12 Post-Stroke Recovery

More than half of all stroke survivors have remaining disabilities and roughly one third of stroke survivors suffer from aphasia. Rehabilitation gives modest improvement in leg function, but no clear benefit on arm function, and actual recovery slowly subsides after the first post-stroke month; no major spontaneous recovery can be expected beyond the 6-month mark. On the other hand, aphasia can improve further even several years after the initial stroke (i.e. longer window for recovery). The degree of recovery is idiosyncratic, despite similar rehabilitation protocols. This may depend on, among other factors, inter-individual variability in vascularization (e.g. a different extent of collaterals or different blood supply from adjacent arteries) or intrinsic reorganizational capability.

12.1 Premises

In a series of duplicate papers since 1993, a Japanese group (Katayama et al 2002, Yamamoto et al 2011) reported subjective improvements in motor performance in a subset (19%) of central post-stroke patients who had mild motor weakness submitted to extradural M1 ICS (<50 Hz). In particular, they examined the correlation between the duration of daily M1 ICS applied over 6 months and motor function assessed on the basis of the Fugl-Meyer Assessment (FMA) score of the patients. In the 6 patients with motor weakness, the FMA score of the upper extremity increased in 4 patients who underwent daily stimulation for less than 4 hours. On the other hand, two patients who were overstimulated to control their complicating post-stroke pain showed decreased FMA scores and worsened motor function due to increased rigidity and/or spasticity: both recovered their motor function after stimulation was restricted to less than 4 hours. Nuti et al (2012) – among others – reported that 10 out of 38 (26%) patients prospectively submitted to M1 ICS for chronic pain declared a benefit in their motor function. Eight presented objective evidence of recovered dexterity for rapid alternating movements, due to relief of spasticity. They found a significant correlation between thalamic lesions and benefits in motor performance. Thus, ICS per se may partially contribute to overall improvement.

Over the past decade or so, noninvasive cortical stimulation (rTMS, tDCS) has been employed in order to enhance recovery from stroke, especially subcortical stroke. However, a review of published controlled studies found no consistent beneficial effects of rTMS (8-30% transient benefit), a trend only for improvement in activities of daily living and only limited evidence for a beneficial effect of rTMS on aphasia and neglect (Raffin and Siebner 2014). Anodal tDCS has been found to benefit arm motor
function in chronic stroke paretics, but the small sample size and the very low to low quality of the studies (n=15; 455 patients) mitigate this conclusion (Raffin and Siebner 2014, Elsner et al 2014). In addition, there is also substantial intersubject variability in their effects. Regardless, experience with noninvasive CS suggests that:

1. targeting may depend on the stage of stroke,
2. multisite stimulation should be an option, e.g. stimulating simultaneously or consecutively M1 or premotor, parietal and cerebellar cortex in the ipsi or contralesional hemisphere,
3. repeated daily sessions might be better - with prolongation of the aftereffects and cumulative effects- but nonetheless suboptimal,
4. a night of sleep might be indicated to resensitize the brain to stimulation (Night stim-OFF),
5. CS and rehabilitation can be additive, with the choice of activity critical for the success of the therapy (constraint-induced therapy not additive)
6. while stimulation applied after 12 months of stroke incurs no risk of interfering with spontaneous neuroplastic changes, there is some sparse evidence that benefit might accrue from subacute stimulation (within 2 weeks), although at this point negative consequences cannot be ruled out. Direct stimulation around lesioned M1 might increase metabolism and trigger excitotoxicity in the penumbra.
7. right Pars Triangularis (BA 45), a site in the inferior frontal gyrus, is the most effective target for aphasics.

12.2 Clinical Studies of Extradural Cortical Stimulaton

Direct stimulation of the cortex via implanted extradural electrodes (ICS) has been simultaneously and independently attempted for the first time in 2002 by Canavero (Canavero et al 2006) and, under the aegis of NorthStar Neuroscience, a now defunct US neurostimulation company, Brown, as an adjunct to standard rehabilitation. This line of research has been then pursued by Kim and a few other groups (Table 12.1).

The conclusion is that, while simple stimulation may be beneficial, combined protocols of temporary cortical stimulation and physiotherapy produce the best results. Rehabilitation with stimulation may cement these improvements by causing persistent anatomical changes, also explaining persistence of functional improvement after withdrawal of ICS. Importantly, improvement after ICS is observed long after further recovery is thought to be no longer possible (Fig.12.1-4).
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Infarct Location</th>
<th>Aim of CS Device</th>
<th>Target structures</th>
<th>Duration of CS</th>
<th>Parameters Of CS</th>
<th>-Effect of CS -Complications</th>
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<tbody>
<tr>
<td>Brown et al (2003)</td>
<td>1</td>
<td>SCI (implanted 2002)</td>
<td>Upper arm motor Ipsi MI (fMRI hotspot)</td>
<td>3 weeks</td>
<td>4,5mA, 50Hz, 100 μs stimulation during rehabilitative training</td>
<td>-UEFM improved by 10 points, Hand dexterity ↑ -none -able to grasp a pen and to write letters. This improvement persisted for at least four weeks after conclusion of rehab.</td>
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<tr>
<td>Canavero et al (2006)</td>
<td>1</td>
<td>CI (implanted 2002)</td>
<td>Motor and language</td>
<td>Bilateral M1/PMC 6 months</td>
<td>Continuous, 3-3.7 V, 50 or 130 Hz, 210μsec</td>
<td>-Modest improvement of motor arm impairment &amp; aphasia -none</td>
<td></td>
</tr>
<tr>
<td>Brown et al (2006)</td>
<td>8 (+8 ctrls: rehabilitation only)</td>
<td>SCI or CI</td>
<td>Upper arm motor Perirolandic fMRI- activated area</td>
<td>3 weeks</td>
<td>Bipolar stimulation during rehabilitative training Half-threshold or 6.5 mA, 50Hz, 250μsec</td>
<td>-UEFM from 35.3±7.8 to 45.5 ± 10,8 -1 infection, 1 breakage -prospective, randomized, multicenter study. Improvements persisted throughout the 12-week follow-up assessment (study week 16). In comparison, lesser improvements in control patients occurred within the first two weeks and then seemed to decrease over time.</td>
<td></td>
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<tr>
<td>Authors</td>
<td>Year</td>
<td>N</td>
<td>Infarct Location</td>
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<tr>
<td>Levy et al.</td>
<td>2008</td>
<td>12</td>
<td>SCI or CI</td>
<td>Paddle + IPG</td>
<td>Perirolandic fMRI</td>
<td>6 weeks</td>
<td>Bipolar stimulation + rehabilitative training (2.5 hours daily); Half-threshold or 6.5 mA, 50 or 101 Hz, 250μsec. 3 anodes + 3 cathodes (1.8 cm² stimulation area)</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>2008</td>
<td>(+12 ctrls)</td>
<td>Time since CVA: 4 mos-8 yrs</td>
<td>Time since CVA: 4 mos-8 yrs</td>
<td>Time since CVA: 4 mos-8 yrs</td>
<td>Time since CVA: 4 mos-8 yrs</td>
<td>Time since CVA: 4 mos-8 yrs</td>
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</table>

Table 12.1: Studies of Epidural Cortical Stimulation for post-stroke rehabilitation
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<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>N Infarct</th>
<th>Aim of CS Device</th>
<th>Target structures</th>
<th>Duration of CS</th>
<th>Parameters Of CS</th>
<th>-Effect of CS -Complications</th>
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<tr>
<td>Northstar’s Everest Pivotal Study (press release, 2008)</td>
<td>2004-2008</td>
<td>91 (+55 ctrls)</td>
<td>SCI or CI (moderate-severe)</td>
<td>Perirolandic fMRI-activated area (pts without perirolandic hotspot excluded)</td>
<td>6 weeks (5 days/week in weeks 1-4 and 3 days/week for weeks 5-6)</td>
<td>Bipolar stimulation + task-oriented rehabilitative training (2.5 hours daily); Half-threshold or 6.5 mA, 50 Hz, 250 μsec</td>
<td>At the 4-week follow-up, 30.8% of active group obtained =/&gt;4.5 points improvement (UEFM) and =/&gt;0.21 points (AMAT) versus 29.1% of controls (Δ= 1.7, P 0.41= NS; preset primary end point: 20% absolute difference). Responders had a smaller fraction of the CST injured vs non-responders (44% vs 72%, p&lt;0.04) and rarely had severe tract injury. Responders had more often preserved motor responses on intraoperative stimulation (67% vs 27%, p&lt;0.05); responders with elicitable motor responses also had lower rate of MI injury vs those without motor responses (0% vs 33%, p&lt;0.05) and higher gray matter volume in areas including MI.</td>
</tr>
<tr>
<td>Harvey et al 2004-2009</td>
<td>2008</td>
<td>2 SCI &amp; CI</td>
<td>-Motor &amp; language -Paddle + IPG</td>
<td>Ipsi MI+PMC &amp; Broca’s area</td>
<td>6 months</td>
<td>Unipolar &amp; Continuous 5V, 50Hz, 200 μsec</td>
<td>-UEFM from 8 to 27 in one; 35 to 42 in the other Marked language improvement -none</td>
</tr>
<tr>
<td>Nouri and Cramer (2011)</td>
<td>2011</td>
<td>2 SCI &amp; CI</td>
<td>-Motor recovery -Paddle + IPG</td>
<td>Perirolandic fMRI-activated area (pts without perirolandic hotspot excluded)</td>
<td>12 weeks (5 days/week in weeks 1-4 and 3 days/week for weeks 5-6)</td>
<td>Bipolar stimulation + task-oriented rehabilitative training (2.5 hours daily); Half-threshold or 6.5 mA, 50 Hz, 250 μsec</td>
<td>At the 4-week follow-up, 30.8% of active group obtained =/&gt;4.5 points improvement (UEFM) and =/&gt;0.21 points (AMAT) versus 29.1% of controls (Δ= 1.7, P 0.41= NS; preset primary end point: 20% absolute difference). Responders had a smaller fraction of the CST injured vs non-responders (44% vs 72%, p&lt;0.04) and rarely had severe tract injury. Responders had more often preserved motor responses on intraoperative stimulation (67% vs 27%, p&lt;0.05); responders with elicitable motor responses also had lower rate of MI injury vs those without motor responses (0% vs 33%, p&lt;0.05) and higher gray matter volume in areas including MI.</td>
</tr>
<tr>
<td>Kim et al (2008)</td>
<td>2008</td>
<td>2 SCI &amp; CI</td>
<td>-Motor recovery -Paddle + IPG</td>
<td>Perirolandic fMRI-activated area (pts without perirolandic hotspot excluded)</td>
<td>6 weeks (5 days/week in weeks 1-4 and 3 days/week for weeks 5-6)</td>
<td>Bipolar stimulation + task-oriented rehabilitative training (2.5 hours daily); Half-threshold or 6.5 mA, 50 Hz, 250 μsec</td>
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<th>Parameters Of CS</th>
<th>-Effect of CS -Complications</th>
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<tr>
<td>Kim et al (2010)</td>
<td>2</td>
<td>SCI &amp; CI (infarct was too large to be improved with single perirolandic stimulation)</td>
<td>Pt 1: severe hemiplegia associated with large cortical frontal and parietal infarct in the right frontoparietal area. The patient could neither stand independently or walk; Pt 2: hemiplegia and aphasia due to cortical infarct in the left middle cerebral artery territory.</td>
<td>Two paddle electrodes covering frontal and parietal area in the right hemisphere, followed by dual cortical stimulation with concurrent rehabilitative training in patient 1. Two paddle electrodes were implanted to cover pre-motor and motor cortex in patient 2.</td>
<td>6 months</td>
<td>NA</td>
<td>Both patients had intensive rehabilitative training for more than 6 months with no beneficial results. Pt 1: after 6 months of stimulation, the patient could walk with a good posture. Pt 2: After similar treatment, the motor function was markedly improved.</td>
</tr>
<tr>
<td>Cherney et al (2010)</td>
<td>4 pts (vs 4 ctrls)</td>
<td>time since CVA (left carotid artery): =/&gt;12 mos</td>
<td>FMR hot spot intersecting activations during a week, 6 tasks overlying BA6 ventral. Craniotomy flap. 2x3 grid (2.6x2.7cm in total area).</td>
<td>FMR hot spot intersecting activations during a week, 6 tasks overlying BA6 ventral. Craniotomy flap. 2x3 grid (2.6x2.7cm in total area).</td>
<td>50 Hz, 6.5 mA (4.75 mA in 1).</td>
<td>Single-blind. Randomised, controlled safety study. Non-fluent aphasia, slow agrammatic output &amp; apraxia of speech. NorthStar Neuroscience study. Mean WAB-AQ change from baseline: 8 points (6 week f-up) and 12.3 points (12 week f-up). Underpowered!</td>
<td>In matched patient pairs, none with mild-moderate aphasia achieved a 5 point change on WAB/AQ, but study pts had greater changes at all time points. Pts with moderate and moderate/severe aphasia reached a 5 point change on WAB/AQ. Ctrls had larger lesions (although nonsignificant). Most marked benefit in more severe aphasia. Benefit associated with decrease in total brain activation during language tasks on fMR.</td>
</tr>
<tr>
<td>Authors</td>
<td>N</td>
<td>Infarct Location</td>
<td>Aim of CS Device</td>
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<tr>
<td>Balossier et al (2012, 2013)</td>
<td>1 pt</td>
<td>Left external capsular CVA</td>
<td>Control of pain craniotomy, fMR aided neuronavigation. RESUME straddling MI and SI behind Broca's area</td>
<td>Continuous stimulation, 50 Hz, 60-120 μs, 3-3.65V</td>
<td>PT developed central post-stroke pain, right periorbital region and cheek. Paroxysms triggered by cold and reading; allodynia. VAS 8-10. 5 years later: VAS 2-3. double-blind evaluation. Mild Broca's aphasia + severe speech apraxia. <em>Aphasia regressed</em> (verbal fluency, text reading) during stim ON At 5 years, semantic and phonemic improvement during stim ON less than initially seen After 6 years, sudden pain and aphasia relapse due to battery depletion. Benefit recaptured, with significant improvement in phonemic verbal fluency and text reading.</td>
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Fig. 12.1: Chronic subcortical infarct in the right internal capsule. This 51-year-old man with a chronic subcortical infarct 8 months before and moderately spastic arm and clumsy hand underwent ICS of the premotor and primary motor cortex. Diffusion imaging of MRI demonstrates the lesion in the right internal capsular area (A). fMRI images on a wrist flexion–extension task of the paretic arm failed to show activation of MI in both hemispheres. Six months' stimulation with rehabilitative training improved the mobility and spasticity of his hands, thus enabling him to drive a car again. In addition, his Functional Independence Measure (FIM) score improved in self-care, mobility, and locomotion. This patient had left hemiparesis with spastic upper extremity. A paddle electrode was implanted to cover premotor and hand/arm MI (B). After 6 months' stimulation and rehabilitative training, the patient can drive a car with improved FIM scores.

Fig. 12.2: Chronic cortical infarct in the left middle cerebral artery territory. T1-wighted image shows the cortical infarct in the left middle cerebral artery territory (A). This 39-year old patient with a cortical infarct 18 months earlier presented severe dysphagia and hemiparesis. Two 4x4 cm paddle electrodes were implanted to cover Broca’s area plus premotor and MI cortices (B). After 6 months of stimulation (1 to 5V over 1 month, 200 μs, 50 Hz) and rehabilitation (two hours every day), the patient regained communication ability and improved motor function of the right limbs.
Fig. 12.3: Massive cortical infarct in the right hemisphere. T1-weighted image shows a diffuse fronto-parietal cortical infarct (A). This 67 year old patient could only stand with maximal assistance, otherwise he was bed-ridden, despite long-term intensive rehabilitation. fMRI on flexion-extension of the knee showed diffuse activation in posterior parietal areas. Two paddle electrodes were implanted to cover the frontal (near supplementary motor cortex) and posterior parietal area (network stimulation) in order to achieve maximal coverage (B). After stimulation and rehabilitative training for 6 months, he began to stand independently and walk 200 m.
Fig. 12.4: Massive corticosubcortical infarct in a young adult (A). fMR scans showing a widespread hotspot on moving the paretic shoulder (rest of the arm plagic) (B,C). Bihemispheric stimulation covering frontal motor areas (D,E)
12.3 Mechanisms Subserving Recovery

The mechanisms subserving recovery are not well understood and it appears that several mechanisms may be at work simultaneously. ICS is known to modulate GABA and reactivate lesional and perilesional plasticity (Canavero et al 2006); the role of plasticity is also evinced by the long (months) after-effects of ICS. Long-Term Potentiation (LTP) and a cause-effect link between excitability changes and motor behavior have not been proven directly in man. Strengthening of latent neural pathways is another possibility. ICS, like other stimulation techniques, can also act via stochastic resonance, i.e. a small increase in noise improves signal processing in nonlinear systems that work in a context of low signal-to-noise ratio; this biases endogenous and cortical and corticosubcortical neural oscillations.

Intraoperative stimulation may immediately induce observable finger contractions that were not voluntarily possible prior to stimulation, implicating marginally effective circuits. In cases where no contractions are elicited, benefits may nonetheless be obtained by inducing new cortico-cortical connections to form new local networks by incorporating perilesional areas. Likewise, improvement would not occur only as an indirect result of electrical inhibition of confounding regions of hyperactivity.

12.4 Surgical Technique

12.4.1 Preoperative Evaluation

Candidates for ICS are chronic stroke patients who do not show further clinical improvements six months following a stroke. Although most patients reported in the literature underwent ICS no later than 3 years post-stroke, at least one received surgery 8 years later. Perhaps, there is no upper limit to duration of chronic stroke for ICS. Patients should be cognitively competent and motivated to adhere to long-term rehabilitation. Exclusion criteria are medical comorbidities that contraindicate rehabilitation or general anesthesia, epilepsy, other neurological diseases and compound strokes. Candidates should be evaluated with MR Tractography (DTI) and single-pulse TMS to assess the pyramidal tract. Motor activation fMR is indicated, but the task should correspond with the parts of the body targeted by rehabilitation. Noninvasive stimulation may have prognostic value as of subsequent ICS and help select the best parameters by highlighting facilitatory or inhibitory effects: this has yet to be explored in this context.
12.4.2 Targets

Targets employed in the published literature include the premotor cortex (PMC), MI (when spared) and SI, posterior parietal cortex, singly or combined (bifocal or network stimulation), uni- or bi-hemispherically. Yet, the ideal way to improve on blinded application of CS is provided by optimal site-finding protocols, either rTMS- or neuroimaging-driven, as these account for individual variability (Cramer et al. 2003) in clinical factors such as lesion size and volume that could differentially influence the mechanisms of neuroplasticity in each patient. For example, one site that may be optimal in a patient with a small lesion may not be appropriate for another patient with more extensive damage. The extent of transcallosal disinhibition, or propensity of involvement of the perilesional and potentially beneficial contralateral homologs, differs among patients, and therefore, site-finding protocols help to meet individual treatment needs. The choice of the appropriate site for stimulation is key, as the electrode paddles usually employed are not large enough to cover extensive target areas singly. Both stimulating large or focal areas may have theoretical advantages and disadvantages. One should also be reminded that scars (and CSF) may shunt the induced current with mislocalization of stimulation.

Spontaneous improvement is mediated either by reintegration or increased connectivity within perilesional areas. Yet, both published evidence and our experience prove that the perirolandic cortex does not qualify as a universal target for all patients, despite similar presentation of imaging and clinical findings. Peri-infarct activation is not directly correlated with the magnitude of motor recovery (Cramer et al. 2006) and lack of motor-task activations on fMRI cannot be relied upon for selection of patients: one of Kim’s patients showed no activation on fMRI, yet was markedly improved, whereas in many patients, intraoperative stimulation elicited no motor response (Levy et al. 2008), despite fMR hot spots. Data suggest that patients presenting near normal MI/SI activation on fMRI would not be good candidates, as maximal usage implies no further reserve (Loubinoux 2007). In this sense, a low baseline cortical activity may represent underuse of surviving cortical resources (but also damage with little available resource to activate or enhance). A simple increase in corticospinal excitability might facilitate volitional recruitment of corticomotor output neurons, but effects of stimulation are not mediated by simply changing motor cortex excitability. Presence or absence of fMR activation is not directly related to surgical outcome and selection of target based on the results of fMR may be confusing, as areas of fMRI activation may really be a specific reorganization of motor representation or just a by-process unrelated to actual recovery. In other words, while functional neuroimaging data can demonstrate the process of functional reorganization – generally over multiple, bilateral areas, they cannot be used to make a definitive surgical decision. Likewise, results of ICS in chronic stroke patients with cortical infarcts may show variable results: perirolandic cortex stimulation produces
variable results in patients with apparently similar neurologic conditions. *Modulating ipsilesional M1 is unlikely to benefit all patients.*

PMC has a direct connection with spinal motor neurons, although of lesser magnitude than the primary motor pathways: unmasking of this latent pathway may form a new motor pathway (Leuthardt et al 2009: ipsilesional PMC). Also, it is heavily connected with both MI and SMA (engaged in the temporal organization of movements) and a restitution of ipsilesional effective connectivity between SMA and M1 underlies improved motor performance after stroke (Grefkes et al 2010). Yet, ICS centered on the premotor cortex does not guarantee clinical improvement, even for small subcortical infarcts. Interestingly, the coupling between SMA and M1 is inhibitory and the SMA may act as an interface between motor and limbic systems for processing emotionally rich cue for motor acts: therefore, emotionally rich visual cues could be more effective than neutral ones in motor rehabilitation (Oliveri et al 2003).

Enhancement of somatosensory input leads to improvement of motor performance in stroke patients. M1 and S1 display a striking capacity to reorganize and are anatomically and functionally highly interconnected. Direct electrical stimulation of the somatosensory cortex (S1) may be used as an amplifier to substitute for peripheral electrical stimulation in terms of strengthening the sensory input, leading to improved recovery. As for the posterior parietal lobe, this is connected with PMC, while the inferior parietal lobe with SMA.

The unaffected hemisphere is also known to be associated with post-stroke motor recovery. It is said that an abnormal increase in interhemispheric inhibition from the contralesional to the ipsilesional hemisphere contributes to motor impairment, including aphasia and neglect (interhemispheric dysbalance model). Thus suppressing cortical overexcitability in the contralesional hemisphere or boosting cortical excitability in the ipsilesional hemisphere will release the ipsilesional cortex from excessive interhemispheric inhibition and improve neural processing in the lesioned hemisphere. However, this simplistic theory is negated by studies reporting negative results and transcallosal mediated excitability changes do not occur in all patients. Moreover, suppressing activity in contralesional M1 may be contraindicated in more severe stroke patients—a fact contrary to the commonly held view that the contralesional hemisphere takes over in large strokes, since this might reduce the excitability of ipsilateral descending pathways that may be important in some patients (Bradnam et al 2013). In the only case of bihemispheric ICS (Canavero et al 2006), ICS with facilitatory parameters in the unaffected hemisphere produced mixed effects, both positive and negative, pointing to a complex role of the unaffected hemisphere in motor recovery.

The recovery of language follows similar lines. Targets of course differ depending on the type of aphasia (expressive vs receptive) and the extent of the infarct. In aphasia cases, 6 different sites in the right inferior frontal gyrus should be stimulated with rTMS (600 pulses, 1 Hz). Sites include the mouth area in the motor cortex, pars opercularis (POp; BA 44), three separate sites on pars triangularis (PTrdorsal
posterior, ventral posterior and anterior PTr), and the pars orbitalis (BA 47). The same can be carried out contralesionally. In those with fluent aphasia, either the right or left superior temporal gyrus (STG) should be stimulated. Studies show that the perilesional area adjacent to Broca’s area is the single most important area for the recovery of expressive aphasia and is the primary target for ICS (Kim et al. 2008). Intriguingly, there is growing evidence suggesting a functional connectivity between language areas (including Broca’s and Wernicke’s) and regions mediating hand motor function. It remains to be clarified whether stimulation of the perilesional area adjacent to Broca’s area may enhance cortical hand function or vice versa (Kim et al., unpublished observations), although it is known that stimulation outside the language areas can improve aphasia (Canavero et al 2006). The right hemisphere may take up language all by itself, if areas of the left hemisphere responsible for language are extensively damaged. Yet, the right arcuate fasciculus is rudimentary (Schlaug et al 2011).

### 12.4.3 Single Vs Multi-Site Stimulation

Single-site stimulation of the perilesional area has been the major option in ICS. This strategy may work if the cortical infarct is not extensive or limited to the subcortical area. If the infarct area is large or involves cortical and subcortical areas simultaneously, with widespread disruption of corticocortical connections, premotor cortex or MI/SI stimulation often is ineffective. ICS of a larger area, or even network stimulation, is required. Combined stimulation including PMC + SI + PPC may be beneficial for improving the motor outcome. As the electrode cannot cover the entire brain, the number and placement of electrodes should be modified depending on the goal of treatment. For instance, a patient with complete hemiplegia may wish to regain locomotor ability rather than fine hand motricity. In this situation, the electrode(s) may be placed more superiorly to cover leg representation areas in MI or peri-infarct areas adjacent to leg function. Dual-site, ipsi- or bihemispherical, CS (Canavero et al 2006, Shin et al 2010) has the ability to recruit more corticospinal/bulbar fibers and simultaneous stimulation of functionally related areas might prove better.

### 12.4.4 Parameters of Stimulation

Since it takes several weeks to months to observe clinical recovery, the choice of parameters cannot be based on acute clinical effects. Also, inter-individual variability makes it difficult to determine uniformly optimal parameters. One important caveat is that brain atrophy is often observed among stroke patients and this must be taken into account when setting amplitude.
Stimulation should always be subthreshold, and parameters must be decided empirically (6.5 mA in Brown et al 2006 and Levy et al 2008). Kim generally employs continuous-mode stimulation at 5V, 50Hz, and 200μs of pulse duration. Canavero et al (2006) tried both low and high frequency stimulation and found mixed effects. Kim uses anodal and unipolar stimulation, in order to reach deeper regions, in particular deeper “leg representation areas” in the inter-hemispheric fissure. Finally, “inhibitory” CS does not always induce local inhibition, but may be facilitative in some patients.

12.4.5 Duration of Stimulation

We make a strong case for longer periods of stimulation, i.e. 4-6 months (Canavero et al 2006, Kim et al 2008) versus 4-6 weeks reported in other series (Brown et al 2006, Levy et al 2008). Three-to-four weeks of stimulation are, in our experience, of limited value. Some patients began to show improvement after four months of stimulation, with recovery continuing even after removal of the stimulation devices. ICS is usually provided during the rehabilitative training, as it is believed to support brain plasticity and facilitate the learning process. Thus, about three hours of stimulation with concurrent rehabilitative training has been reported (Brown et al 2006, Levy et al 2008). Alternatively, continuous stimulation has been employed and found beneficial, despite possible neuronal fatigue (Canavero et al 2006, Kim et al 2008). Data indicate that two hours of stimulation every twelve hours may achieve the same effects of continuous stimulation (unpublished data). We think that the duration of stimulation must be individualized, depending on the extent and location of the stroke. For larger infarcts, longer durations of stimulation may be required.

12.4.6 Technique of Implantation

12.4.6.1 Types of Electrodes
The strip electrode as usually employed for ICS is adequate to recruit cortical areas involved in functional reorganization. However, approximation of two or more strip electrodes may be indicated.

12.4.6.2 Preoperative Mapping
Identification of the intraparietal sulcus is important when planning fronto-parietal network stimulation. Similar to the junction between the precentral sulcus and superior and inferior frontal sulci in the frontal lobe, the post central sulcus is joined by the horizontally-running intraparietal sulcus. This sulcus divides the parietal lobe into the superior and inferior parietal lobes. However, it is not easy to identify the
sulci without the aid of neuronavigation and curvilinear plus multiplanar imaging. In the end, the neurosurgeon’s judgment is required to convert neuroimages to “real-life” surgery. If pairs of electrodes are elected, simple anatomical landmarks (using MRI combined with fMRI) can be employed to determine the target, without the use of neuronavigation.

12.4.6.3 Craniotomy and Electrode Implantation

Implantation of the electrode can be performed under either local or general anesthesia. General anesthesia may be risky in older patients with associated comorbidities. In such cases, neuro-leptoanalgesia is an option, particularly with non-flap techniques. Subdural placement would be indicated in severely atrophic brains, but is unsafe. One or two burr holes are enough when inserting the strip electrode extradurally. A burr hole is made based on the length of the strip electrode and the direction of placement over the cortex. Strip electrodes are usually positioned to cover the premotor and motor cortex, integrating imaging data. A burr hole is fashioned immediately anterior to M1. Alternatively, a small (3-5 cm) flap craniotomy may be fashioned. Intraoperative stimulation of M1 may not always evoke muscle twitches, depending on damage to the corticospinal tract. If two paddles are placed epidurally to cover the premotor and part of motor cortex areas, the anterior electrode can be placed just behind the coronal suture, and the upper and lower one can be adjusted, depending on the activation pattern on fMRI. If the electrode is positioned on the inferior frontal (Broca’s) or other cortical areas, a similar procedure is employed. In case of a flap, electrodes need to be tightly anchored to increase the contact, to keep blood out of the space between electrode and dura, and to prevent the migration of the electrode. Seepage of blood into the space between the dura and the electrode may hinder delivery of the electrical stimulation and therefore decrease the efficacy of treatment. The electrode is connected with a lead, which is subcutaneously tunneled and connected to the neural stimulator, which is usually implanted subclavicularly in the anterior chest or axillary area.

12.4.6.4 Postoperative Management

Antibiotics are administered according to local policies and regulations. Two or three days following the procedure, the patient may be discharged, but is rescheduled for a parameters-setting session. Initially, the threshold for eliciting a motor response in the contralateral extremity is determined by trains of stimulation (3 seconds of a train at 50 Hz, 100-250μs, starting from 0.5 V). Amplitude is gradually increased until movement is observed or up to 10V. If the patient showed a positive response to movement during intraoperative testing, movement of the contralateral extremity can be expected; otherwise, even high voltages are likely to be ineffectual. Rehabilitation is usually started two weeks after the placement of electrode. The current is gradually
increased up to half threshold for four weeks (up to 4-5V), while searching for side effects of stimulation. Stimulation for aphasia does not elicit motor responses and thus is ramped up to 5V only, to avoid possible side effects. The dose of stimulation can be modified depending on the severity of the neurological deficit. If the patient has a mild neurological deficit, two hours of stimulation every twelve hours may suffice. Continuous stimulation is indicated in severely compromised brains. It is important to administer rehabilitation while the stimulator is on, for synergy to occur. Noninvasive CS has been applied before physiotherapy to prime the cortex or during or after to consolidate. No noticeable stimulation–related complications such as seizures, abnormal behavior, or decline of neurological functions have been reported up to now, with the exclusion of one seizure in the trial of Levy et al (2008). Rehabilitation is usually performed using peripheral parts of the body. Given the limited scientific evidence, no indication can be offered as to which rehabilitative technique is best associated to ICS, except to underscore the need of individualization of the rehabilitative process to the patient’s physical and cognitive disabilities. A few caveats apply: 1) behaviors can compete and training in one behavior can have negative consequences for another; 2) a plastic nervous system can respond positively, but also negatively, to suboptimal rehabilitation strategies; 3) the best rehabilitation should be general, not task-specific; 4) the effect of sleep for consolidation should be taken into account. It has been suggested that, since plasticity saturates when neuronal circuits adapt to long-term stimulation, intensive rehabilitation during the all-important first three months after CVA, should be interrupted after 6 weeks by a week of no therapy (relaxation phase) (Butz et al 2009).

### 12.5 Outcome and Outcome Predictors

In general, after a stroke, initial mild leg paresis is four times as likely to recover compared with severe leg paresis and better outcomes may be expected in subcortical infarcts compared with cortical infarcts, whereas there is no significant difference between motor recovery in hemispheric and brain stem infarcts. Preservation of both parts of the corticospinal tract and thalamic circuitry is a major determinant of the quality of hand-motor recovery following acute brain ischemia in adults. Recovery of function after a stroke is also better for proximal arm function than distal. Sensory deficit is a poor prognostic sign. Currently, the only favorable prognostic sign is the ability to elicit intraoperative motor responses. It may be that more stimulation with more complex tasks is required needed in extensive strokes. ICS plus rehabilitation is said to promote recovery at a level above what is observed after CIMT (Levy et al 2008) and results of CS persist in time. It led to 5- 40% improvement of the original neurological deficit and activities of daily living in successful cases, with benefit persisting > 6 months in almost all cases. New predictive markers, perhaps based on
MR spectroscopy (GABA levels), resting state MR (connectivity analysis), DTI or EEG patterns are needed.

12.6 Conclusion

Although investigational, ICS may be indicated for chronic stroke patients whose neurological deficit has not improved after initial rehabilitative training. Unlike tDCS and rTMS, ICS can provide longer – even continuous- stimulation, because the stimulator is fully implanted. The failure of the EVEREST trial (Table 1) should not put off surgeons wishing to embark on this technique. The failure of this trial was likely due to too temporally short rehabilitation and faulty inclusion criteria, based on a one-size-fits-them-all approach.

Patients were only implanted on the affected MI/SI and a fixed frequency was set for all patients. EVEREST used the fMR hotspot for hand/wrist/finger movement, with rehabilitation targeting shoulder, elbow and distal joints during reach/grasp and self-care. As shown by available data, in several patients other cortical areas must be included (see above). Dual or triple stimulation of functionally-related areas may “salvage” patients that might not benefit from single stimulation. A TMS study found that bilateral rTMS exceeded the algebraic sum of the separate stimulation of each MI (Strens et al 2003). Also, in EVEREST, only 16% of patients showed evoked intraoperative movements as compared with 100% and 42% of patients in phase I and II trials respectively: those who did showed greater improvement than controls.

Future studies should explore concurrent drug administration (an, in the near future, stem cells) and even stimulation of neurogenesis. Reducing the excitability of the lesioned M1 before training (rather than enhance it) in order to increase the range of plastic changes triggered by physiotherapy is an option (Hummel et al 2008). Another interesting possibility lies in coupling Brain-Machine Interfaces with cortical stimulation for brain-state dependent stimulation (Gharabaghi et al 2014).

In conclusion, cortical stimulation to enhance recovery after ischemic stroke represents a new treatment paradigm that may extend our ability to reverse the devastating effects of cerebrovascular disease. Long-term stimulation is required to observe the effect of functional reorganization. Once the stimulation effect plateaus, further stimulation is unnecessary. Such stimulation may be effective long after recovery from the acute phase has ceased. A variety of disabilities follow stroke attacks, including cognitive impairment and depression: simple correction of motor or language deficits may fail to improve quality of life, but multi-target ICS might.

On the other hand, ICS does not hold promise for ALS: for instance, in one case, no effect was evinced (M1 ICS, hand knob, parallel, bipolar 0-3, 1 hour bid, 5-8V, 3Hz or 30Hz at 8V) (Di Lazzaro et al 2010).
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