Chapter 7

Synaptic Plasticity by Afferent Electrical Stimulation

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Additional information is available at the end of the chapter

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Abstract

The effect of afferent electrical stimulation on synaptic plasticity within the sensorimotor cortex will be discussed. Afferent electrical stimulation induces a down regulation of inhibitory neural circuits and plays a critical role in strengthening excitatory synapses. Synaptic modifications such as long-term potentiation (LTP) mechanisms could be a crucial mechanism underlying this stimulation-induced cortical plasticity. LTP and long-term depression (LTD) of synaptic transmission are crucial factors for activity-dependent changes in the strength of synaptic connections. Many studies demonstrated that these pathways play an important role in cortical synaptic plasticity. Repeated activation of excitatory synapses induces both short-term potentiation (STP) and LTP. Both types of synaptic potentiation affect N-methyl-D-aspartate glutamate receptors leading to the formation of new synapses or the unmasking of excitatory amino acid receptors on motor neurons. This increased excitability localized within the sensorimotor cortex may reflect an increase in neuronal activity as a result of a dynamic interaction of various synaptic and cellular mechanisms due to the local processing of afferent electrical input to the sensorimotor cortex. The chapter reviews also the large number of studies using fMRI and TMS to examine the effects of afferent electrical input from the hand on the excitability of human sensorimotor cortex.

Keywords: neuromodulation, afferent electrical stimulation, long-term potentiation (LTP), sensorimotor cortex, stroke rehabilitation

1. Introduction

In the development of neurobiology, it was generally thought that synapses simply transfer information between one neuron and another neuron or between one neuron and a muscle cell. Further, it was thought that established connections during development are relatively

fixed in their strength. However, up to now, the current opinion in neurobiology is that most synapses are highly plastic and are able to change their strength depending on their own activity or through synaptic input from another pathway. It is generally accepted that synaptic plasticity is the basic mechanism for learning and memory and reorganization in brain damage.

Synaptic plasticity can be divided into an intrinsic and extrinsic synaptic plasticity. Intrinsic synaptic plasticity refers to changes in the strength of a synapse by its own activity. Extrinsic synaptic plasticity is a change in the strength of a synapse by synaptic input through another pathway. For this change in the strength of a synapse through input from another pathway, there is a widely accepted model in neurobiology called long-term potentiation (LTP) that links synaptic plasticity with memory and long-term depression (LTD). The chapter will discuss the effect of afferent electrical (AE) stimulation on synaptic transmission and synaptic plasticity in general and especially within the sensorimotor cortex with a special protocol using whole-hand afferent electrical stimulation with a wire glove. Results from AE stimulation provide evidence for the induction of synaptic plasticity within the sensorimotor cortex leading to a reduced short interval intracortical inhibition (SICI) and an increased intracortical facilitation (ICF) and consequently to an increased motor cortex excitability, as verified with functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) techniques.

AE stimulation has been proven to induce changes in synaptic transmission and synaptic plasticity within the sensorimotor cortex [1]. An increased blood oxygen level dependent (BOLD) response after 30 min of AE stimulation within the sensorimotor cortex has been shown by fMRI [2]. 30 min of AE stimulation is able to modulate the corticospinal excitability as well as the activity of intracortical inhibitory and excitatory circuits that can be detected by TMS [3]. These conditioning effects could be measured up to 2 h post stimulation [2]. This exploration has strengthened the understanding that electrical peripheral nerve stimulation is a powerful tool to induce sustained excitability increases as well as rapidly evolving neuroplastic changes of the human sensorimotor cortex. Up to now, the optimal set of parameters for afferent electrical stimulation for the modulation of the corticomotor output is not exactly known [4]. Stimulation intensity appeared to have the strongest relationship to motor cortical excitability, whereas frequency has been shown to modulate motor-evoked potential (MEP) amplitudes [5]. Furthermore, different levels of afferent electrical stimulation were investigated—sham, sub-threshold (below the threshold for sensory perception)/50 Hz, sensory (above the threshold for sensory perception)/2 and 50 Hz, and motor level/2 Hz.

2. Synaptic plasticity by afferent electrical stimulation in BOLD imaging

2.1. Neurophysiology of afferent electrical stimulation

Afferent electrical stimulation generates synchronous tonic input to the brain due to depolarization of a large diameter group, Ia and Ib afferents, and to a lesser extent group II afferents of the hand, as it is the case in functional and neuromuscular electrical stimulation [6–10]. The

electrical input is transmitted to the spinal cord posterior column nuclei, the ventral posterolateral nucleus of the thalamus, and to the Brodmann areas 3a, 2, and 4 of the brain cortex [11–14]. The hand is a rich source of proprioceptive input to the brain via the afferents because the hand's intrinsic muscles have high-density muscle spindles [15, 16], a large number of joint receptors, as well as Golgi tendon organs [17, 18] with a portion of the tendons within the hand but belonging to the forearm muscles [10]. In addition, there are definite experimental findings that confirm that proprioceptive and exteroceptive somatosensory afferents of groups Ia (primary large muscle afferents), Ib (afferents from Golgi organs), and group II (slow and rapidly adapting skin afferents, secondary thin muscle afferents) have short latency projections to the contralateral sensorimotor cortex, particularly BA 3a, 1, 2, and 4 [14, 19, 20]. For the afferent route to the primary motor cortex M1, a projection from BA 3a is discussed [21]. By applying afferent electrical stimulation there will be afferents involved that "sense the body's own movement" [22]. In several positron emission tomography (PET) and fMRI studies, it was confirmed that vibration to the hand palm of healthy adult humans activates the contralateral primary sensorimotor (SM1), the supplementary motor area (SMA), and the secondary somatosensory cortex S2 bilaterally [23–25].

2.2. Methodology of afferent electrical stimulation

Continuous whole-hand afferent electrical stimulation with a wire glove (WG, **Figure 1**) is a potential tool that can induce neuromodulatory effects within the sensorimotor cortex. For ipsilateral neuromodulatory effects, cortical projections of Ia, Ib, II afferents, and transcallosal projections from the contralateral brain cortex are supposed [26, 27].

The wire glove is connected to a two-channel transcutaneous electrical nerve stimulation (TENS) stimulator. The WG acts as the anode, and carbon film surface electrodes above the tendons of the forearm flexors and extensors just proximal to the wrist act as cathodes (**Figure 1**). Before fitting the hand to the WG, conductive jelly should be applied over the whole hand. A train of 50-Hz stimuli with a pulse width of 300 μs is used for stimulation (**Figure 2**).

Depending on the skin resistance, the amplitude for the threshold of sensation lies between 2.0 and 4.0 mA and the level for supra-threshold stimulation is set to 120% of the threshold of sensation level. For sham, the stimulator is set to 0 mA, and healthy volunteers are told to be stimulated below the level of sensation. AE stimulation is applied for 30 min to the relaxed right or left hand [3]. Pulse width is set to 300 μs (**Figure 2**).

The level for sub-threshold stimulation is set to 80% of the threshold of sensation level. At the sensory level, (120% of the threshold of sensation level) electromyography (EMG) did not show any muscle contractions. For somatosensory AE stimulation, the frequency is set at 50 Hz and for motor AE stimulation at 2 Hz. The current stimulus amplitude for 50 Hz ranges from 2.0 to about 5.0 mA. For the motor level, the intensity is increased from the sensory threshold level until slight motor contractions of all small hand muscles are visible. The current stimulus amplitude for the motor level is about 10.0 mA. The sham stimulation is carried out identically, but the stimulation amplitude is set to 0 mA. Subjects are not informed about the stimulation level and are instructed to distract attention from the stimulation.

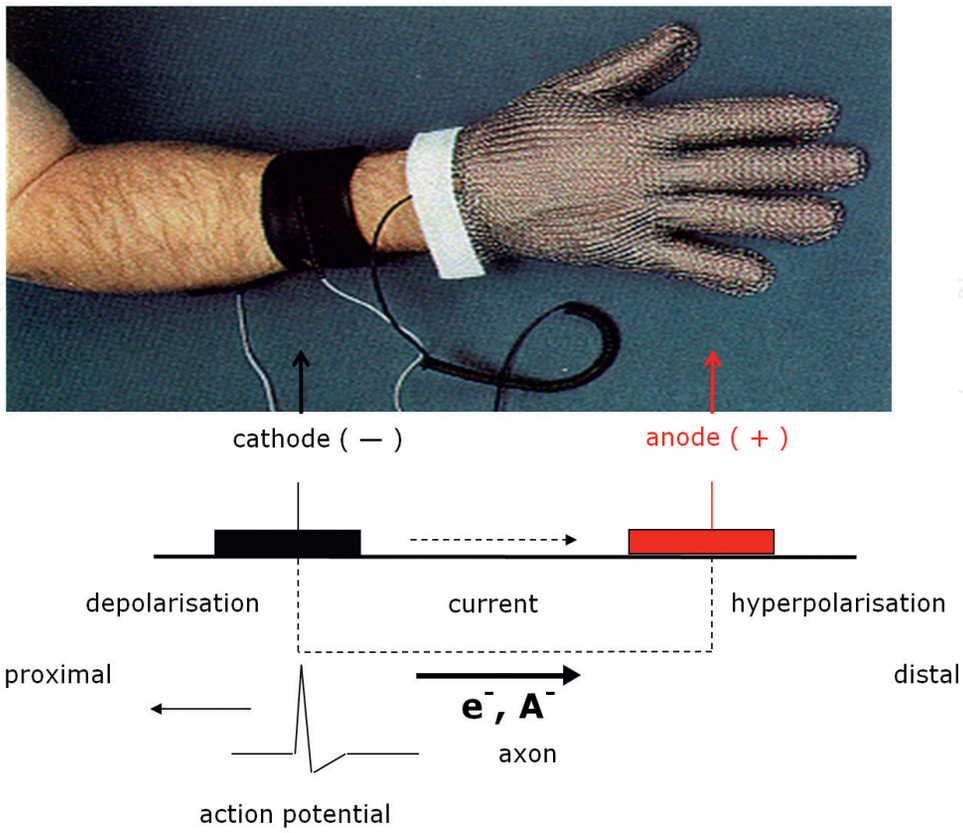

Figure 1. Wire glove: a two-channel stimulator delivers a train of 50-Hz stimuli (pulse width 300 ms) with the amplitude for somatosensory and motor stimulation, ranging from 2.0 to 10.0 MA. The wire glove acts as a common anode. The cathodes are placed over the tendons of the forearm flexors and extensors. Beneath the electrodes over the forearm flexors and extensors, the action potentials for the AE stimulation are elicited.

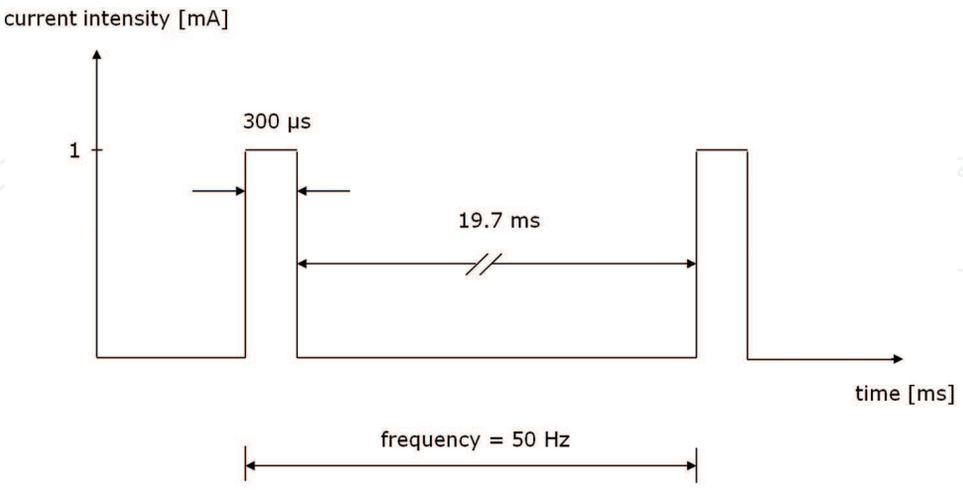

Figure 2. Current pulse: with a rectangular pulse with a width of 300 µs and a frequency of 2/50 Hz, the AE stimulation is continuous for 30 min. The current intensities range between 2 (somatosensory threshold) and 10 mA (motor threshold).

2.3. BOLD modulation by afferent electrical stimulation

Neuromodulatory effects of afferent electrical stimulation are already proven by fMRI [2, 28] applying self-paced simple finger movements. During finger-to-thumb-tapping with a frequency of about 2 Hz in fMRI movement-related BOLD responses of several brain areas are well known in the contra and ipsilateral hemisphere within the pre- and postcentral gyrus, the medial and superior frontal gyrus, and on both cerebellar hemispheres with a dominance ipsilaterally to the active left hand (**Figure 3**).

Neuronal activation within these areas is expected and has been reported by other investigators who studied the activity of human cortical motor areas during self-paced finger movements [29–31]. In a classical pre-/post-study design, a baseline finger-to-thumb tapping paradigm is run in fMRI (**Figure 4**).

Post 30 min of whole-hand afferent electrical stimulation of the tapping hand, the finger-to-thumb tapping paradigm in fMRI shows an increase of brain activation measured by the corresponding BOLD response on both hemispheres within the pre- and post-central as well as the medial frontal gyrus (**Figure 5**).

The left SMA shows augmented brain activation as well. The finding that an increase of movement-related responses is absent when the sham paradigm is applied further confirms the validity of these results. Obviously, afferent electrical stimulation can change motor cortex representation bilaterally within the primary and secondary sensorimotor cortex and consequently has the potential to induce neuroplasticity in neurorehabilitation. The detected increased BOLD responses reflect an increased neuronal activity due to augmented afferent proprioceptive and exteroceptive inputs to the sensorimotor cortex [32]. Logothetis could demonstrate a strong correlation between spatially localized BOLD response and local field potentials. AE stimulation of group Ia and Ib afferents and their

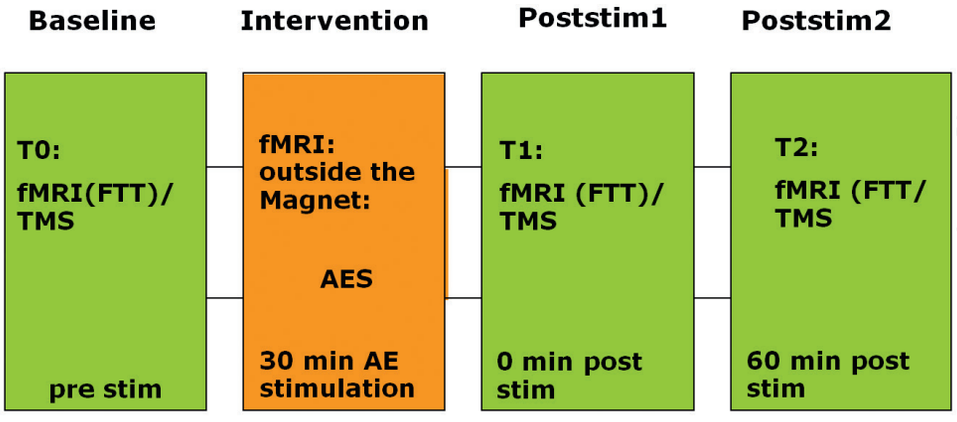

Figure 3. Classical pre-/post-design for studying synaptic plasticity: at T0 baseline measurement (finger-to-thumb tapping in fMRI, TMS) prior to 30-min AE stimulation, at T1 first measurement (fMRI/TMS) post stimulation (post stimulation 1) and at T2 60-min post-AE stimulation second measurement (fMRI/TMS) post stimulation (post stimulation 2).

direct transcallosal projections induce augmented local field potentials (LFP) for at least several minutes within the sensorimotor cortex that was already proven in somatosensory-evoked potential studies [13]. Augmented LFPs change intramotorcortical excitability with a larger recruitment by a motor task. AE stimulation addresses especially group Ia and Ib and to a lesser extent group II afferents and thus should augment sensorimotor LFPs. AE stimulation in stroke patients after a daily stimulation training program over several weeks improved motor performance [33–35], obviously by an increased motoneuron recruitment due to augmented motorcortical excitability leading to synaptic plasticity with intracortical facilitation and unmasking of preexisting silent synapses [36–41]. Horizontal connections transversing the superficial layers of the sensorimotor cortex are capable of both increases and decreases in strength and synaptic efficacy [42, 43]. A persistent high-frequency input enhances the motoneuron recruitment with probably a synaptic modification through long-term potentiation (LTP). Post-tetanic potentiation is unlikely because the neuromodulation lasts at least 2 h (**Figure 6**).

However, in the literature, there is evidence for a cortical origin of the modulation of cortical motoneuron excitability by afferent electrical input [1, 26, 44]. The multimodal integration cortex in the superior (SPL) and inferior (IPL) parietal lobule receives sensory information of

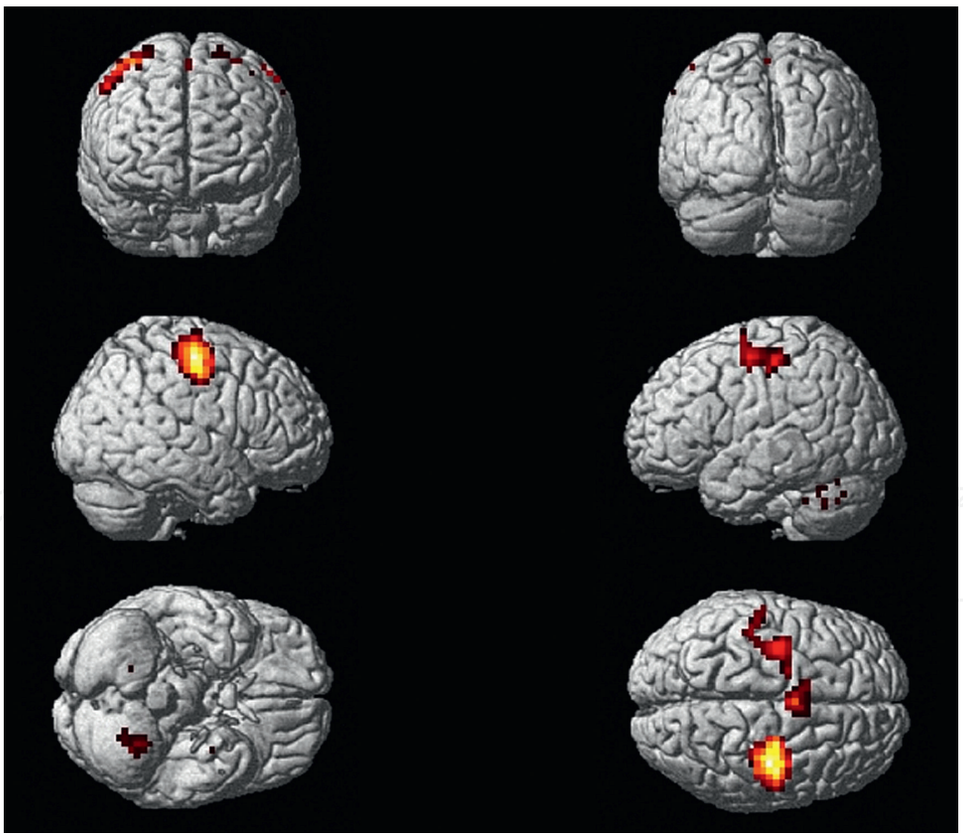

Figure 4. BOLD response during the test motor task (TMT): contra and ipsilaterally within the SM1, premotor area (PM), and SMA as well as in both cerebellar hemispheres with a dominance of the left hemisphere ipsilaterally to the stimulated hand.

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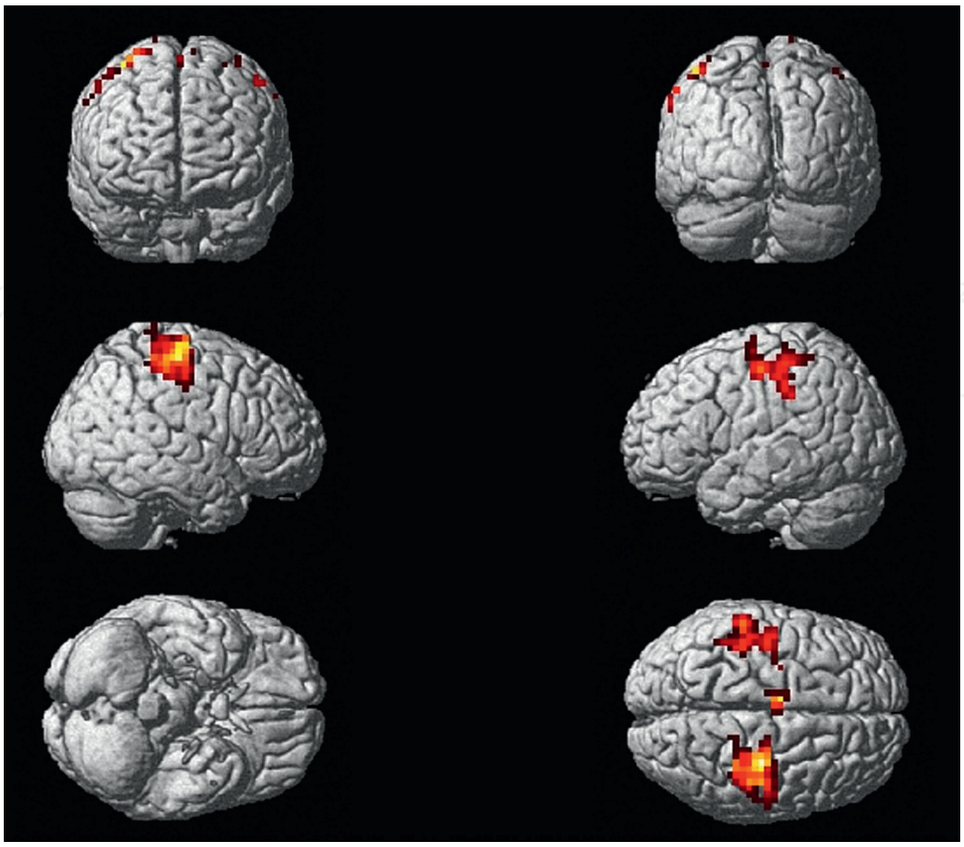

Figure 5. Between-condition analysis in fMRI: conditioned motor task at T1 (CMT1)—test motor task at T0 shows an increase of BOLD response during CMT1 of the contralateral hemisphere within SM1, PM, and IPL and of the ipsilateral hemisphere within SM1, PM, IPL, SMA, and cingulate gyrus (GC).

different modalities and transforms it into information for proper action. In IPL, proprioceptive, exterozeptive, premotor, and visual information converges during grasping with the hand. IPL is involved in sensorimotor transformations to convert retinal signals of target locations into a pattern of peripheral motor output to muscles to move the hand to the target [45, 46]. The information for these target movements will be processed primarily by the group Ia and Ib afferents, which are especially addressed by the afferent electrical stimulation. Thus, the IPL activity in the conditioned motor task immediately after the AE stimulation (CMT1) indicates direct input bilaterally to IPL that is very important for the neurorehabilitation for visually guided movements and the eye-hand coordination (**Figure 3**). Increased IPL activity after daily AE stimulation for 3 months in stroke patients concurs also with an improvement of neglect [33, 34]. Increased proprioceptive and exteroceptive input to the brain has also the potential of lowering muscle tone, which is in agreement with described beneficial effects of AE stimulation on spasticity [33, 34, 45, 46].

The increased BOLD responses were supposed to be due to a precapillary vascular response or to reduced sensorimotor network thresholds. Wu et al. [47] demonstrated in 2005 that median nerve stimulation elicited an enduring increase in task-related perfusion and BOLD responses in the cortical thumb representation in the absence of changes in baseline blood

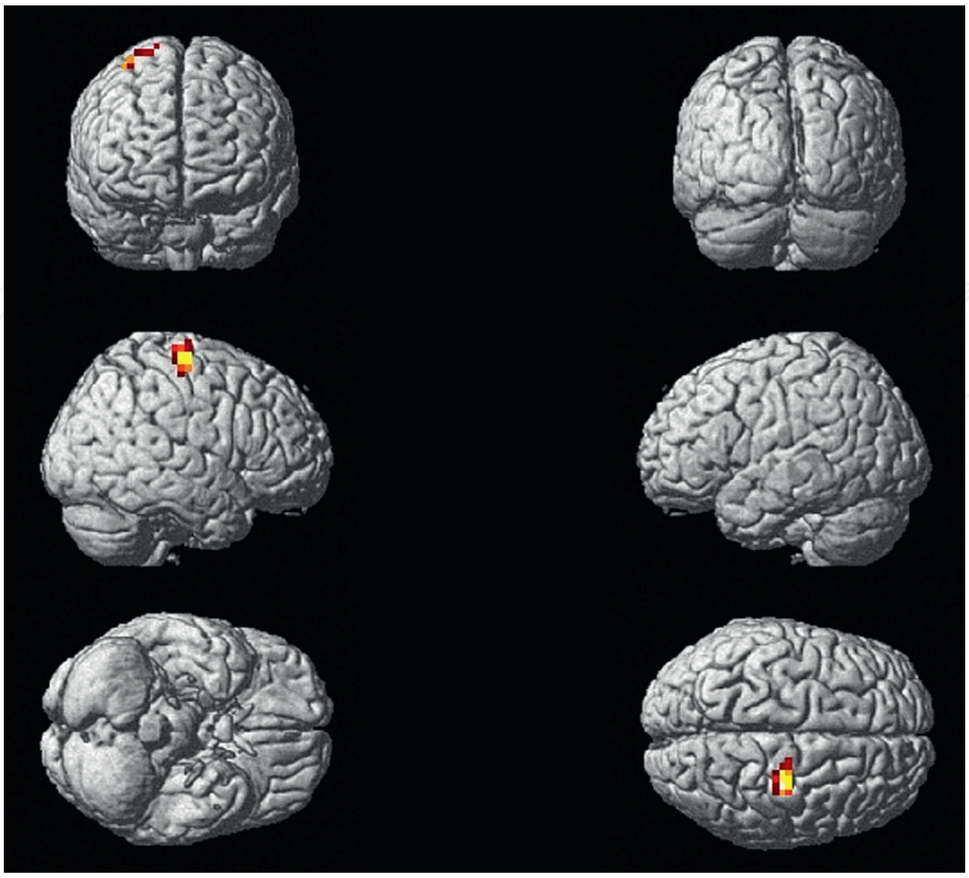

Figure 6. Between-condition analysis in fMRI: conditioned motor task at T2 (CMT2)—test motor task at T0 shows still an increase of BOLD response 2 h post stimulation with brain activation declining nearly to TMT level.

flow. Consecutively, the increased BOLD response was associated with increased cortical excitability but was still unclear.

3. Synaptic plasticity by afferent electrical stimulation in TMS

3.1. Background

With transcranial magnetic stimulation (TMS, excitatory and inhibitory circuits of the human motor cortex can be studied. Many studies have used TMS to investigate the effect of AE stimulation of the hand on motor cortex excitability with the paired-pulse technique, demonstrating a reduction of SICI [48, 49]. By a preceding electrical stimulus to a mixed or cutaneous nerve Motor Evoked Potentials (MEPs) are affected and show a smaller amplitude [48, 50–52]. AE stimulation of the hand showed conflicting results with no effect on MEP amplitudes, MEP amplitude facilitation, MEP amplitude inhibition, or both [12, 53–61], depending on the parameters used [62–65] on disparate effects of stimuli on different motoneuron pools, on different experimental settings (e.g., single pulses versus stimulus trains, various stimulus intensities, relaxed versus contracted target muscles), and on different stimulation and recording sites. Low-amplitude vibration of a muscle increased MEP amplitudes and decreased the effectiveness of SICI [66, 67].

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BOLD signal intensity changes prior to and after constraint-induced movement therapy (CIMT) within the sensory and motor cortex proved a close correlation with SICI and ICF in paired-pulse TMS [68]. With TMS effects of AE stimulation on the motor system, its duration can be investigated very easily, yielding to information about the excitability of the motor cortex, and they help to clarify the physiological basis of variations in BOLD responses by AE stimulation. In case of a specific vascular response of the precapillary microvasculature independent from neuronal effects, TMS parameters should not change after afferent electrical stimulation.

3.2. TMS methodology

Again, a classical pre-/post-design is implemented (**Figure 4**) with a baseline TMS assessment (T0), AE stimulation for 30 min, a further TMS assessment (T1), a resting period for 1 h, and a third TMS assessment (T2). The experimental setup includes four different AE stimulation levels in randomized order: (1) sham, (2) sub-threshold with 50 Hz (sub-threshold/50 Hz), (3) sensory with 50 Hz (sensory/50 Hz), and (4) AE stimulation at motor level with 2 Hz (motor/2 Hz). At motor level, 2 Hz is chosen to avoid painful tetanic muscle contraction. Between sessions, there is at least an interim time of 5 days. Paired-pulse TMS is performed using a bi-stimulation module. A figure-of-eight coil with external loop diameter of 90 mm is applied for motor responses in the right first dorsal interosseus (FDI) muscle at the lowest motor threshold (MT, **Figure 7**).

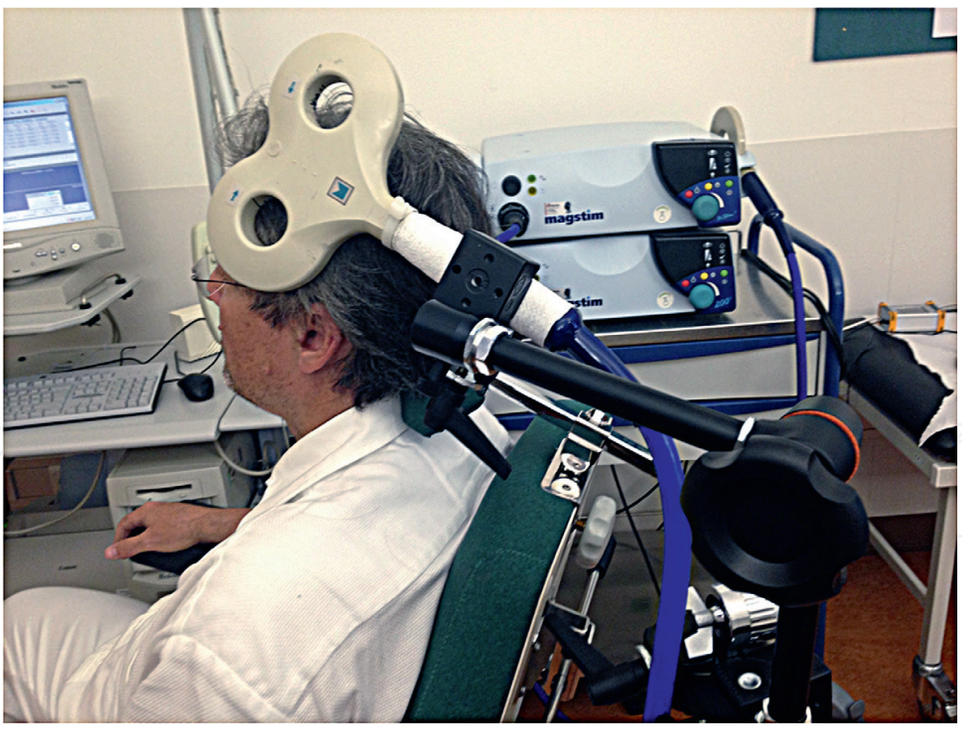

Figure 7. TMS experimental setup: a figure-of-eight coil (external loop diameter of 90 mm) is held over the left motor cortex at the optimum scalp position to elicit motor responses in the right FDI muscle at the lowest MT. The intersection of the coil is placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline to induce postero-anterior current flow. Surface muscle responses are obtained via two 9-mm diameter of Ag-AgCl electrodes with the active electrode applied over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. Muscle responses are amplified and filtered (bandwidth 8–2000 Hz).

The coil is held tangentially to the scalp with a 45° angle away from the midline for postero-anterior current flow. Muscle responses are recorded with 9-mm diameter of Ag-AgCl electrodes over the belly of the first dorsal interosseus (FDI) and the metacarpophalangeal joint of the index finger and are amplified and filtered (bandwidth 8–2000 Hz). The minimum stimulus intensity that produces an MEP at rest of 50 μV in three out of five trials defines the resting motor threshold (RMT). Then MEP recruitment curve (RC) with TMS intensities of 90, 100, 110, 120, 130, 140, 150, and 160 of the MT is measured. RC is recorded in T0, T1 and T2 measurements. For each stimulator, output intensity of five pulses is delivered with randomized stimulus intensity. The first MEP for each trial is discarded because of startle and reflex responses. Short interval cortical inhibition (SICI) is performed according to the technique of paired magnetic stimulation [69]. The conditioning and the test stimuli are set at 80 and 120% of MT, respectively. Inhibitory interstimulus intervals (ISIs) of 3 ms and facilitatory ISIs with 13 ms are applied. Conditioned and unconditioned trials are randomized. If MT after T0 for the paired-pulse measurement is changed, the stimulus intensity is adjusted to the corresponding MT in T1 and T2. The actual amplitudes after correction relate to those before AE stimulation. Usually paired-pulse TMS studies are carried out in 20–30 subjects with half of the subjects assigned to the verum and half to the control group. The verum group undergoes afferent electrical stimulation and the control group undergoes sham stimulation. Subjects are seated in a comfortable reclining chair during TMS measurements, afferent electrical stimulation, and at rest. Both hands are placed relaxed on soft supports beside the body [3].

3.3. Modulation of TMS parameters by afferent electrical stimulation

MT in TMS is thought to reflect the neuronal membrane excitability because it is increased by drugs that block voltage-gated sodium channels but not by drugs influencing neuronal synaptic transmission [70–72]. MT measured at baseline varies between 37 and 45% of maximum stimulator output among subjects. As shown in **Figure 8**, AE stimulation of 30 min has a significant decreasing effect on MT. This effect is obviously related to the strong effect of AE stimulation since the control group does not show any differences in MT. Post-hoc comparisons shows reliable MT decreases immediately after and 1 h after AE stimulation [3, 73].

Compared to MT, the MEP recruitment curve assesses neurons that are intrinsically less excitable or spatially further away from the center of activation by TMS. Increasing the TMS intensities from 90, 100, 110, 120, 130, 140, 150 to 160% of the MT determined for each subject MEP recruitment curves that show an increasing left-sided shift with increasing current intensity after the 30-min period of AE stimulation. **Figure 9** presents the effect of AE stimulation on MEP recruitment curves measured at T0 and T1.

No other effects are found reliable. However, whereas the control group shows any effects on amplitudes after time and no interaction effects of “stimulus intensity” and “time”, the group with verum AE stimulation shows the important reliable main effect of “time” with increased amplitudes after AE stimulation. The interaction effect does not reach significance. In both post-stimulation conditions (T1 and T2), the recruitment curve is increased compared to T0. Post-hoc comparisons at each intensity level reveal that at lower and mid-range intensities, MEP increases are significant both in T1 and T2 compared to T0. At higher stimulus

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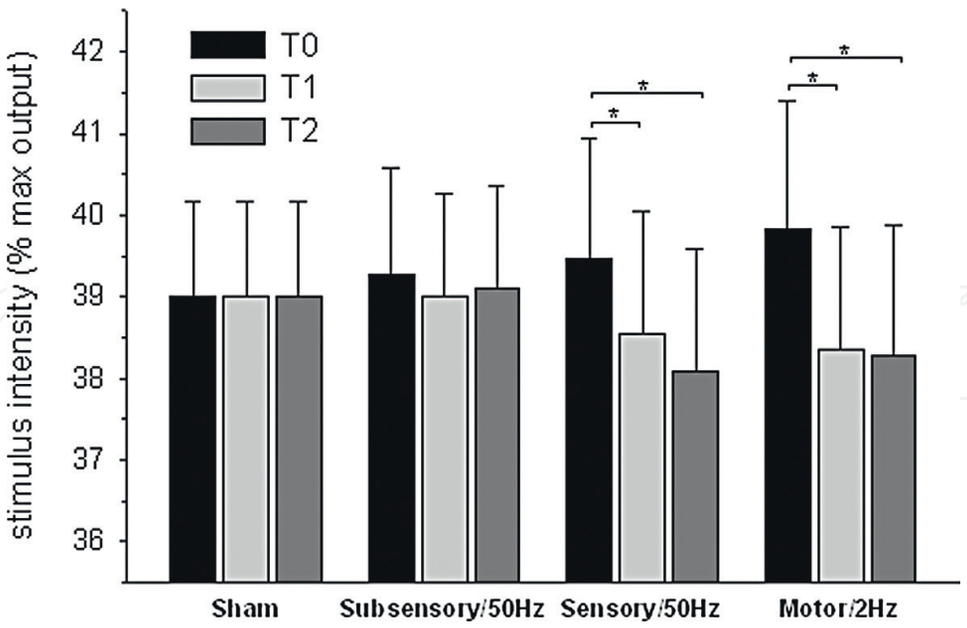

Figure 8. Resting motor threshold expressed as percentage of maximum stimulator output for the FDI muscle before (T0), immediately after (T1), and 1 h after (T2) afferent electrical stimulation with sub-sensory, sensory/50 Hz, and motor level electrical stimulation intensity as well as sham stimulation. Values plotted as mean (S.E.M). * indicates significant difference ($p < 0.05$) from T0. For sham stimulation there is no change of the resting motor threshold at T1 and T2 compared to the baseline measurement.

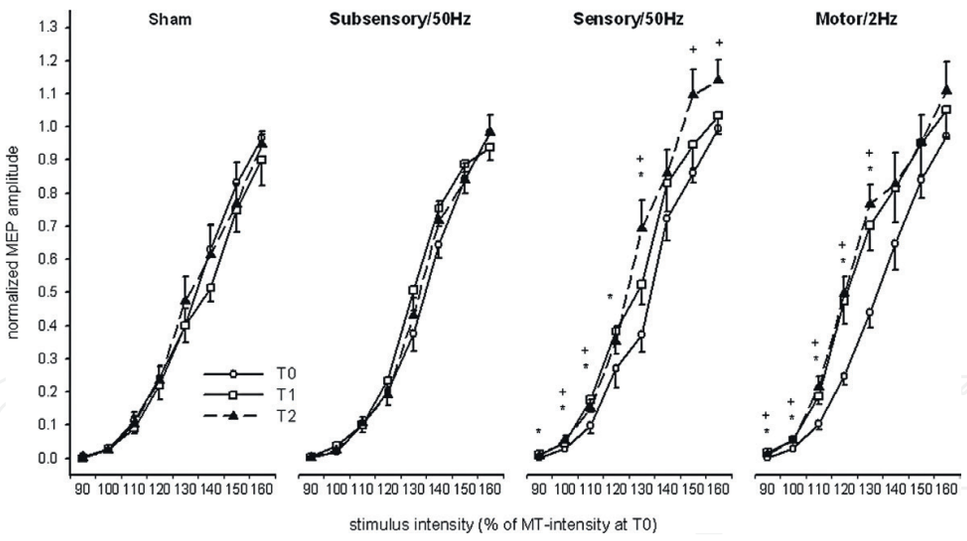

Figure 9. MEP recruitment curves before (T0), after (T1), and 1 h after (T2) AE stimulation at sub-sensory, sensory/50 Hz, motor level, and sham stimulation. MEPs are normalized to the mean MEPmax at T0. Mean (S.E.M.) of the normalized MEP amplitude is plotted for each stimulus intensity. * indicates significant difference ($p < 0.05$) between T1/T0 and (+) significant difference ($p < 0.05$) between T2/T0. A left-sided shift can be seen with increasing current intensities.

intensities (140–160% of MTT0 intensity), the tendency is partly kept although not reaching significance level (**Figure 9**). Additionally, post-hoc group comparisons of each intensity level are conducted and show reliable differences between AE and sham at T1 and T2. A two-factorial ANOVA with factors "group" and "stimulus intensity" is applied that does not reveal any difference in groups at T0.

Since paired-pulse TMS gives access to the motor cortex independently of spinal or peripheral mechanisms, it allows the evaluation of the intracortical circuits [3, 73]. There is good evidence that the interaction between a sub-threshold conditioning stimulus and a supra-threshold test stimulus at short interstimulus intervals (1–5 ms) relies on activation of c-aminobutyric acid (GABA)—in particular GABAA—circuits in the motor cortex. **Figure 10** shows the effect of AE stimulation on SICI and ICF.

Here, apart from the inherent effect of "interstimulus interval (ISI)", the three-factorial ANOVA reveals also a main effect of "time" and an interaction effect between "time" and "group". No other effects are found reliable. Follow-up ANOVAs for each group separately confirmed the effect of "ISI" for controls and AE stimulation group, respectively, but found a reliable effect of "time" only for the group who received verum AE stimulation. Other effects are not found reliable. Generally, in the verum group, the MEP inhibition at 3 ms is reduced and the facilitation at 13 ms is increased compared to T0 at T1 and T2. These changes do not reach significance for T1 but do so for T2 as post-hoc comparisons reveal. The circuit underlying intracortical facilitation is less well understood and is thought to be mediated by glutamate. Moreover, the downregulation of inhibitory neural circuits seems to play also a critical role in strengthening excitatory synapses. Current data suggest that afferent electrical stimulation also has a direct effect on the excitability of the intracortical circuits responsible for SICI and ICF at a cortical level. Conversely, no changes in spinal motor excitability (amplitude and persistence of F waves) are currently observed.

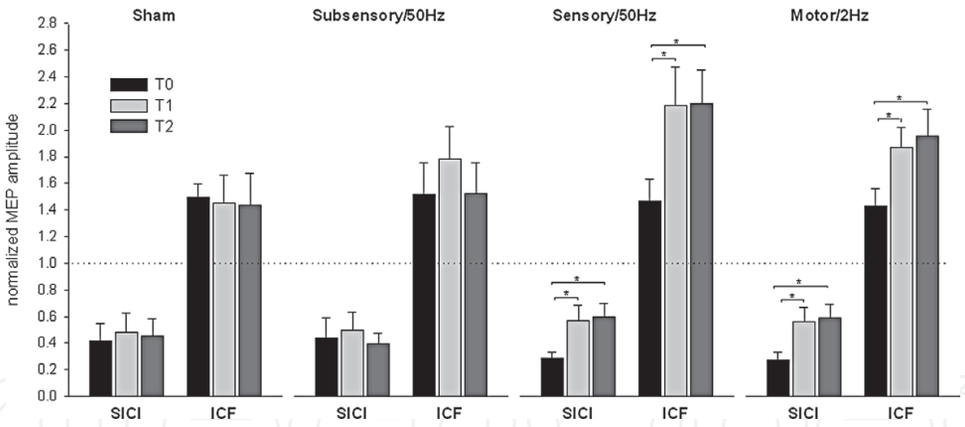

Figure 10. Paired-pulse TMS stimulation: before (T0), after (T1), and 1 h after (T2) AE stimulation at sensory/2 Hz level. The values for intracortical inhibition and ICF are normalized to their corresponding values in single-pulse stimulation for each condition and are then plotted as the mean (S.E.M). * indicates significant difference ($p < 0.05$) from T0. At T1 and T2, a decrease of SICI can be seen; ICF is significantly increased at T2.

4. Discussion

From these pre-/post-AE stimulation studies, we learn that changes in motor cortex excitability outlast AE stimulation up to 2 h and intracortical excitability is significantly enhanced 1 h after AE stimulation and not significantly increased immediately after the AE stimulation. Up to now, this late excitability enhancement remains unclear. Maybe an intracortical synaptic

reorganization LTP is the underlying mechanism for the delayed facilitation. The stimulation-induced cortical plasticity may be due to synaptic modification such as LTP. LTP, as well as LTD of synaptic transmission, had been suggested to be responsible for activity-dependent changes in the strength of synaptic connections and efficiency of synaptic signal transduction since its discovery in the early 1970s of the last century [74]. But the outcome of synaptic modifications on behavioral changes induced by stimuli that drive LTP- or LTD-like processes is not well known today, especially not in patients with brain lesions. STP and LTP are induced by repeated activation of excitatory synapses with N-methyl-ᴅ-aspartate glutamate receptors leading to the formation of new synapses or the unmasking of other excitatory amino acid receptors on motor neurons [75]. Also, remote modulation of motor cortex excitability may be involved including additional cortical and subcortical structures connected with the primary motor cortex. The increased excitability may reflect an increased neuronal activity due to dynamic interaction between various synaptic and cellular mechanisms that locally process the augmented afferent proprioceptive and exteroceptive input to the sensorimotor cortex [26]. The strongest neuromodulatory changes could be achieved with stimulation of the highest intensity (motor level). Defining proper stimulation parameters, in particular with regard to stimulation intensities and frequencies, will provide an important basis for further therapeutic applications of afferent electrical stimulation in neurorehabilitation, especially in stroke patients or patients after traumatic brain injury.

In conclusion, the increased cortical excitability leads to an extension of neuronal activity. The time course of neurophysiological effects, as measured by TMS, and also seen in fMRI BOLD responses, suggests a prolonged clinical efficacy of AE stimulation. Further studies should focus on the issue whether more specialized stimulation protocols in particular with regard to stimulation intensities and frequencies can prolong the modulatory effects on the sensorimotor cortex through plastic changes in synaptic efficacy and thus can sub-serve a long-term rehabilitation process of impaired motor functions of the hand after brain lesions [76]. This finding of increased motor cortical excitability after afferent electrical stimulation can help develop new rehabilitation strategies in combination with physical and occupational therapy.

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