



# Sensory Afferent Stimulation

# 9

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## 9.1 Introduction

Sensory afferent stimulation is a method of non-invasive brain stimulation (NIBS) that induces neuromodulation especially at the synaptic level in the area of the sensorimotor cortex [1–3]. In sensory afferent electrical stimulation (SAES), electrical stimuli are used in continuous series or in time-structured stimulation patterns, which trigger peripheral action potentials in afferent nerve fibers, which lead to an increased sensory afferent input into the sensorimotor centers in the brain. SAES is currently developing into a promising adjuvant intervention in the field of NIBS in combination with conventional sensorimotor therapy in a temporal correlation to improve the outcome in neurorehabilitation.

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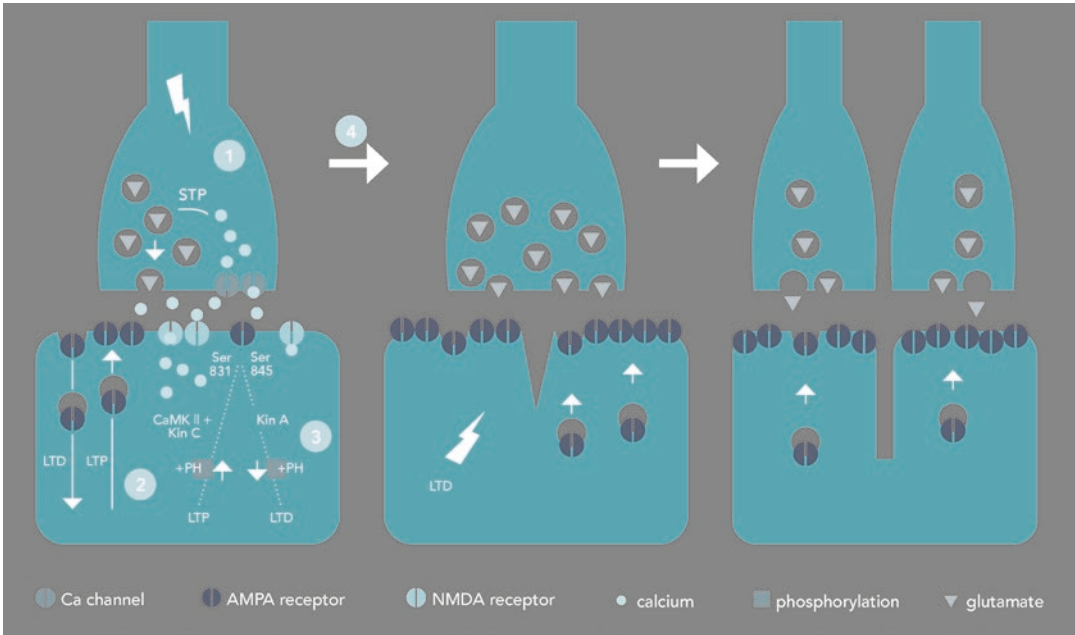
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## 9.2 Sensory Afferent Stimulation

### 9.2.1 Neurobiology of Sensory Afferent Stimulation

Synapses can be highly plastic and change the strength of their synaptic transmission due to an “intrinsic” change in their own activity or a change in the synaptic input from other nerve cells “extrinsically”. Intrinsic and extrinsic synaptic plasticity are considered to be the basic neurobiological mechanisms for memory, learning, and restitution of lost functions.

The model of long-term potentiation (LTP) and long-term depression (LTD) (Ⓐ and Ⓑ in Fig. 9.1) describes an extrinsic change in the strength of a synaptic transmission [4]. Sensory afferent stimulations induce neuromodulatory effects in the area of short-term plasticity (STP, Ⓒ in Fig. 9.1) and structural neuroplasticity with sprouting of new synapses (synaptic sprouting, Ⓓ in Fig. 9.1) and the formation of new anatomical connections (wiring) in the nervous system. Due to the increased sensory afferent input in SAES (Ⓔ lightning symbol ⚡ in Fig. 9.1), more glutamate is released from the presynaptic vesicles into the synaptic cleft. This happens with almost complete opening of the AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, which leads to a strong  $\text{Na}^+$  influx into the cell with a strong depolarization of the cell membrane. Through glutamate binding to the



**Fig. 9.1** Increased sensory-afferent input ( $\lambda$ ) induces neuroplasticity in the short-term (①), the long-term (② and ③), and the structural areas (④). Depending on the type of sensory-afferent stimulation, the synaptic transmission

can be increased (LTP, long-term potentiation) or reduced (LTD, long-term depression). With LTD, the mechanisms of the LTP can be reversed again (②, ③, and ④)

NMDA (*N*-methyl-D-aspartate, NMDA) receptor and strong depolarization of the cell membrane, the  $Mg^{2+}$  ions, which block the NMDA receptor, can also diffuse out, causing it to become a massive  $Ca^{2+}$  influx at the NMDA receptor into the cell which leads to a number of intracellular signaling pathways with enzyme induction. Depending on the type of sensory afferent input, LTP increases and LTD decreases synaptic transmission. In LTP there is also an increased incorporation of AMPA receptors into the postsynaptic membrane and activation of calcium/calmodulin-dependent kinase II (CaMK II), which with kinase C (Kin C) leads to a phosphorylation (+PH) of the subunit GluR1 of the AMPA receptor of the amino acid Serine 831 (Ser 831). This increases the conductivity of the AMPA receptor ( $\uparrow$ ), combined with a massive influx of ions into the cell, which maintains LTP (② in Fig. 9.1). Together with kinase A, there is a phosphorylation (+PH) of the amino acid Serine 845 (Ser 845) of GluR1, which reduces the synaptic transmission ( $\downarrow$ ) and initiates the LTD (③ in Fig. 9.1).

The LTP further increases the density of the AMPA receptors in the postsynaptic membrane, which leads to a splitting of the postsynaptic membrane with the formation of new synapses (④ in Fig. 9.1). In this way, new neuronal networks can be built up permanently, combined with new behavioral skills or with the restitution of lost functions. Depending on the type of sensory afferent stimulation, a LTD can also be induced, which counteracts the LTP and can reverse it (e.g., downregulation of the LTP upregulated AMPA receptors in the postsynaptic membrane, ④ in Fig. 9.1) [5].

With a single stimulation lasting at least 30 min, the duration of the neuromodulatory effects is in the range of a few hours [6–8], whereby with prolongation and repetition of the stimulation a sustainable prolongation of the effects is possible. The optimal parameters and stimulation patterns for the stimulation are not yet exactly known [9]. In addition to the frequency, the stimulation intensity seems to have the greatest influence on neuromodulation [8].

The stimulation depolarizes afferent proprioceptive and exteroceptive nerve fibers of group Ia (thick afferents of the muscle spindles), Ib (thick afferents of the tendon receptors and Golgi organs), and group II (slowly and quickly adapting afferents of the mechanoreceptors of the skin and the  $\gamma$ -fibers of the muscle spindle) with short latency [10–12]. The afferent signals are further forwarded in the posterior funicles and in the spinocerebellar tract of the spinal cord to the brain stem, to the ventroposterolateral nucleus of the thalamus with projection to the contra- and ipsilateral sensorimotor cortex in the Brodmann areas (BA) 3a, 2, 1 and 4 and to the cerebellum [13–15]. In addition to the direct afferents, BA 4 (primary motor cortex, M1) also receives projections from BA 3a, 2 and 1 [16] as well as transcallosal projections from the contralateral cerebral cortex [17–19]. In their small intrinsic muscles, the hand and foot have a high density of muscle spindles [20, 21], joint receptors, and Golgi tendon organs [10, 22,

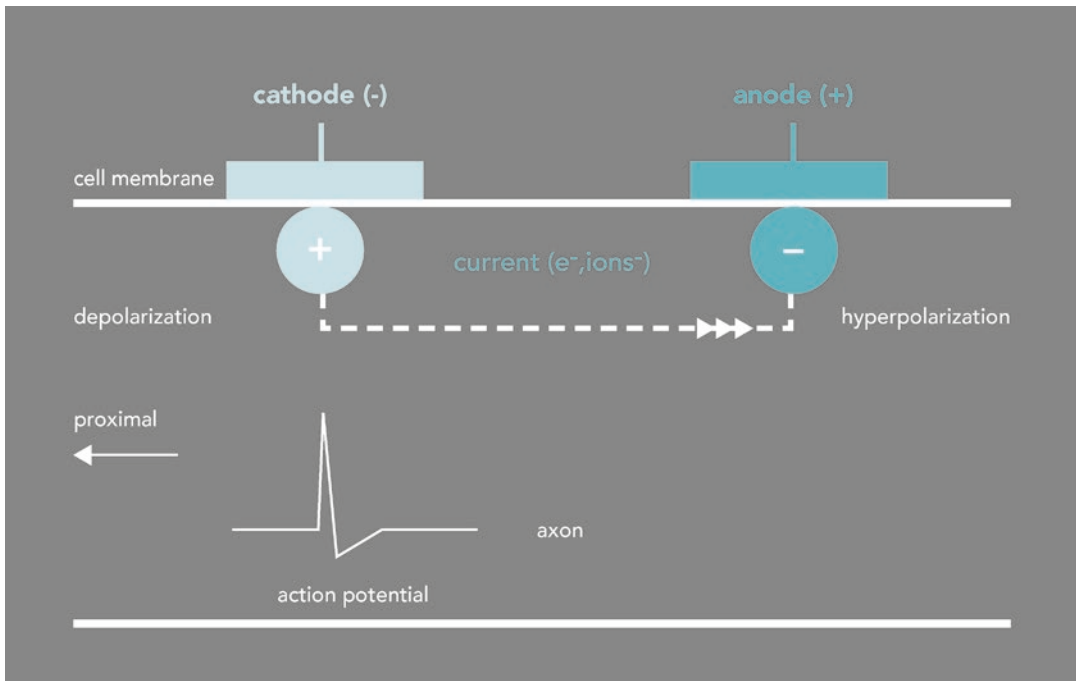
23], which is why these muscles are an abundant source of proprioceptive inputs for the spinal cord and brain. Proprio- and exteroceptive afferents are the basis for the perception of kinesthetics in the brain [24].

#### Summary

In sensory afferent stimulation, nerve fibers of deep and fine surface sensitivity are stimulated with the induction of short-term, long-term, and structural neuroplasticity in the brain.

### 9.2.2 Sensory Afferent Electrical Stimulation

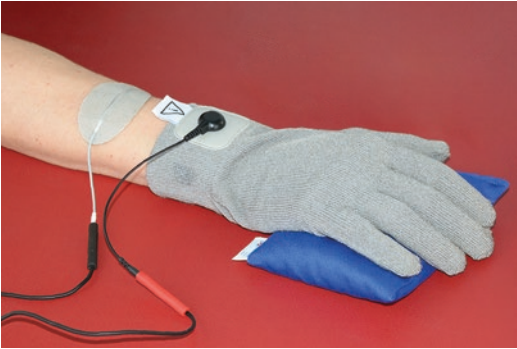
In SAES, action potentials are triggered below the stimulating cathode by extra- and intracellular ion currents with depolarization of the cell membrane (Fig. 9.2).



**Fig. 9.2** With SAES (sensory afferent electrical stimulation), the current flows from the cathode in all spatial directions in the extracellular space (ECS) and thus also vertically through the cell membrane, in order to continue to flow intracellularly along the electric field lines (arrows) to the anode, from where it flows again vertically through the cell membrane into the ECS. Negative charges (electrons, e<sup>-</sup>, and

negatively charged ions, “-”) are shifted along the course of the peripheral nerve fibers primarily intracellularly towards the anode (arrows) with local hyperpolarization of the membrane, positive charges (positively charged ions, “+”) toward the cathode with local depolarization of the membrane. The action potentials for the sensory afferent input into the brain are then triggered under the cathode

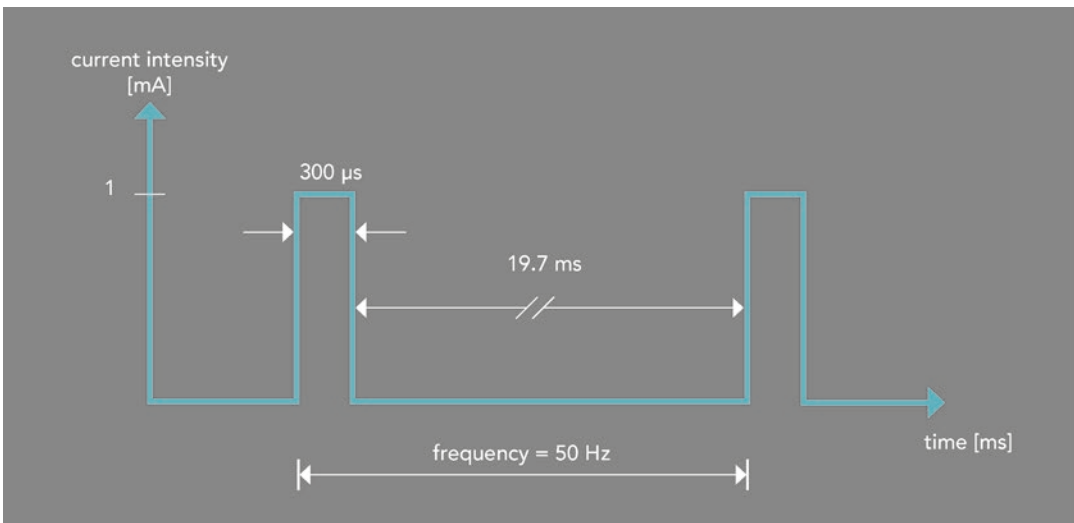
Ordinary self-adhesive electrodes are used, like in nerve or neuromuscular stimulation. A more increased sensory afferent input can also be induced with anodes in the form of an electrode glove (mesh glove, MG) (Fig. 9.3) or an electrode sock (mesh sock, MS), which is due to the stimulated size of the skin area to bring about a particularly strong neuromodulatory input in the sensorimotor cortex.



**Fig. 9.3** With mesh glove stimulation, the afferent action potentials are triggered in the three hand nerves (N. radialis, medianus et ulnaris) under the dorsal and palmar cathode on the forearm

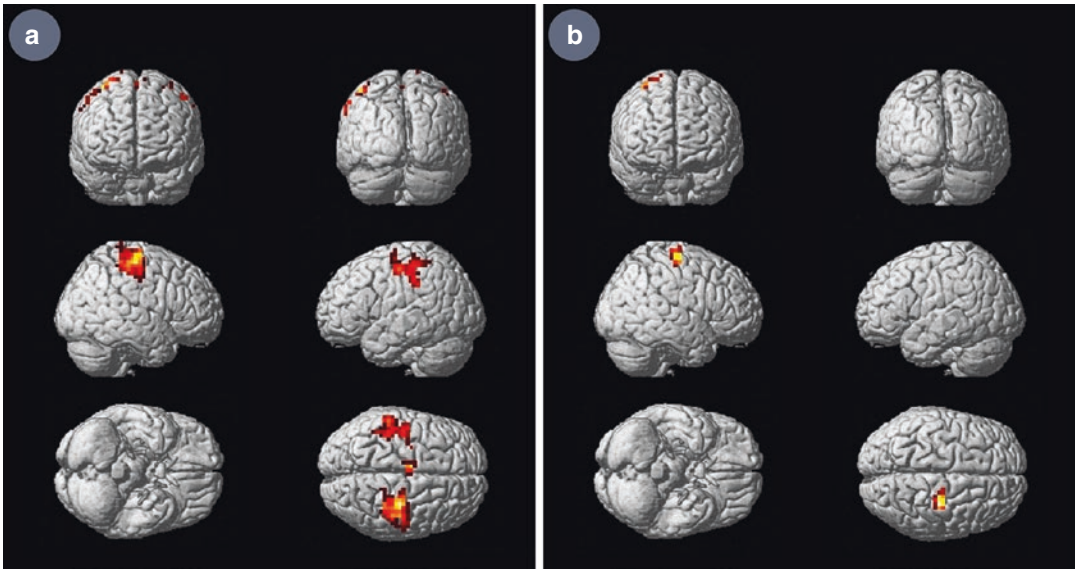
MG or MS are connected to a two-channel electrical stimulation device and function as anode, carbon surface electrodes over the tendons of the flexors and extensors on the forearm or lower leg as cathodes (Fig. 9.3). The current is applied in a pulsed manner. The pulse shape is rectangular or trapezoidal and mono- or biphasic with a frequency of 50 Hz and a pulse width of 300  $\mu$ s. The stimulation is carried out for 30–60 min (Fig. 9.4).

Neuromodulatory effects through SAES can be demonstrated in fMRI (functional Magnetic Resonance Imaging) with a finger-to-thumb tap paradigm (Test Motor Task, TMT) with a self-selected frequency of approximately 2 Hz in a pre-/post-design [6, 25]. With TMT, brain activity in the form of the so-called BOLD effect (Blood Oxygenation Level Dependent, BOLD) is detected in the contra- and ipsilateral hemisphere in the pre- and postcentral gyrus, in the superior frontal gyrus and in both halves of the cerebellum with a dominance ipsilateral to the tapping hand. After 30 min of SAES, finger-to-thumb tapping (Conditioned Motor Task 1, CMT1) shows an increase in brain activity in both hemispheres in



**Fig. 9.4** Current pulse with SAES (sensory afferent electrical stimulation): rectangular pulse with a width of 300  $\mu$ s and a frequency of 50 Hz. The duration of the stimulation is at least 30 min at a sensitive level (at approx. 5 mA, depending on skin resistance), which already results in inducing neuroplasticity in the long-term range (LTP, long-term potentiation; LTD, long-term depres-

sion). At the motor level, the current intensities are higher (up to approx. 10 mA, depending on skin resistance). Due to its higher effectiveness, SAES also uses protocols with a shorter stimulation duration (10–30 min) at the motor level. The frequencies vary between 1 and 50 Hz, the pulse width between 100 and 1000  $\mu$ s, depending on the level of stimulation (Table 9.1)



**Fig. 9.5** (a) Subtraction analysis (CMT1–TMT) in fMRI (functional magnetic resonance imaging): Conditioned Motor Task at T1 (CMT1)–Test Motor Task (TMT) at T0 shows an increase in the BOLD (Blood Oxygenation Level Dependent) response during CMT1 in the contralateral hemisphere within SM1 (sensorimotor cortex), within the premotor cortex (PM), in the inferior parietal lobule (IPL) and in the ipsilateral hemisphere within SM1, PM, IPL, SMA (supplementary motor area) and the cingulate

gyrus (CG). (b) Subtraction analysis (CMT2–TMT): Conditioned Motor Task at T2 (CMT2)–Test Motor Task (TMT) at T0 two hours after the end of the afferent electrical stimulation. The increase in the BOLD response in the sensorimotor cortex in CMT1 has almost fallen back to the BOLD level in TMT, except for a residual increased level contralateral to the stimulated hand in SM1 (sensorimotor cortex)

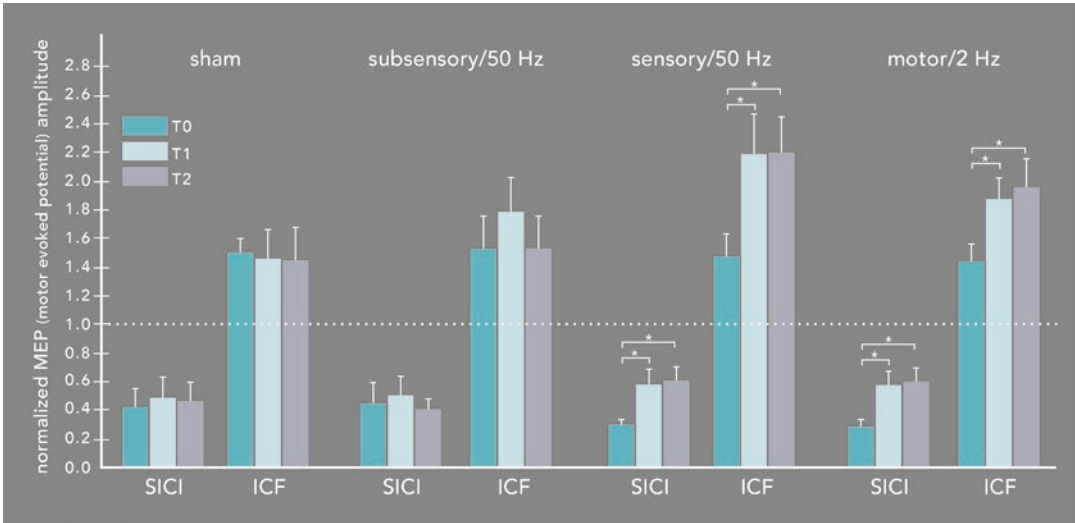
the pre- and postcentral brain regions as well as in the superior frontal gyrus (supplementary motor area, SMA) and in the middle frontal gyrus. Fig. 9.5a shows the subtraction image of the BOLD response for the CMT1 after 30 min of SAES minus the BOLD response for the TMT before the SAES. The “net BOLD effect” corresponds to the increase in brain activity induced by the SAES when finger-to-thumb tapping after the SAES, which is still visible two hours after the end of the SAES contralateral in the area of the sensorimotor cortex (SM1) of the active hand, but has otherwise already subsided (Fig. 9.5b).

At the motor neuronal level, the net BOLD effect corresponds to an increased level of activity of the motor cortex, as has been demonstrated in Transcranial Magnetic Stimulation (TMS) studies and with intracortical recordings in monkeys [3, 7, 26]. Accordingly, SAES can shift intracortical excitability parameters such as short interval intracortical inhibition (SICI) or intra-

cortical facilitation (ICF) in the direction of disinhibition of the motor cortex (Fig. 9.6).

The sham stimulation without current flow showed no disinhibition, the subsensitive SAES with 50 Hz an incipient and the SAES with 120% of the sensitive level and 50 Hz showed a clear shift in the excitability parameters in the direction of disinhibition of the motor cortex. Another interesting result of these studies is that the SAES already shows visible rhythmic muscle contractions at the motor level and at a frequency of 2 Hz similarly good neuromodulatory effects in the motor cortex as the SAES at the sensitive level. The lower frequency is apparently compensated for by an increased current intensity (Fig. 9.6). A strong correlation between spatially localized BOLD response and local field potentials could also be demonstrated [26]. SAES evidently induces an increased local field potential (LFP) in the sensorimotor cortex for at least a few minutes, which has already been demonstrated with





**Fig. 9.6** TMS stimulation with paired TMS (transcranial magnetic stimulation) pulses: before (T0), after (T1), and one hour after (T2) mesh glove (MG) stimulation with sensory afferent stimulation at 50 Hz (“Subsensory” = 80% of the sensitive threshold, “Sensory” = 120% of the sensitive threshold) and 2 Hz (“Motor” = motor level). The values for short intracortical inhibition (SICI) and intra-

cortical facilitation (ICF) are normalized for each condition to their corresponding values for single pulse stimulation and then plotted as a mean value (SEM, standard error of the mean). The asterisk (\*) indicates a significant difference ( $p < 0.05$ ) compared to T0. A significant decrease in SICI and a significant increase in ICF can be seen at T1 and T2

somatosensitive evoked potentials (SSEP) [15]. Augmented LFPs change the intracortical excitability of the motor cortex in the direction of disinhibition and facilitation with stronger recruitment of the motor neurons involved in finger-to-thumb tapping with additional functional gain, as could be shown in stroke patients treated with SAES in combination with daily motor therapy for three months compared to those treated only with motor therapy [27–29]. The SAES induces this increased motor neuron recruitment by transforming pre-existing silent synapses into functional synapses via an increased presynaptic release of glutamate, the reduction of inhibition by  $\gamma$ -aminobutyric acid (GABA), and the upregulation of postsynaptic AMPA receptors with unmasking of latent intracortical horizontal connections (Fig. 9.1) [30–32].

During a SAES of at least 30 min, the LTP is already involved, since the neuromodulation can still be detected after two hours (Fig. 9.5b). During a SAES of less than 30 min, only longer-

lasting forms of STP such as post-tetanic potentiation or augmentation are observed (Fig. 9.1). During augmentation, there is an increase in the release of transmitters from the presynaptic vesicles in the range of seconds; in post-tetanic potentiation, the increase in transmitter release continues for a few minutes after the repetitive electrical stimulus has ceased [33]. So far, it is not known at what duration of the SAES the LTP begins. To date, it is also not known to what extent the neuromodulatory effects can be further enhanced upon SAES >30 min. However, there is consensus that the sustainability of the SAES can be increased by increasing the duration of stimulation and by increasing the number of sessions. There are currently no recommendations for the duration of stimulation and the number of sessions based on a good level of evidence. In numerous clinical studies, the duration of the SAES is three to six weeks with daily sessions of 30–60 min in length.

Depending on the skin resistance, the current strength for the sensitive threshold is between 2

**Table 9.1** Recommended parameters of SAES (sensory afferent electrical stimulation) in therapy

level	current	pulse width	frequency	pulse shape	duration
motoric	6-10 mA	100-300 $\mu$ s	1-5 Hz	mono-/biphasic, rectangle, (trapezoid)	10-30 min
sensitive	2-5 mA	250-1000 $\mu$ s	10-50 Hz	mono-/biphasic, rectangle, (trapezoid)	30-60 min

and 4 mA. In therapy, for supra-threshold stimulation at a sensitive level, the current strength is set to 120% of the sensitive threshold for a duration of 30–60 min at a frequency between 10 and 50 Hz [7]. At this level, electromyography does not yet show any muscle contractions. For stimulation at the motor level in therapy, the current intensity is increased until slight contractions of the small hand muscles are visible, which is reached at approximately 6–10 mA, depending on the skin resistance. A frequency between 1 and 5 Hz is chosen to avoid tetanic contractions of the muscles. The stimulation is carried out over a period of 10–30 min. The SAES then changes to a peripheral neuromuscular stimulation as in the peripheral functional electrical stimulation (FES) (Table 9.1). Fig. 9.6 shows that SAES at a sensitive level with 50 Hz increases the excitability of the motor cortex similarly effective as peripheral neuromuscular stimulation with 2 Hz.

#### Summary

The SAES with 50 Hz at a sensitive level increases the excitability of the motor cortex similarly effective as peripheral neuromuscular stimulation with 2 Hz.

## 9.3 SAES in Neurorehabilitation

### 9.3.1 Sensorimotor Paresis After Stroke

SAES has been known to induce cortical neuroplasticity for several decades. It offers the possibility of non-invasive neuromodulation in stroke patients with sensorimotor paresis in the subacute and chronic phase [9]. The acute phase has not yet been adequately investigated, in particular the question of the connection between SAES and an increased release of excitotoxic amino acids in the acute phase of the stroke. In patients after a stroke with a chronic sensorimotor paresis of the upper or lower extremity without further improvement through conventional sensorimotor therapy, the SAES has shown an improvement in the sensorimotor performance of the affected extremity [27, 28, 34]. In particular, there was a positive effect on a spastically increased tone of the affected extremity. The SAES was performed for half an hour every day for three months. As the neuromodulatory effect of a 30-min SAES treatment lasts for up to two hours [6, 7], the opportunity arises to combine it with a subsequent sensorimotor therapy. Thereby, the SAES should be applied within one hour prior to sensorimotor therapy.

In a recently published meta-analysis it was found that the SAES in combination with neurological standard rehabilitation in this temporal correlation in the chronic phase after stroke could improve significantly the maximum torque of the affected hand during dorsiflexion and also the performance in the Timed up and go test [35]. The Ashworth score for spasticity was reduced, but not significantly. Overall, it was possible to conclude in this meta-analysis that SAES can improve impaired motor functions of the lower extremity in the early phase and impaired motor functions of the upper and lower extremity in the chronic phase, without significant effects on spasticity. In particular, longer periods of SAES combined with sensorimotor therapy over several weeks showed positive effects on impaired sensorimotor functions.

So far, six randomized, controlled (RCT) studies have dealt with SAES in the rehabilitation of stroke patients with sensorimotor paresis of the upper extremity:

Yozbatiran et al. (2006) [36] examined motor exercises of the upper extremity with and without SAES with kinesthesia and position detection tests, a hand function test, and a hand movement scale before and after treatment. There was no significant difference between the groups after the treatment with regard to the hand movement scores and the kinesthesia and position detection tests. In the SAES group, however, there was a significant improvement in hand function after the treatment [36].

McDonnell et al. (2007) [37] combined the SAES with task-specific training (“grip lift” task), which showed significant improvements compared to the control group.

Conforto et al. (2010) [38] combined the SAES of the hand with two different stimulation intensities 1 and 2 ( $1 < 2$ ) in patients with subacute stroke before motor training. The stimulation intensity 1 showed a greater improvement in the Jebsen-Taylor test after the first month of stimulation with a decrease in the difference two and three months after the intervention with no difference in the other motor function tests [38].

Fleming et al. (2015) [39] examined task-specific training in combination with SAES with

regard to the function of the upper extremities and the arm use in patients in the chronic stage after stroke. Immediately after the intervention, there was great improvement in the ARAT scores, which was no longer detectable three and six months after the intervention [39].

Since several randomized controlled studies have so far demonstrated a benefit of SAES in stroke patients with sensorimotor paresis, which was also confirmed in a meta-analysis [35], a recommendation at evidence level A can be given for the use of SAES in sensorimotor rehabilitation after a stroke for the lower extremity in the subacute phase and for the upper and lower extremity in the chronic phase.

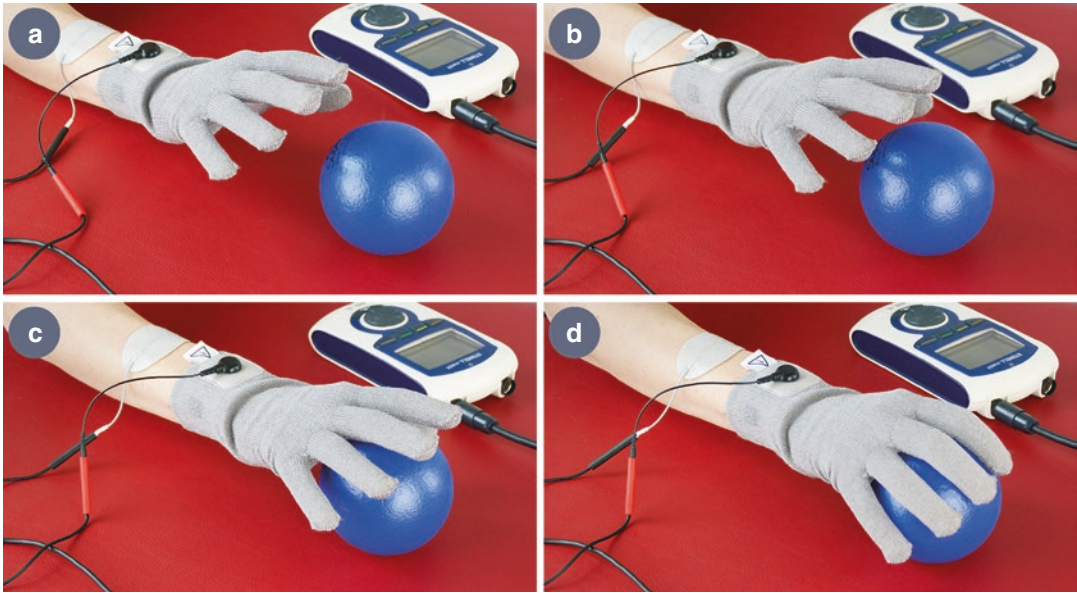
#### Summary

With regard to the adjuvant use of SAES in sensorimotor therapy after stroke, a recommendation at evidence level A can be given for the upper and lower extremity in the chronic phase and for the lower extremity in the subacute phase.

### 9.3.2 Therapy of Neglect

The SAES is also used in neglect therapy. So far, various modalities of sensory afferent inputs (optokinetic, vibration of the neck muscles, vestibular and magnetic stimuli, SAES) have been investigated, which showed an impressive reduction in neglect [40, 41]. Sensory afferent input of various modalities (e.g., proprio-/exteroceptive, visual, vestibular, auditory) into the brain is achieved through multimodal integration in sensory afferent centers of a higher order (especially in the parietal lobe in the superior parietal lobule, SPL, and in the inferior parietal lobule, IPL) converted into information for voluntary, purposeful motor actions. In particular, proprioceptive, exteroceptive, premotor, and visual information converge in SPL and IPL when grasping with the hand. In the case of multimodal integration, the IPL is mainly involved in the transformation of retinal signals from targeted objects into a motor action pattern for voluntary, visually controlled,





**Fig. 9.7** Visually controlled, targeted gripping of a ball while applying SAES (sensory afferent electrical stimulation) with the mesh glove. (a) start movement, (b) reaching the object, (c) gripping the object, (d) manipulate the object. A task-oriented context of SAES may bring an

additional therapeutic effect in neglect, in sensorimotor paresis or for motor learning. However, this has not yet been scientifically proven in randomized, controlled studies

targeted movements in relation to the targeted object and is of great importance for eye-hand coordination (e.g., grasping a ball with the hand; Fig. 9.7) [42, 43].

The information running to the brain for voluntary, visually controlled, targeted movements is primarily transmitted by the Ia and Ib nerve fibers, which are primarily excited in the SAES. The bilaterally increased activity in the IPL demonstrated in the fMRI in the conditioned motor task immediately after the SAES indicates an increased bilateral afferent sensory input in the IPL by the SAES (Figs. 9.5a and 9.7) [6]. Daily 30-min SAES treatments for stroke patients for three months also led to a clinical improvement in neglect, as has already been demonstrated in several studies [28, 44, 45].

With peripheral FES, peripheral nerves and the muscles innervated by them are stimulated at the same time, triggering muscle contractions, which is why this additional intensive stimulation

of muscle spindles, Golgi tendon, and joint receptors in comparison to SAES provides an additional sensory afferent input or boost to the brain and especially to the higher-order sensory afferent centers with a possibly greater effect than with the SAES. However, a direct comparison between SAES and peripheral FES with regard to the benefit in unilateral neglect has not yet been carried out. Nevertheless, a recently published randomized controlled study in patients in the acute phase after stroke with multimodal, unilateral neglect clearly demonstrates the benefit of peripheral FES on the affected side, the benefit of a combination of peripheral FES with conventional therapy of prism adjustment for neglect was greater than with peripheral FES or prism adjustment alone. The treatments were carried out 50 min a day, five times a week for a total of three weeks [46]. Since no larger randomized studies exist for the SAES in neglect, but several clinical studies speak for the benefit of the SAES

in neglect, a recommendation at evidence level B can be given for the use of the SAES in the treatment of neglect.

#### Summary

A recommendation at evidence level B can currently be given for the adjuvant use of SAES in the treatment of neglect.

## 9.4 Discussion

The SAES induces a modulation in the nervous system in the area of short-term and long-term as well as structural neuroplasticity; this through an increased proprioceptive and exteroceptive input into the nervous system with the consequence of increased activity of the motor cortex [17]. Many studies suggest that this plasticity is mainly induced at the level of the synapses in the area of the sensorimotor cortex. With the adjuvant use of SAES in neurorehabilitation in combination with subsequent motor therapy, the overall outcome can be improved compared to motor therapy alone, as randomized, controlled studies have shown. The strongest modulation with the SAES can be achieved with a current intensity at the motor level depending on the skin resistance with 6–10 mA at a low frequency (2 Hz) with a similarly good effect of an SAES with a current intensity at a sensitive level depending on the skin resistance with 2–5 mA and a frequency of 50 Hz, although there is currently no optimized stimulation protocol with regard to the stimulation parameters. The modulatory effects last up to two hours after at least 30 min of stimulation. The current study situation suggests that an increase in the duration of the stimulation and an increase in the number of sessions can prolong the sustainability of the modulatory effects. Furthermore, there is a consensus that a pulsed current application is superior to a continuous one, although the optimal pulse shape is still unclear. Furthermore, there is still a lack of clarity regarding the pulse rate. The further optimization of the SAES stimulation protocols for therapy will be decisive for further application in neurorehabilitation. Also,

there is still no data on the benefit of time-complex, structured stimulation protocols, which could further increase the neuromodulatory effect of the SAES and thus better support a long-term rehabilitation process for brain and spinal cord damage. In addition, it has not yet been clarified whether the SAES can enhance therapeutic effects in a task-oriented context (Fig. 9.7). In particular, there is currently the question of whether the SAES can promote motor learning in a task-oriented context. In a study published in 2014, an improvement in performance compared to the group with sham stimulation in a nine-hole peg test during a SAES with a mesh glove was described even one week after initial training [47]. In addition, there is currently a lack of comparative studies between the SAES and other methods of non-invasive brain stimulation to promote neuroplasticity such as the FES, the repetitive transcranial magnetic stimulation (rTMS), or the transcranial direct current stimulation (tDCS).

In the future, it will be important to further optimize the current stimulation protocols for the SAES and to combine these in an appropriate manner with the conventional methods of neurorehabilitation to optimally promote the rehabilitation process in the brain and spinal cord. In addition, a combination of the SAES with other methods of non-invasive brain stimulation, such as the rTMS, and the application in a task-oriented context could further increase the therapeutic potential of the SAES.

Finally, Table 9.1 gives recommendations based on the current study situation for setting the parameters of the SAES in therapy.

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