of disability resulting from chronic stroke. Animal studies have demonstrated that acute limb deafferentation results in rapid changes in receptive fields in the somatosensory cortex of both hemispheres. In healthy humans, hand anesthesia also leads to bilateral cortical reorganization. Changing the excitability of one motor cortex by either transcranial magnetic stimulation or ischemic nerve block applied to the contralateral hand leads to lasting modulation of cortical excitability and processing in the non-deafferented hemisphere. These findings indicate that modulation of activity in one hemisphere could be used to change activity in the other hemisphere. In healthy volunteers, ischemic nerve block applied to one hand has been shown to induce behavioral gains in tactile discriminative skills in the contralateral non-deafferented hand. A crucial question for neurorehabilitation is whether cortical reorganization and behavioral gains demonstrated in animals and in healthy humans can be translated into effective rehabilitative strategies geared to enhance functional recovery in patients with chronic stroke. In the present experiments, the principles of neuroplasticity as previously tested in animals and healthy volunteers were applied to a group of chronic stroke patients. Consistent with interhemispheric competition models of motor processing, it was hypothized that cutaneous anesthesia of the healthy hand elicits transient site-specific improvements in motor performance of the paretic hand in patients with chronic stroke. To test the hypothesis two experiments with chronic stroke patients with predominantly motor deficits were performed. In experiment I, 13 chronic stroke patients performed motor tasks with the paretic hand and

arm during cutaneous anesthesia of the healthy hand (target) and healthy leg (control). Motor performance of a finger tapping task and as control of a wrist flexion task was measured. Anesthesia of the healthy hand led to a significant improvement in tapping speed in the paretic hand. The effect started rapidly after onset of anesthesia, peaked at the end of the anesthetic procedure, and outlasted the anesthesia period by at least 20 minutes. The effect was topographically specific because (a) it was not found with anesthesia of the healthy leg; and (b) anesthesia of the healthy hand improved performance in the dynamic distal-finger motor task but not in the wrist-flexion task, which predominantly engages forearm muscles proximal to the anesthetic level. The gains in tapping speed were more prominent in patients with relative better motor function suggesting that a “minimum” degree of function may be required for this effect to occur. After successful completing experiment I, experiment II was conducted as a pilot study. Seven chronic stroke patients performed a motor learning task with the paretic hand during cutaneous anesthesia of the healthy hand, healthy leg and during a No-intervention condition. In the No-intervention condition, patients showed no implicit learning but performance in the motor learning task improved significantly with anesthesia of the healthy hand. During leg anesthesia even a tendency for decreased performance compared to the No-intervention condition was found. Overall these findings support the view that somatosensory input from the healthy hand influences motor performance in the paretic hand. Anesthesia of the healthy hand in patients with chronic stroke may have decreased the inhibitory drive from the deafferented intact hand representation over the homologous representation in the affected hemisphere, resulting in the documented improvement. In particular well recovering patients seem to have the capacity for reorganization within the injured hemisphere. These patients may profit most from down regulation of inhibitory activity of the healthy hemisphere. Thus, it is possible that modulation of somatosensory input originating in the intact hand could enhance the beneficial effects of training. Poorly recovering patients seem to depend more on compensatory activity of the healthy hemisphere.

VI. 2 Zusammenfassung

Der Schlaganfall gilt als eine der Hauptursachen chronischer Behinderung in der westlichen Welt. Zwei Drittel der betroffenen Patienten leiden an neurologischen Defiziten und mindestens 50% weisen motorische Defizite, insbesondere der Hand, auf. Neben wiederholtem und intensivem Üben gibt es nur wenige therapeutische Optionen und keine allgemein akzeptierten Behandlungskonzepte Schlaganfall-bedingter motorischer Beeinträchtigungen. In tierexperimentellen Untersuchungen konnte gezeigt werden, dass eine akute Deafferentiation einer Extremität zu schnellen Veränderungen in den rezeptiven Feldern des sensorischen Cortex' beider Hemisphären führt. Beim gesunden Menschen führt eine Deafferentiation der Hand durch Anästhesie ebenfalls zu einer bilateralen, kortikalen Reorganisation. Eine Änderung der Erregbarkeit des motorischen Cortex' - entweder durch transkranielle Magnetstimulation oder ischämische Nervenblockade der kontralateralen Hand - führt zu einer Veränderung der kortikalen Erregbarkeit und der Verarbeitungsprozesse auch in der nicht-deafferenzierten Hemisphäre. Diese Befunde weisen darauf hin, dass die Modulation der Aktivität einer Hemisphäre genutzt werden kann, um die Aktivität der anderen Hemisphäre zu beeinflussen. Für gesunde Probanden konnte bereits gezeigt werden, dass durch die ischämische Nervenblockade einer Hand die taktile Diskriminationsfähigkeit der kontralateralen, nicht-deafferentierten Hand verbessert werden kann. Es stellt sich die Frage, ob die kortikale Reorganisation und die funktionellen Verbesserungen, wie sie bei Versuchstieren und gesunden Probanden gefunden wurden, in effektive Strategien zur Verbesserung der Rehabilitation motorischer Funktionen bei Patienten mit chronischem Schlaganfall übertragen werden können. Entsprechend dem Modell des interhemisphärischen Wettbewerbs motorischer Prozesse wurde im Rahmen dieser Arbeit der Frage nachgegangen, ob es möglich ist, durch Anästhesie der gesunden Hand die motorische Funktion der paretischen Hand zu beeinflussen und somit eine erfolgreiche Methode für den Einsatz in der Neurorehabilitation einzuführen. Es wurde die Hypothese aufgestellt, dass eine Anästhesie der gesunden Hand transiente lokalitätsspezifische Verbesserungen der motorischen

Leistungen der paretischen Hand bei Patienten mit chronischem Schlaganfall hervorruft. Zur Überprüfung der Hypothese wurden zwei Experimentserien bei chronischen Schlaganfallpatienten mit überwiegend motorischen Defiziten durchgeführt. Im Experiment I führten 13 chronische Schlaganfallpatienten motorische Aufgaben mit der paretischen Hand bzw. dem paretischen Arm während einer kutanen Anästhesie des gesunden Armes (Experimentalbedingung) und des gesunden Beines (Kontrollbedingung) durch. Es wurden die Leistungen während einer Finger-Klopf-Aufgabe (finger tapping) und - als Kontrolle - einer Handgelenk-Beuge-Aufgabe (wrist flexion) untersucht. Die Anästhesie der gesunden Hand führte zu einer signifikanten Verbesserung der Klopfgeschwindigkeit der paretischen Hand im Vergleich zum Ausgangswert. Dieser Effekt begann rasch nach Beginn der Anästhesie, erreichte sein Maximum am Ende der Anästhesieprozedur und überdauerte die Anästhesieperiode um mindestens 20 Minuten. Der Effekt war topographisch spezifisch weil er (a) nicht während der Anästhesie des gesunden Beines auftrat, und weil (b) die Anästhesie der intakten Hand die Leistung in der Finger-Klopf-Aufgabe aber nicht in der Handgelenk-Beuge-Aufgabe, die überwiegend die Unterarmmuskulatur proximal zur deafferentierten Muskulatur beansprucht, verbesserte. Die Steigerung der Klopfgeschwindigkeit war für Patienten mit besserer motorischer Funktion deutlicher, was vermuten lässt, dass ein “Minimum” an Funktionsfähigkeit erforderlich sein könnte, um durch eine Deafferentierung eine Verbesserung der Leistung zu erzielen. Nach erfolgreichem Abschluss des ersten Experimentes wurde das zweite Experiment als Pilotstudie entworfen. Hier führten sieben chronische Schlaganfallpatienten eine Aufgabe zum motorischen Lernen (serielle Reaktionszeit-Aufgabe) mit der paretischen Hand, während Anästhesie der gesunden Hand, des gesunden Beines sowie ohne Anästhesie, durch. Ohne Anästhesie zeigten die Patienten keinerlei implizites Lernen. Die Anästhesie der gesunden Hand führte zu einer signifikanten Leistungssteigerung, die sich bei Anästhesie des gesunden Beines nicht zeigte. Insgesamt stützen die Befunde die Annahme, dass durch Modulation spezifischer Afferenzen zur gesunden Hemisphäre die motorische Funktion der paretischen Hand beeinflusst werden kann. Eine Anästhesie der gesunden Hand scheint bei Patienten mit chronischem

Schlaganfall zu einer Reduktion des inhibitorischen Einflusses der deafferentierten Handareale der gesunden Hemisphäre auf die homologen Areale in der betroffenen Hemisphäre und somit zu den hier beschriebenen Funktionsverbesserungen in der paretischen Hand zu führen. Insbesondere Patienten, die besser von ihren motorischen Funktionseinbußen genesen sind, scheinen auf reorganisatorische Mechanismen innerhalb der betroffenen Hemisphäre zurückgreifen zu können. Sie profitieren von einer Unterdrückung der inhibitorischen Aktivität der gesunden Hemisphäre. Für diese Patienten ist es der Hypothese entsprechend möglich, durch Modulation sensorischer Afferenzen der gesunden Hand in Kombination mit Training der paretischen Hand eine Verbesserung der Rehabilitationserfolge zu erzielen. Patienten deren Funktionsrestitution weniger erfolgreich verläuft, scheinen hingegen eher auf die kompensatorische Aktivität der gesunden Hemisphäre angewiesen zu sein.

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Supplement

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

INSTITUTE: National Institute of Neurological Disorders and Stroke

STUDY NUMBER: 03-N-0135 PRINCIPAL INVESTIGATOR: Leonardo G. Cohen, M.D.

STUDY TITLE: Improved Function in the Paretic Hand of Chronic Stroke Patients by Transient Deafferentation of the Intact Upper Extremity.

Latest IRB Review: Initial Review 2/19/03
Latest Amendment Approved: N/A
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Facts that led us to this study:

Results from previous studies in humans suggest that after a stroke the intact side of the brain might negatively influence the affected side, the part of the brain that has been injured.

So the idea is to inhibit the healthy side, thereby improving function of the injured hand. This "inhibition" is achieved by applying a procedure called "ischemic nerve block" to your unaffected arm or leg.

In previous studies on healthy volunteers, we showed that the function in one hand is improved when an ischemic nerve block is applied to the forearm of the other hand.

MEDICAL RECORD	**CONTINUATION SHEET for either:** **NIH 2514-1, Consent to Participate in A Clinical Research Study** **NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study**

STUDY NUMBER: 03-N-0135 CONTINUATION: page 2 of 6 pages

Purpose of Study:

The purpose of this study is to find out if the functional improvement, as demonstrated in healthy volunteers, can also be found in the affected hand of patients with chronic impairment after stroke.

Procedures:

You will come to the NIH and undergo a clinical and neurological exam if you have not had one recently.

You may be asked to participate in one of two different studies. Please, check the box that applies:

☐

Patient with persistent numbness

Tactile spatial acuity task (= assessing the sensitivity of your fingertip to discriminate shapes):
In up to 7 different sessions you will undergo the following study:

In the first session, we will obtain an MRI scan of your head if you did not have one within the previous 6 months. Additionally, you will be given a short test with test called the Mini Mental State Examination.

In sessions 2, 3 and 4 we will practice a tactile spatial acuity task with you several times, to achieve an optimal performance. In the tactile task, you will have to rate the orientation of a grating that is applied to the pad of the second finger of your affected hand.

In session 5, you will first be asked to do the tactile spatial acuity task several times Then, a procedure called ischemic nerve block (INB), see below, will be applied to your healthy forearm. Approximately. 25 minutes later, you will be asked to do the tactile spatial acuity task again. Subsequently, the INB will be released, and 20 minutes later, you will be asked to do the tactile spatial acuity task again. Should any technical difficulties arise during this session, we will repeat the procedure in session 6.

Session 7 will be identical to session 5, except the INB will be applied immediately above the ankle instead of the forearm.

The order of sessions 5 and 7 might be reversed. All sessions will last about 2 hours

☐

Patient with persistent motor impairment

Pinch muscle strength task ("Pinch grip"):
In up to 7 different sessions you will undergo the following study:

In the first session, we will obtain an MRI scan of your head if you did not have one within the previous 6 months. Additionally, you will be given a short test called the Mini Mental State Examination.

In sessions 2, 3 and 4 we will practice a motor task with you several times, to achieve an optimal performance. The motor task will be a rhythmic, repetitive pinch grip at frequency of 1 every ten seconds, paced by a metronome. You will be asked to perform the pinch grips at maximal strength.

In session 5, you will first be asked to do the pinch grip task several times Then, a procedure called ischemic nerve block (INB), see below, will be applied to your healthy forearm. Approximately 25 minutes later, you will be asked to do the pinch grip task again. Subsequently, the INB will be released, and 20 minutes later, you will be asked to do the pinch grip task again. Should any technical difficulties arise during this session, we will repeat the procedure in session 6.

Session 7 will be identical to session 5, except the INB will be applied immediately above the ankle instead of the forearm.

The order of sessions 5 and 7 might be reversed. All sessions will last about 2 hours.

Ischemic Nerve Block (inflation of a blood pressure cuff around the forearm):

We will inflate a blood pressure cuff around the arm, approximately at the level of the elbow for approximately 35 minutes, up to a maximum of 50 minutes. During and immediately following the procedure you will feel numbness, tingling, and loss of muscle strength, as well as discoloration of the forearm and hand, all of these transient effects. These unpleasant sensations usually disappear within minutes following cuff deflation (see below). In a different session, the cuff will be inflated around the calf. The discomfort associated with this type of testing is usually described as well tolerable and we have performed the procedure for many years in many different subjects in the absence of complications.

Magnetic Resonance Imaging Scan (MRI):

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves instead of X-rays to obtain images of body organs and tissues. This technique is more sensitive than X-rays in some circumstances. Since X-rays are not used, there is no radiation exposure.

The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie still on a table that can slide in and out of the cylinder. Scanning time varies from 20 minutes to 3 hours, with most scans lasting between 45 and 90 minutes. You may be asked to lie still for up to a few minutes at a time. While the scanner takes pictures, you will hear loud knocking and pulsing noises, and you will wear earplugs to muffle the sound. Individuals with fear of confined spaces may become anxious during this procedure. You will be able to communicate with the MRI staff at all times, and you may ask to be moved out of the machine at anytime.

You are at risk for injury from the MRI magnet if you have a pacemaker, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. You will be screened for these conditions prior to the study, and if you have any of these conditions, you will not receive an MRI

scan. If you have a question about any metal objects being present in your body, you should ask your physician to verify this with an x-ray. In addition, all magnetic objects (for example, watches, coins, jewelry, credit cards) must be removed before entering the MRI scan room. You will be asked to complete a MRI screening form and to sign a separate MRI consent for each MRI.

Discomforts, side effects, hazards:

The main discomforts or side effects are discussed below.

Testing of pinch muscle strength ("pinch grip"):

There are no known discomforts of this procedure other than the discomfort associated with immobilization and muscle fatigue due to task performance.

Testing of tactile acuity:

There are no known discomforts of this procedure other than the discomfort associated with immobilization and the need to concentrate on the task at hand.

Ischemic Nerve Block (inflation of a blood pressure cuff around the forearm):

Uncomfortable sensations that you will experience include discomfort under the cuff, numbness and tingling affecting the hand and forearm below the cuff, sensation of cold and paleness below the cuff, and difficulties moving the hand below the cuff. We want to reassure you that in most cases, these sensations will disappear within minutes after cuff deflation and that, if you feel that this procedure involves more discomfort than you want to sustain, you can stop the study at any time. Very rarely (0.15% or less of cases) there may be a delay of recovery of muscle strength over hours, swelling or skin discoloration. There are no known long term or longer lasting side effects.

Magnetic Resonance Imaging (MRI):

The main discomfort associated with this procedure is the need to lie still for the duration of the study. The machine is somewhat confining and this might result in fear of the closed space. Air conditioning will keep the temperature in comfortable levels. If you feel cold, we will place a cover. Fast movement of the head may result rarely in a metallic taste in the mouth. Remember that you can be removed from the scanner any time you wish. You may not participate in this specific study if you have a cardiac pacemaker, neural pacemaker, metal fragments (e.g. from occupational exposure) or surgical clips in or near the brain, eye, or blood vessels, cochlear or eye implants, because MRI can disrupt these objects.

Benefits to you:

There are no direct benefits to you. We hope to increase the motor performance / the tactile spatial acuity of your affected hand during the ischemic nerve block. If an improvement in performance occurs, it will likely be temporary. If there are long-term benefits from this, or even if you indeed will have an improvement in performance, cannot be guaranteed. You will not receive direct benefit from this protocol.

MEDICAL RECORD	**CONTINUATION SHEET for either:** **NIH 2514-1, Consent to Participate in A Clinical Research Study** **NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study**

STUDY NUMBER: 03-N-0135 CONTINUATION: page 5 of 6 pages

Payments you will receive:

The maximal financial compensation for research-related inconveniences will be $ 290 with and $ 250 without MRI for the complete experiment. You are free to withdraw at any time without penalty.

	Per procedure	No. of sessions	Total
1st hour	$20.00	7	$140.00
Each additional hour	$10.00	7	$70.00
4 inconvenience units	$40.00	1	$40.00
MRI	$40.00	1	$40.00
Maximum		7	$290.00

Please remember that this is a research study and that your participation is completely voluntary. You may withdraw at any time. If any injury should be caused to you as a result of any of these procedures, you will be provided with appropriate acute medical care at the Clinical Center.

Research findings from these studies will be published in articles in scientific journals, however your name will not be used.

We will share any significant new findings with you.

Alternative Treatments:

You may choose not to participate in this study as an alternative to treatment.

Confidentiality:

The information gathered during this study will be kept confidential to the extent that the law allows. You should know that these results may be published for scientific purposes, provided your identity is not revealed. You should also understand that your performance during test sessions might be videotaped. These videotapes may be used for medical purposes but your identity will not be revealed.

Withdrawal and Termination:

You should understand that you are free to withdraw your consent and to discontinue participation in this project at any time. You should also understand that your participation in this study might be ended without your consent if the investigator determines that it is in your best interests or if you significantly fail to follow the study procedures. After the study is finished, we will share any significant new findings with you.

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient

STUDY NUMBER: 03-N-0135 CONTINUATION: page 6 of 6 pages

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Leonardo G. Cohen, M.D., or Ms. Shashi Ravindran, R.N., M.P.H., at: Building: 10, Room 5S-208, Telephone: (301) 402-1916..

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)
The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 19, 2003 THROUGH FEBRUARY 19, 2004.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

PATIENT IDENTIFICATION	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet) • Adult Patient or • Parent, for Minor Patient NIH-2514-1 (5-98) P.A.: 09-25-0099 File in Section 4: Protocol Consent

Supplement

MEDICAL RECORD	Outpatient Progress Notes

Mr./Mrs.....patient#.....has been studied under the protocol 03-N-0135, "Improved function in the paretic hand of chronic stroke patients by transient deafferentation of the intact upper extremity".
He/She received a procedure called "ischemic nerve block" on the nonparetic forearm / calf for a total of ..... minutes. The patient also performed voluntary movements with his/her paretic hand for ..... minutes. The patient was evaluated and experienced no complications or side effects.

Check list

Discomforts, complications, side effects:

No (initialize) _____

Yes (describe,) _____ (use additional pages if needed)

Special Instructions to the Patient: Yes / No

Consent Form:
Original signed in chart: _____

Copy given to patient _____

Copy given to RN for filing ----------

Signature of Assoc Investigator _____
Date and time _____
Name of Assoc Investigator _____

Co-signature

_____
Leonardo G. Cohen, M.D.
Principal Investigator

Supplement

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an expianation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	____

Rev 10/1/2003

Supplement

MMSE™

Date of Examination ___/___/___ Examiner _____

Name _____ Age _____ Years of School Completed _____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)	
What is the...	**year?**	_____	0	1
	season?	_____	0	1
	month of the year?	_____	0	1
	day of the week?	_____	0	1
	date?	_____	0	1

ORIENTATION TO PLACE*

Where are we now? What is the...

state (province)**?**	_____	0	1
county (or city/town)**?**	_____	0	1
city/town (or part of city/neighborhood)**?**	_____	0	1
building (name or type)**?**	_____	0	1
floor of the building (room number or address)**?**	_____	0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... APPLE [*pause*], **PENNY** [*pause*], **TABLE** [*pause*]. **Now repeat those words back to me.**
[*Repeat up to 5 times, but score only the first trial.*]

APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [*Serial 7s*]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0	1
If needed, say: **Keep going.**	[86]	_____	0	1
If needed, say: **Keep going.**	[79]	_____	0	1
If needed, say: **Keep going.**	[72]	_____	0	1
If needed, say: **Keep going.**	[65]	_____	0	1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. →

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9 8 7 6 5 4 3 2 Reorder #RO-4740 Printed in the U.S.A.

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
but score only the backward spelling.

(D = 1)	(L = 1)	(R = 1)	(O = 1)	(W = 1)	(0 to 5)
____	____	____	____	____	____

RECALL	RESPONSE	SCORE (circle one)	
What were those three words I asked you to remember? [*Do not offer any hints.*]			
APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1

NAMING*

What is this? [*Point to a pencil or pen.*]	_____	0	1
What is this? [*Point to a watch.*]	_____	0	1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS.	_____	0	1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [*pause*], **fold it in half** [*pause*], **and put it on the floor (*or* table).**

TAKE IN RIGHT HAND	_____	0	1
FOLD IN HALF	_____	0	1
PUT ON FLOOR (*or* TABLE)	_____	0	1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES	_____	0	1

WRITING

Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**] 0 1

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1

Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Total Score =	_____
(*Sum all item scores.*)	(30 points max.)

Assessment of level of consciousness.

Alert/ Responsive	**Drowsy**	**Stuporous**	**Comatose/ Unresponsive**

Supplement

ALZHEIMER'S PROJECT (A)

NEUROPSYCHOLOGICAL EVALUATION

CASE # ___ ___ ___ SSN ___ ___ ___ ___ ___ ___ ___ ___ ___ (1-12)

HANDEDNESS INVENTORY (OLDFIELD)

Test 1

Instructions: "I am going to ask you about 10 common activities. I want you to tell me which hand you usually use when you do that activity. If you always use one hand and would never use the other, say "always my right hand" or "always my left hand". If you usually use a certain hand but sometimes use the other for that activity say "usually my right hand". If you use both hands equally, say"both". Record the responses.

	Left hand		Both	Right hand		
	Always	Usually	Equal	Usually	Always	
1. Writing	1	2	3	4	5	(13)
2. Drawing	1	2	3	4	5	(14)
3. Throwing	1	2	3	4	5	(15)
4. Scissors use	1	2	3	4	5	(16)
5. Using a toothbrush	1	2	3	4	5	(17)
6. Using a knife (without a fork)	1	2	3	4	5	(18)
7. Using a spoon	1	2	3	4	5	(19)
8. The upper hand when using a broom	1	2	3	4	5	(20)
9. Holding a match while striking it	1	2	3	4	5	(21)
10. Opening a box lid	1	2	3	4	5	(22)
Totals:	___	___	___	___	___	(23-32)

Total LH: ___ ___ (33-34)

Total RH: ___ ___ (35-36)

LQ: ___ ___ ___ (37-39)

Code: ___ Date: MO ___ ___ DA ___ ___ YR ___ ___ (40-46)

Remarks:

The Fugl-Meyer Evaluation

LOWER EXTREMITY

Reflex activity	Achilles:		0 - No reflex activity or 2 - Reflex activity
	Patellar:		
Flexor Synergy	Hip flexion:		0 Cannot be performed; 1 Partial motion; 2 Full motion
	Knee flexion:		
	Ankle dorsi/flexion:		
Extensor Synergy	Hip extension:		0 No motion; 1 Weak motion; 2 Almost full strength compared to normal
	Adduction:		
	Knee extension:		
	Plantarflexion		
LE Coordt'n/Speed	Tremor:		0 - Marked tremor; 1 - Slight tremor; 2 - No tremor
5 repetitions	Dysmetria:		0 - Pronounced or unsystematic; 1 - Slight or systematic; 2 - No dysmetria
	Speed:		0 - Six seconds slower than unaffected side; 1 - Two to 5 seconds slower; 2 - <2 seconds difference

Sitting

UPPER EXTREMITY

UE Reflexes	Biceps:		0 No reflex activity can be elicited; 2 Reflex activity can be elicited
	Triceps:		
Flexor Synergy	Elevation:		0 Cannot be performed at all; 1 Performed partly; 2 Performed faultlessly
	shoulder retraction:		
	Abdct'n (at least 90):		
	external rotation:		
	elbow flexion		
	forearm supination to ear		
Extensor Synergy	shldr abdct'n/int rot:		0 - Can't be performed at all;1 Performed partly; 2 Performed faultlessly
	elbow extension:		
	forearm pronated to knee:		
Movem't Combing Synergies	Hand to L-spine:		0 No specific action performed; 1 Hand must pass anterior iliac spine; 2 Action performed faultlessly
	Shldr flex'n to 90 elbow at 0:		0 Arm is immediately abducted or elbow flexes at start of motion; 1 Abduction or elbow flexion occurs in later phase; 2 faultless motion
	Pronat'n/supnt'n of forearm with elbow at 90, shldr at 0:		0 Correct posit'n of shoulder elbow can't be attained, and/or pronat'n/supinat'n can't be performed at all 1Active pronat'n or supinat'n is performed even w/in a limited ROM and at the same timethe shoulder and elbow are correctly posit'ned 2 Complete pronat'n & supinat'n w/ correct positions at elbow and shoulder.

The Fugl-Meyer Evaluation

Movem't Out of Synergy

Shldr abdct'n to 90, elbow at 0 and forearm pronat'd:	☐	0 Initial elbow flexion occurs or any deviation from pronated forearm occurs 1 Motion performed partly, or if during motion, elbow is fixed or forearm can't be kept in pronat'n 2 Faultless motion
Shldr flex'n, 90-180 elbow at 0 and forearm in mid pos:	☐	0 Initial flexion of elbow or shoulder abduction occurs 1 Elbow flexion or shoulder abduction, occurs during shoulder flexion 2 Faultless motion
Pront'n/Supint'n of forearm elbow at 0 and shldr betw 30-90 of flexion:	☐	0 Supination and pronation can't be performed at all or elbow and shoulder positions cannot be attained 1 Elbow & shoulder properly positioned and pronation and supination performed in a limited range 2 Faultless motion
NI Reflex Activity — Biceps and/or finger: flexors and triceps:	☐	0 At least 2 of the 3 phasic reflexes are markedly hyperactive 1 One reflext markedly hyperactive or at least two reflexes are lively 2 No more than one reflex is lively and none are hyperactive
WRIST		
a. Stability, elbow at 90, shoulder at 0 degs: *(holding against resistance)*	☐	0 Pt can't dorsiflex wrist to required 15 degs. 1 Dorsiflex'n accomplished, but no resistance is taken; 2 Posit'n maintained w/ some resistance
b. Flex'n/extens'n, elbow at 90, shldr at 0: *(ROM)*	☐	0 Volitional mov't doesn't occur; 1 Pt can't actively move wrist jt t/o total ROM; 2 Faultless mov't
c. Stability, elbow at 0, shoulder at 30 degs:	☐	Same scoring as for item a.
d. Flex'n/extens'n, elbow at 0, shoulder at 30 degs:	☐	Same scoring as for item b.
e. Circumduction:	☐	0 Can't be performed; 1 Jerky mov't or incomplete; 2 Complete smooth mov't
HAND		
a. Finger Mass Flexion:	☐	0 No flexion; 1 Some flexion, not full motion; 2 Complete active flexion (compared to unaffected hand
b. Finger Mass Extension:	☐	0 No extension; 1 Patient can release an active mass flex grip; 2 Full active extension
c. Grasp #1-MP joints extended and PIP & DIPs are flexed. Grasp tested against resistance:	☐	0 Reqd position can't be acquired; 1 Grasp is weak; 2 Grasp is maintained against rel. great resist.
d. Grasp #2-Pt to abduct thumb, 1st CMC & IP jt at 0 degs:	☐	0 Function can't be performed; 1 Scrap of paper interposed betw thumb and index finger can be kept in place, but not against slight tug; 2 Paper is held firmly against a tug

The Fugl-Meyer Evaluation

e. Grasp #3-Pt opposes thumb pad against the pad of index finger. A pencil is interposed:	[ ]	Scoring procedures are the same as item d
f. Grasp #4-Pt grasps a cylinder shaped object (small can), the volar surface of the 1st & 2nd finger against each other:	[ ]	Scoring procedures are the same as item d
g. Grasp #5-Pt grasps a tennis ball:	[ ]	Scoring procedures are the same as item d
Coordinat'n/speed-finger to nose (5 rapid reps)		
Tremor:	[ ]	0 Marked tremor; 1 Slight tremor; 2 No tremor
Dysmetria:	[ ]	0 Pronounce or unsystematic dysmetria; 1 Slight or systematic dysmetria; 2 No dysmetria
Speed:	[ ]	0 Activity more than 6 sec longer than unaffected; 1 2-6 sec longer than unaffected; 2 < 2 sec differenc
LOWER EXTREMITY		
LE Normal Reflexes . Knee flexors		
Patellar		
Achilles	[ ]	0 2/3 are markedly hyperactive; 1 1 Reflex is hyperactive or 2 are lively; 2 No more than 1 reflex lively
Movement Combining Synergies		
(knees in front of chair) Knee flexion beyond 90deg:	[ ]	0 No active mov't: 1 From slightly ext posit'n knee can be flexed but not beyond 90; 2 Knee flex beyond 90
Ankle dorsiflexion:	[ ]	0 No active motion: 1 Partial motion; 2 Full motion
BALANCE		
1.Sit without support	[ ]	0 Can't maintain sitting w/o support; 1 Can sit unsupported < 5 min; 2 Can sit > 5 min
2.Parachute rxn, non-affected side	[ ]	0 Does not abduct shoulder or extend elbow; 1 Impaired reaction; 2 Normal reaction
3.Parachute rxn, affected side	[ ]	Scoring same as item 2.
4.Supported standing	[ ]	0 Can't stand; 1 Stands with max support of others; 2 Stands w/ min support 1 min
5.Stands without support	[ ]	0 Can't stand; 1 Stands less than 1 min or sways; 2 Stands with good balance more than 1 min
6.Stand on unaffected side	[ ]	0 Can't be maintained more than 1-2 secs; 1 stands balanced 4-9 secs; 2 Stands more than 10 secs
7.Stand on affected site	[ ]	Scoring is the same as item 6
Standing		
LOWER EXTREMITY		
Movement out of Synergy		
Hip at 0 degs:		
Knee flexion	[ ]	0 Knee can't flex w/o hip flex; 1 Knee begins flex w/o hip flex, but doesn't get to 90 deg or hip flexes during mov't; 2 Full mov't as described
Ankle dorsiflexion	[ ]	0 No active mov't; 1 Partial mov't; 2 Full mov't

Supplement

Modified Ashworth Scale for Grading Spasticity

(Ashworth B: Preliminary trial of carisoprodal in multiple sclerosis.

Practioner 192:540-542, 1964.)

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved inflexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

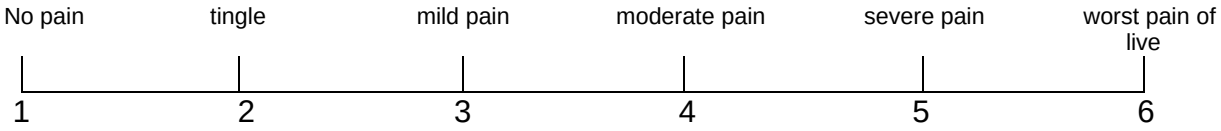
Supplement

Name:
Date:
Day:
Time of measurement: (circle appropriate)

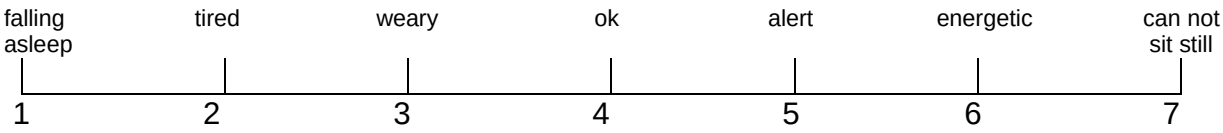
before INB	INB onset	5min	15min	25min
35min	40min	post5	post15	

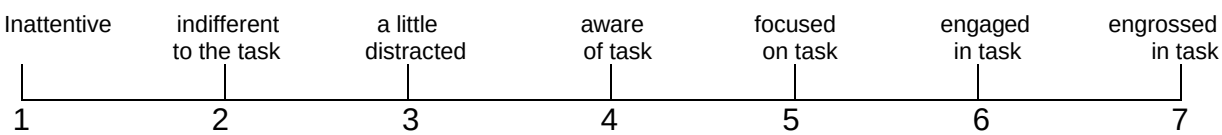
Please read the following scales.
Mark the number, which describes your situation in the best way with a cross.

How would you describe your pain-sensation?



Which of the following words describes your current situation in the best way?





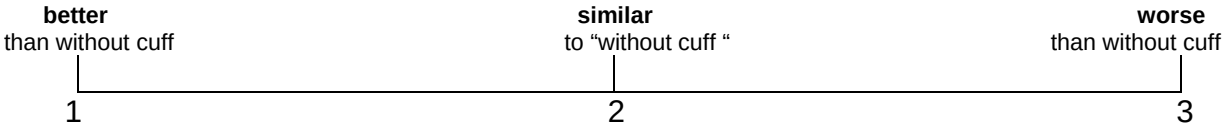
Supplement

Name _____ Date: _____

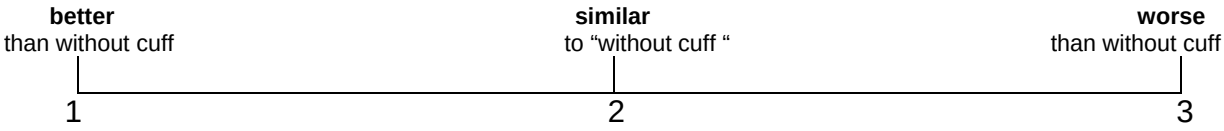
Please circle appropriate

What was your EXPECTATION concerning your performance during the INB-procedure BEFORE THE EXPERIMENTAL SESSION?

I expected that with the inflated cuff around my **forearm** my performance would be

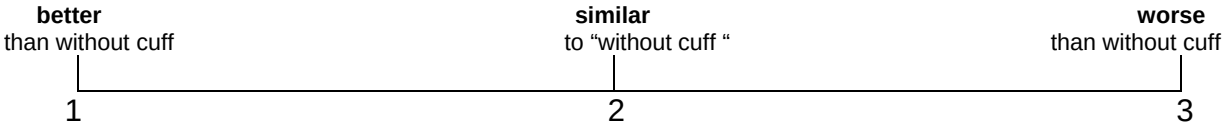


I expected that with inflated cuff around my **leg** my performance would be

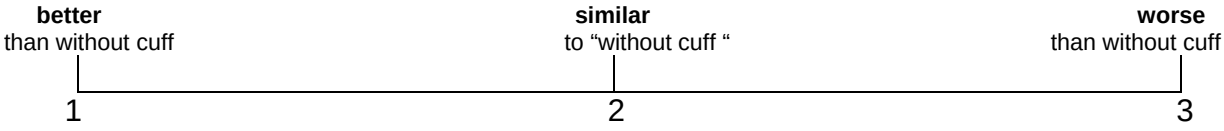


Please rate your PERORMANCE during the INB-procedure

I think with inflated cuff around my **forearm**, my performance was



I think with inflated cuff around my **leg**, my performance was



Supplement

Post Day2 questionnaire for Motor Learning-experiment

1. did you notice anything about the task?

_____

2. did you ever notice any pattern or repeating sequence?

- **If subjects indicate they have, they will be asked to indicate what it was**

3. _____

_____

- **if yes, write it down**

4. _____

_____

5. play the sequences

6. Which strategy did you followed for this task?

_____

_____

Supplement

Instruction for motor tasks

Wrist-Flexion-Task

“Please bend your wrist forward as fast as possible when a GO-signal appears on the screen.
Before each Go-signal, a get ready sign will remind you to look at the cross in the middle of the screen and to be aware that the Go-sign will appear soon. I will start the task now by pressing the space bar.”

Pause (5 sec)

“please get ready. I will start the task now by pressing the space bar.

Finger-Tapping-Task

“Please get ready for the finger tapping task. Press the key as fast as possible, for a total of 10 seconds
Get ready ---and GO”

TAPPING for 10 seconds

- “Stop-thank you-please relax one minute”

1 minute pause

- “Please get ready….Ready steady go”

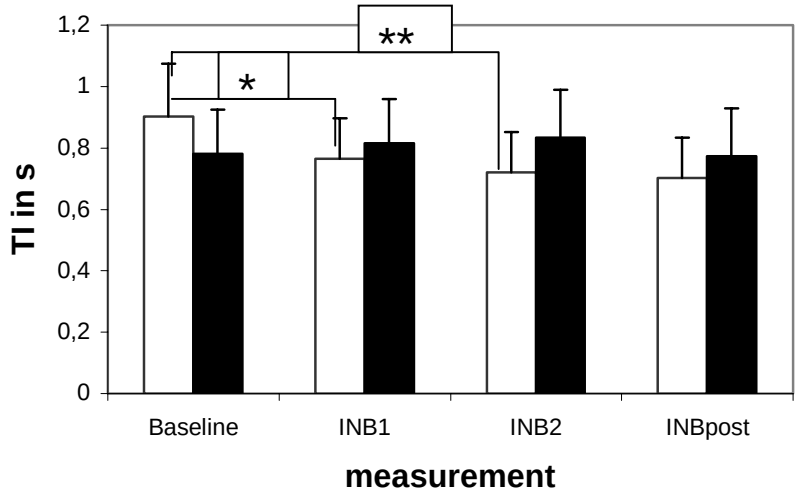
Supplement

Additional Data

Experiment I

Effect of anesthesia on Tapping-Interval (raw data)

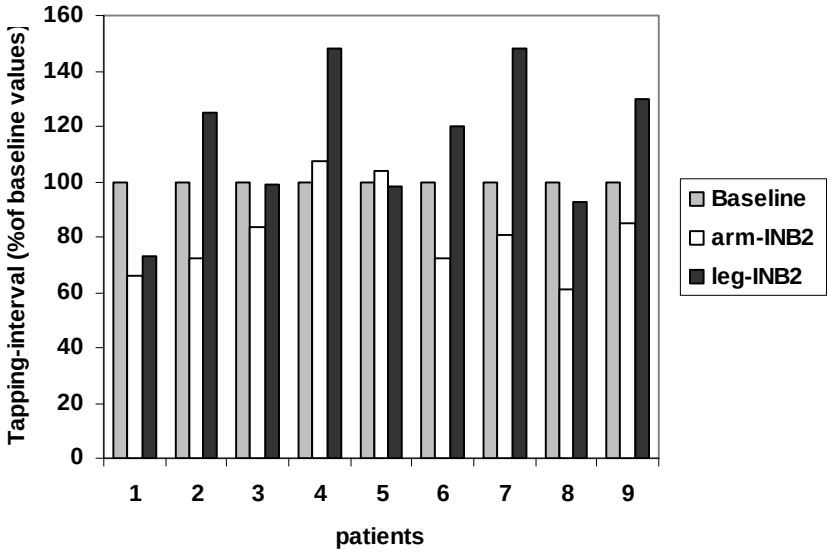
$ANOVA_{RM}$ showed a significant TIME x SITE effect of anesthesia interaction on finger tapping intervals expressed in ms ($F = 2.8$, $p < 0.05$*).



Tapping interval during hand (white bars) and leg (black bars) anesthesia, baseline: measurement before anesthesia; INB1: 1st measurement during anesthesia; INB 2: 2nd measurement during anesthesia; INBpost: measurement 20 minutes after release of cuff; (error bars indicate standard error of the mean)

Supplement

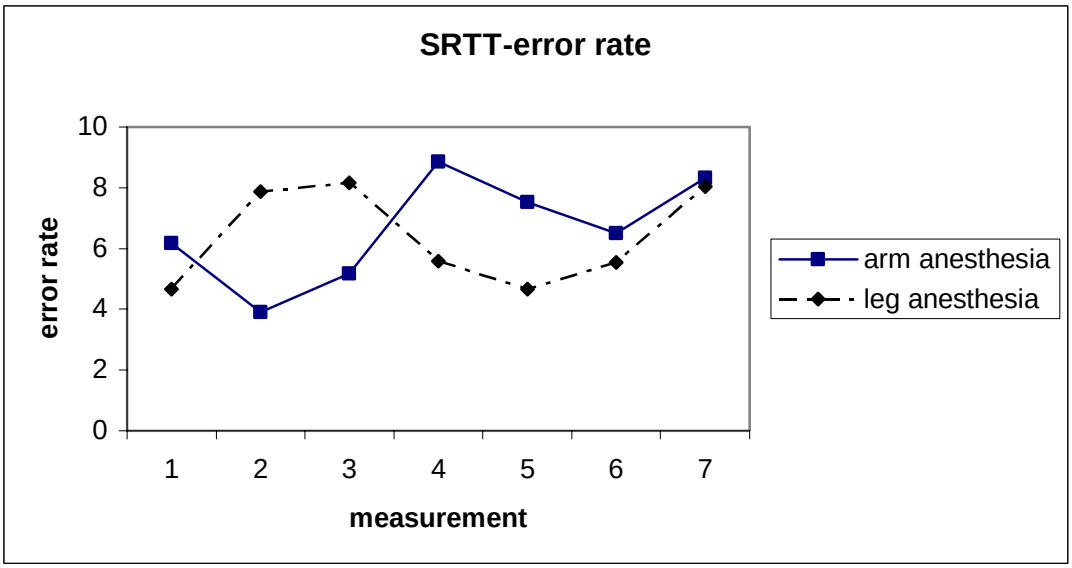
Effect of anesthesia on Tapping-Interval, separated for patients



Tapping interval during Baseline (grey bars), second measurement during arm anesthesia (white bars) and second measurement during leg anesthesia (black bars)

Experiment II

The overall ANOVA$_{RM}$, showed no significant SITE of anesthesia effect on error rate differences



Serial reaction time task: error rate during arm anesthesia and leg anesthesia for each measurement