18 Mechanisms of Action

This chapter explores possible mechanisms of action of ICS by analyzing data from several sources.

18.1 Neuroimaging Studies

Neuroimaging studies of ICS suffer from – among many others (reviewed in Canavero and Bonicalzi 2007: pp 239-254; 2011: pp 271-272)- limited statistical power due to small number of patients, shortcomings of Region-of-Interest (ROI) measurements, inhomogeneity in patients' conditions, group analyses versus single patients, type of CS (extradural versus subdural), target and neuroimaging protocols (SPECT versus PET versus fMRI).

The data available is contradictory (see Box 18.1): whereas two groups found no cortical activation whatsoever below the electrode, i.e. in MI or SI, Saitoh's group observed M1 activation, Canavero and Bonicalzi (1995) rCBF changes in S1, Tsubokawa et al (1991) in MI, and Sol et al (2001) in S1 and M1 bilaterally. Importantly, analogous studies conducted during M1 ICS for Parkinson's disease clearly revealed cortical changes below the electrode (Canavero et al 2002). Orthodromic activity increases brain metabolism, whereas antidromic activity does not (Montgomery 2010), possibly explaining some negative studies. As concerns the thalamus, Peyron et al (2007) found no thalamic rCBF changes, whereas in their previous studies (Garcia-Larrea et al 1997, 1999, 2006) they did. Thalamic metabolic changes have been reported by Tsubokawa et al (1991), Canavero et al (1999), Saitoh et al (2004), Kishima et al (2007) and Ito et al (2011); central pain relief is accompanied by thalamic renormalization (Canavero et al 1999, Pagni and Canavero 1995, Ito et al 2011).

What is clear is that ICS does NOT relieve neuropathic pain by primarily engaging the so-called affective axis (e.g. the cingulate cortex) or the opioid system, as discussed by some authors: lesions abolishing neuropathic pain along the sensory axis (SI-thalamus) silence both the sensory complaint (pain) and the suffering that accompanies it, whereas cingulotomies and opioids, when effective (infrequently), only reduce the affective component (Canavero and Bonicalzi 2011). Studies show that M1 ICS has a preferential action on the sensory-discriminative aspect of neuropathic pain (Drouot et al 2002, Lefaucheur et al 2009). Patients submitted to ICS show better response by adding S1 as a target of M1 ICS (see Chapters 8 and 9).

Remarkably, M1 rTMS can interfere with the processing of acute laser-induced pain, even if there is an underlying chronic neuropathic pain (Lefaucheur et al 2010).
1- Tsubokawa et al (1991) studied at 4–10 days after implantation of a motor cortex stimulator 7 patients with CP with $^{131}$I-amphetamine SPECT. The rCBF showed a marked increase (+150–200%) in the stimulated cortex (MI/SI) and the ipsilateral thalamic and brainstem area, along with pain abatement. The skin temperature as assessed with thermography in the painful area increased to almost the same level as that in the contralateral non-painful area.

2- Canavero and Bonicalzi (1995) found that parietal cortex stimulation renormalized a locus of SPECT hypoperfusion in the parietal cortex in one patient suffering CCP. Renormalization went along analgesia. In another CP patient, MI ECS renormalized SPECT thalamic hypoperfusion, while providing analgesia (Canavero et al 1999). In several CP patients, Canavero reported parietal and/or frontal and/or thalamic deactivation (Canavero et al 1994).

3- MI ECS has inhibiting effects on SI/MI cortex as well as contralaterally, as reported in a fMRI study of phantom pain (Sol et al 2001).

4- Saitoh et al (2004) submitted a right-sided CPSP patient to subdural M1 subdural ICS, with excellent analgesia (VAS 8 to VAS 1) after 30 minutes of stimulation. H$_2$(15)O PET pre- and post-stimulation revealed significant rCBF increases in left frontal areas (BA9 and 11, BA32) and the left thalamus and decreases in temporo-occipital areas (right BA22 and left BA19). The efficacy of MI CS was mainly related to increased synaptic activity in the thalamus, whereas all other changes were related to emotional processes. The same authors submitted to H$_2$(15)O PET (resolution: 4x4x5mm at FWHM) 6 patients during right-sided 25-40 Hz CS (3 with CP and 3 with BPA pain, all left-sided) (Kishima et al 2007). The PET study was performed 1-3 years after implantation. Stimulation was stopped more than 12 hours before PET. Six PET scans were performed before subdural MI CS. MI CS was run for 30 minutes and 6 PET scans were performed after onset of analgesia and then analyzed considering all patients together with the SPM software. Comparison of rCBF before and after MI CS showed significant rCBF increases after MI CS in the left posterior thalamus (pulvinar) and left posterior insula. No areas of significant rCBF decrease were identified. By comparing early post-MI CS scans with pre-MI CS scans, the authors found significant rCBF increases in the left posterior insula and the right orbitofrontal cortex (BA11) and significant decreases in the right BA9 and the right BA4. By comparing late post-MI CS scans with pre-MI CS scans, the left caudal ACC (BA24) showed significant increases, while comparison between early post-MI CS with late post-MI ECS scans brought out significant rCBF increases in the left SMA (BA6). Unlike the Lyon group’s findings (see below), the ipsilateral (to MI ECS: right) thalamus was not affected. Results were not differentiated between central and peripheral neuropathic pain.

5- A French group (Peyron et al.1995) reported on 2 CP (both spontaneous and evoked) patients, one with a right mesencephalic infarct with left leg pain (spontaneous and evoked) and the latter with a left parietal infarct sparing the thalamus, with right hemisoma pain, bar the face. In case 1, PET at rest showed no cortical abnormality, but right thalamic hypoperfusion (-9%). During MCS, CBF was increased in brainstem, orbitofrontal cortex (OFC), right thalamus and cingulate cortex (CC): 30 minutes after discontinuation, persisting CBF changes were seen in OFC and CC. In case 2, PET at rest showed widespread CBF decrease in left parietal cortex (-35%) and hypoactivity in left thalamus (-10%), this latter being normal on MRI. During MCS, CBF was increased in brainstem, OFC, left thalamus and CC, while the parietal cortex asymmetry was unmodified. Analgesic effects in both patients lasted at least 30 minutes after stopping MCS and this went along sustained CBF changes, particularly in the thalamus. CBF increases were of the order of 7–9%. An important sustained CBF increase was seen in patient 2’s brainstem, while in patient 1 it was delayed, of lesser intensity and shorter duration (patient 2, but not patient 1, also showed modulation of nociceptive flexion reflexes RIII). No change was seen in SI. Thalamic CBF changes were almost superimposable in both patients, but pain relief was satisfactory only in one patient, in whom there was also brainstem activation. CBF changes in OFC and anterior CC (ACC) were stronger and more sustained in the patient with less pain relieving effect of MCS than the other.

Box 18.1: Neuroimaging Studies of Neuropathic Pain
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Garcia-Larrea et al (1997) studied 7 CPSP and 3 PNP (brachial plexus avulsion, BPA, pain) patients submitted to contralateral MI ECS (in 3 medially, i.e., subdurally). H2(15)O PET was done before, during – 5 and 20 minutes – and 30 minutes after a 20 minute session of stimulation. Results were not differentiated between CP and BPA. There was no significant difference in regional cerebral blood flow (rCBF) between the two controls or the two stimulation conditions. The only locus of significant CBF increase during MI ECS was observed in the motor thalamus. Sizable, but insignificant CBF increases during MI ECS were seen in the left insula, BA24–32 and upper mesencephalon (plus a rCBF decrease in BA18–19 bilaterally). No significant change was seen in MI (SI could not be resolved with their machine). All changes were reversible upon stopping MI ECS, although BA24 and mesencephalic changes persisted or even increased slightly after stoppage of MI ECS. They compared 3 patients with 80–100% relief and 4 with less than 40% relief. Mean thalamic CBF was enhanced in both groups with a similar time course, albeit rCBF increase was greater in those with 80%-plus relief. In contrast, mean CBF in BA24-32 appeared to increase during MI ECS only in patients with good relief and to decrease in poor responders, even in individual analyses. The same group (Garcia-Larrea et al. 1999) evaluated 10 patients with CP and BPA (likely including the above-mentioned patients, although time from implantation to PET does not correspond). MI ECS was stopped 24 hours before PET. Four consecutive scans were first recorded (A). Then PET was recorded at 5, 15, 25 and 35 minutes after switching on MI ECS (B). MI ECS was subsequently stopped and PET recorded at 15, 30, 45, 60 and 75 minutes after MCS had been turned off (C). MI ECS (B versus A) was associated with increased rCBF in rostral ACC contralateral to the electrode. During MI ECS stoppage (C versus A) there was strong activation up to 75 minutes after MI ECS discontinuation of rostral ACC, orbitofrontal cortex, basal ganglia and brainstem. MI ECS (B+C versus A) was associated with decreased blood flow immediately below the electrode. Images of CBF changes in the brainstem did not cover the localization of the PAG. They did not find MI ECS activation of SI, a possible consequence of the spatiotemporal resolution (12 mm) limits of their PET machine. The low-threshold analysis (Z-score ≥ 3.5) of the two-step procedure yielded some regions of significant CBF increase: the whole thalamus (ipsilateral to MI ECS), the ACC (mostly contralaterally to MI ECS, plus midline), orbitofrontal areas, a region comprising the insula and descending towards the inferomedial temporal lobe – including amygdala (exclusively contralateral to MI ECS) and the subthalamic-upper brainstem region (ipsilateral to MI ECS). The second (high-threshold) step of the analysis (Z-score ≥ 4) restricted spatially the above results and limited the anatomical region of significant CBF increase to thalamic VL ipsilateral to MCS, with extensions to VA and subthalamic region. Vc was outside the region of increased CBF in both high- and low-threshold analyses. The sequence included condition A (CBF assessed basally, 15 minutes before MI ECS with stimulator turned off for 18 hours), conditions B and C (2 consecutive scans performed respectively after 5 and 20 minutes of continuous MI ECS) and condition D (scan after 30 minutes after MI ECS discontinuation). Pain ratings during PET were 4.8 ± 2.6 during condition A, 4.3 ± 2.9 and 3.69 ± 2.8 in conditions B and C and 3.69 ± 2.8 in condition D. In spite of a trend to pain decrease from A to D, differences were not significant. As far as rCBF changes are concerned, in all cases there was an abrupt CBF increase during the first scan under MI ECS (5 minutes after onset) which remained stable during PET 20 minutes after M1 ICS onset. These effects were reversible 30 minutes after M1 ICS interruption in all sites, except in ACC where rCBF had not yet reverted to pre-stimulation values 30 minutes after MCS discontinuation: here two spots of increased rCBF appeared in right and left ACC/orbito-frontal boundaries (despite unilateral analgesia) and stayed almost so after switching off the stimulator. No significant change related to MI ECS was observed in SI or MI. CBF decreased in BA18–19 areas and were totally reversible upon discontinuation of MI ECS. In CP and BPA patients with >80% versus <20% relief, while lateral thalamic CBF appeared to increase in all patients (albeit to a greater extent – 15% versus 5% – in those relieved), BA32 CBF increased in responders (+5% at 20 minutes), but decreased in non-responders (-10% at 20 minutes); upon close scrutiny, this does not seem a strong finding, as in their two reported CP cases this was not the case. Garcia-Larrea et al (2006) submitted to M1 ICS a patient with left facial central pain due to a left medullary infarct. Although the territory with sensory loss was much wider in the right nonpainful than in the left painful side, PET showed significant rCBF reduction in the right thalamus, contralateral to the small painful area.

Box 18.1: Neuroimaging Studies of Neuropathic Pain
40 Hz M1 ICS afforded 60% relief and PET showed renormalization of the thalamic anomaly. Peyron et al (2007) explored the post-stimulation period using an enlarged temporal window (as long as PET studies allow). 19 morphine-naïve patients suffering brain central pain (13 patients), cord central pain (4 patients) or brachial plexus avulsion (2 patients) were submitted to 35 Hz (180 μs/ 2.5V/cyclical) MI ECS (paddle parallel to rolandic fissure) and subsequent PET scans. Analgesic drugs were not discontinued, bar fast-acting opioids for at least 12 hours before exam. PET resolution was 7 mm. Patients were blinded to M1 ICS status (ON/OFF). After acquisition of baseline scans, the next 4 scans were acquired at 5, 15, 25 and 35 min after MCS onset. MI ICS was then turned off again and 5 further scans were recorded at 15, 30, 45, 60 and 75 minutes. Data were analyzed using SPM2 software and also considered for a functional connectivity analysis (FCA), which examines the temporal correlation of neural events between distributed brain areas. Mean pain relief was 10-40% in 8 patients, 60% in 6 and >80% in 2. Results of ON versus baseline and OFF versus baseline were as follows. Only a limited activation of the pregenual ACC (anatomically connected to MI) contralateral to MI ICS was found in the ON versus baseline comparison. The large majority of activations were found in the OFF versus baseline subtraction in the ipsilateral premotor cortex, the contralateral pregenual (pg) ACC (descending pain control) and midcingulate (noxious processing) and supplementary motor (SMA) area, pallidum, putamen and PAG. Most of the rCBF changes that correlated with long-term analgesia occurred during the 75 minutes subsequent to MI ICS stoppage (after 35 minutes of effective stimulation). There was a correlation between rCBF changes and analgesia in the ON condition in midcingulate cortex (MCC) and pregenual ACC (BA32/24) contralaterally to MCS and in prefrontal cortices (BA10) bilaterally. There was a trend for the midcingulate to be activated in the ON condition with a persisting activation in the OFF condition, while the pregenual ACC still showed increased activity in the OFF condition. Regions whose rCBF increased relative to baseline during MI ECS and correlated positively with analgesia in the OFF condition (after stoppage of MCS) included a large ACC activation, extended from the posterior MCC and anterior MCC to the pregenual ACC, bilaterally, contralateral orbitofrontal cortex and SMA, ipsilateral cerebellum and posterior cingulate cortex, prefrontal cortices and basal ganglia bilaterally, hypothalamus, upper mesencephalon (PAG) and lower pons. These activations were maximal in the OFF condition and correlated with average analgesia. Unlike Saitoh’s group’s findings (see above), MI rCBF below the electrode was not found to change or correlate with pain scores at any time, nor was SI. In the FCA, responses that correlated with analgesia with MI ECS ON were found to correlate also with rCBF changes in other subdivisions of lateral prefrontal cortices, in contralateral orbitofrontal cortex, pgACC, anterior insula, putamen and lower pons. In the OFF condition FCA, significant covariations were found between pgACC and basal ganglia, pgACC and brainstem, pgACC and posterior cingulated cortex. Basal ganglia covaried together bilaterally, but also with posterior cingulate and insular cortices. CBF changes in mesencephalon and lower pons covaried with basal ganglia and with pgACC. The authors concluded that a network comprising the ACC/OFC/medial thalamus and PAG—the same as seen during ECS induced analgesia by other procedures—appears to be the final common pathway of analgesia elicited by ECS (ACC and PAG being opioid-rich areas) and becomes activated ONLY after MI ICS is discontinued. MCC and pgACC activities did not correlate with current pain relief, but with the amount of analgesia obtained after several cycles of MI ICS. The perigenual and subgenual ACC are associated with mood alterations and the production of affective states: they are part of a “ventral affective system” involved in the identification of the emotional significance of a stimulus, production of affective states, and automatic regulation of emotional responses, and also comprise the amygdala, anterior insula and ventral striatum. The mid-posterior cingulate cortex instead is concerned with pain unpleasantness. This study failed to replicate the authors’ previous finding of a significant thalamic rCBF increase, except in the FCA. They concluded that MI ICS-related thalamic activation is phasic and short-lasting, likely a trigger for other activations, and may be averaged out when 35 minutes of MI ICS are lumped together and analyzed as a whole. The same group (Maarrawi et al 2007) submitted a subgroup of the above patients (central pain 7, trigeminal peripheral neuropathic pain 1) to PET with [11C] diprenorphine PET, basally and after 2 months of chronic MI ECS. The two preoperative scans performed at 2 weeks interval did not show significant differences. Medications were kept unchanged. Data were analyzed with SPM99.

Box 18.1: Neuroimaging Studies of Neuropathic Pain
Voxel-wise comparison of preoperative and postoperative PET scans showed a significant decrease of opioid receptor binding postoperatively. Buprenorphine binding decrease (group level analysis) concerned the posterior part of the midbrain (PAG) (-25.6%), anterior middle cingulate cortex (-21.2%), lateral prefrontal cortex (-23.3%) and cerebellum (-18.3%). VAS scores decreases and binding decreases correlated significantly in PAG and anterior MCC (in PFC, there was only a trend). One CP patient got minimal relief from MI ECS (VAS 8 to 7 on MI ECS) and decreases were 16.3% in PAG, 10.3% in aMCC, 10.11% in cerebellum and 17.2% in PFC. The CP patient with the best relief (VAS 8 to 2 on MCS) showed decreases respectively of 37%, 30.3%, 22.2% and 25.5%, which would seem to confirm that the magnitude of decreases significantly correlated with degree of analgesia. Yet, the largest decreases were seen at PAG and PFC levels in a patient who had a VAS 7-to-2 relief, at aMCC level in the patient with the best analgesia, at cerebellar level in one with a VAS 8-to-5 change. The authors suggest that binding decreases were not due to loss of opioid receptors (as seen in some studies of central pain), but to increased endogenous opioid secretion and resulting decreased receptor availability to exogenous diprenorphine and a possible reactive down-regulation and internalization of receptors. The authors' conclusion was that MCS triggers endogenous opioid secretion in part of the remaining medial pain system unaffected by opioid receptor loss in CPSP. The involved circuit would include MI that projects to PACG which in turn projects to ACC. In an almost duplicate paper, they (Maarrawi et al 2013) analyzed 15 patients (10 CPSP, 4 PNP, 1 mixed spinal case) submitted again to [11C] diprenorphine (D) PET pre- and post-MCS and matched the findings against a group of 11 healthy (!!!) subjects. Correlation of opioid binding with pain relief after 7 months of MCS was significant, especially contralaterally to pain, within the cingulate (anterior and perigenual) cortex, orbitofrontal cortex, mesencephalon, contralateral insula, PAG and cerebellum. Correlations between mean binding potential values in these areas and the percentage of pain relief for paroxysmal and continuous pain ratings were significant in contralateral and ipsilateral insula, ACC/MCC, OFC, thalamus and PAG. These correlations held for both CP and PNP. Patients with binding potential lower than the range of controls (healthy patients!!!) in the thalamus, PAG and contralateral insula did not obtain benefit from MCS (pain relief <30%). These conclusion are nixed by poor opioid responsiveness of CP (Canavero and Bonicalzi 2011). They (Garcia-Larrea et al. 1999) also recorded CO2 laser-evoked potentials (LEPs) and flexion nociceptive reflex (RIII) in a subgroup of these same patients. LEPs (amplitude and latency of each component) and RIII (surface) were studied with M1 ICS turned off, on and at least 30 minutes after M1 ICS interruption. LEPs were obtained after stimulation of both the painful and the intact side, while RIII was obtained after stimulation of the painful side only. In one patient, after stimulation of the non-affected side, LEP amplitudes of the vertex component decreased significantly during active stimulation. In the group as a whole, after stimulation of the non-affected side, LEP amplitudes tended to decrease under M1 ICS, although not statistically significantly. RIII was not modified in the three conditions. Electrophysiological responses did not correlate with VAS. There was a lack of any significant acute change in SEPs during MI ECS in any of the recorded patients with central lesions. None of the 4 patients whose nociceptive reflexes remained unmodified by M1 ICS was satisfied with the attained analgesia. Although the 7 patients with CP had sizable epidural SEPs during intraoperative monitoring, only 4 retained scalp-recorded SEPs of enough amplitude to permit assessment of M1 ICS effects. Parietal somatosensory responses up to 50 ms post-stimulus did not exhibit any significant change in amplitude, latency or topography in relation to M1 ICS. Thus, significant modulation of spinal nociceptive reflexes was seen during MI ECS in 3/7 patients, while it was unchanged in 4. Modification thereof corresponded in every case to attenuation of the responses during M1 ICS. Two of 3 patients with M1 ICS-related reflex attenuation experienced good to very good relief, while the third reported >60% abatement of allostodyia during M1 ICS, but only 30% of spontaneous pain.

5-Ito et al (2011) assessed 4 CPSP patients who responded to MCS to pre- (within 1 week before MCS) and post- (2 weeks after MCS, stimulation OFF) stimulation 18F-FDG PET. A semiquantitative analysis was conducted (NEUROFLEXER software/NEUROSTAT template) on 17 regions of interest both in the cerebrum, brainstem and cerebellum. The only significant asymmetry was found in the thalamus (basal ratio: 0.81, ratio during analgesia: 0.89). In particular, the improvement in CMR-Glu asymmetry was noteworthy in 3 cases without thalamic injury. The therapeutic effect was proportional to the improvement of the PET asymmetry.

Box 18.1: Neuroimaging Studies of Neuropathic Pain
18.2 Neurophysiology Studies

Katayama et al (1988) recorded descending volleys from the spinal extradural space after direct stimulation of the exposed cortex in anesthetized patients during neurosurgery. They described recruitment of probable D (irect) and I(ndirect) waves, with D waves having the lowest threshold for monopolar anodal (rather than cathodal) stimulation.

An opposite result was reported by Hanajima et al (2002), who found that, in awake pain or movement disorders patients, chronic stimulation through a quadripolar strip electrode placed directly on the arachnoid in the subdural space over M1 appears to activate low threshold (short chronaxie and refractory period) neural elements – probably myelinated axons- likely at cortical level. These, in turn, may activate corticospinal neurons (producing detectable effects on motoneurons) and inhibitory neurons in the cortex. The facilitation was larger (lower threshold) with cathodal (-) than with anodal (+) monopolar stimulation (which excluded corticospinal neuron axons) in most, but not all, patients (3.9:1 ratio, range 0.9-11.1). Anodal stimulation was less effective, maybe because in the awake state interneurons are better activated.

Di Lazzaro et al (2004) compared the pattern of activation produced by TMS and extradural electrical stimulation of M1 in a single awake patient who had both a cortical extradural electrode implanted over the motor area parallel to the central sulcus for treatment of face central pain, and an extradural electrode inserted into the spinal extradural space. The recordings showed that suprathreshold extradural M1 stimulation can evoke multiple descending waves: an I1 and an I2 wave, with the same latency as magnetic postero-anterior stimulation, together with a delayed I3 wave. ICS also evoked an earlier probable D wave that had a slightly later onset than that after lateromedial TMS stimulation. It might be that the D wave evoked by ICS originates closer to the cell body of the pyramidal neurons than the conventional D wave, perhaps at the initial segment rather than at some distance down the axon. Thus, extradural stimulation of M1 can produce repetitive excitation of corticospinal neurons. The order of recruitment of the volleys, and the latency of the D and I3 waves may be slightly different from that seen after TMS. This suggests that there may be subtle differences in populations of cortical excitatory and inhibitory neurons activated by the two forms of stimulation, presumably related to differences in the focality and distribution of the electric field produced by the two methods of stimulation. It was suggested that, in order to improve clinical effects of rTMS, changing the orientation of the coil by 90° (from postero-anterior to latero-medial) may make it more “ICS-like” and thus more effective. However, these authors did not study the descending volleys generated by bipolar EMCS at lower stimulus intensities, as used for chronic therapeutic stimulation.

Yamamoto et al (2007) investigated the corticospinal motor evoked potential (MEP) as an intraoperative index for the placement of stimulation electrodes in the epidural space over M1. A grid of plate electrodes was placed in the epidural space to
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cover M1, S1, and premotor cortex employing a magnetic resonance imaging-guided neuronavigation system in two patients with CPSP. The D-wave of the corticospinal MEP was recorded with a flexible wire electrode placed in the epidural space of the spinal cord during anodal monopolar stimulation of each plate electrode under general anesthesia. The grid electrode was fixed in position with dural sutures and the craniotomy closed. The effect of pain reduction induced by anodal monopolar stimulation of the same plate electrodes was examined using the visual analogue scale (VAS) on a separate day in the awake state without anesthesia. Comparison of the percentage VAS reduction and the recorded amplitude of the D-wave employing the same stimulation electrode revealed significant correlations in both cases. The grid electrode was then replaced with two paddle electrodes over the hand and foot areas, and the optimum positions were identified by D-wave recording before electrode fixation. Both patients reported satisfactory pain alleviation with lower stimulation voltages than usually required for patients with similar symptoms, i.e. the site of stimulation producing the best pain relief corresponded to the location of the cortical contacts evoking the largest D-waves. However, these D-waves were produced during a screening phase by using 0.2-ms duration monophasic rectangular stimuli delivered at very low frequency (2 Hz) and high (suprathreshold) intensity (30 mA). These parameters of cortical stimulation are fully unusual for chronic therapeutic M1 ICS. Therefore, these authors did not demonstrate that therapeutic M1 ICS elicited D-waves, but only that recording D-waves to suprathreshold anodal stimulation could help to determine the optimal site for chronic stimulation.

Lefaucheur et al (2010) studied the descending volleys in two anesthetized patients with peripheral hand neuropathic pain successfully treated by M1 ICS (2 quadripolar leads perpendicular to the central sulcus, 40Hz, 60 μs, 2V), who also had an implanted epidural cervical electrodes for spinal cord stimulation. Recordings were carried out under general anesthesia. Drugs had not been weaned prior to recordings. Low-intensity cathodal M1 ICS produced I2-waves, reflecting transsynaptic activation of corticospinal tract fibers. Conversely, low-intensity anodal M1 ICS produced D-waves, reflecting direct activation of corticospinal tract fibers. These D-waves were delayed by 0.6–0.8 ms compared to those produced by lateromedial-oriented TMS. A similar delay (0.4 ms) was observed by Di Lazzaro et al. (above) using high-intensity bipolar M1 ICS. Compared to TMS, M1 ICS could recruit slower conducting fibers or excite corticospinal fibers at a more proximal site. Low-intensity bipolar EMCS mostly produced I3-waves and not a combination of D- and I2-waves. These results suggest that bipolar stimulation is not simply a “bifocal” stimulation that would have corresponded to the addition of the responses to monopolar anodal and cathodal stimulations. Anodal and cathodal electrical fields likely overlap and the neuronal activity produced near the anode and near the cathode, respectively, can interact with each other (Manola and Holsheimer 2009) The magnitude of these interactions depends on the center-to-center distance between the electrodes. The bipolar M1 ICS configuration providing optimal chronic pain relief produced mostly
late I-waves at low intensity (below motor threshold) and also D- and early I-waves at high intensity (above motor threshold). As stimulus intensity increased, the induced electrical field likely spread and went deeper into the brain, recruiting more fibers. These results confirmed modelization studies in which M1 ICS could produce analgesia by recruiting horizontal fibers in the upper cortical layers of precentral gyrus rather than by directly exciting the pyramidal tract (Manola and Holsheimer 2009). The descending volleys produced by the optimal M1 ICS configuration for pain treatment are closer to those produced by PA-oriented TMS than LM-oriented TMS: indeed, LM-oriented TMS preferentially recruits D-waves at low intensity, whereas PA-oriented TMS recruits I-waves. Thus, M1 ICS and PA-oriented TMS likely activates similar neural circuits and this latter may truly act as a tool to predict the outcome of subsequent M1 ICS. AP-oriented TMS should be even more effective, since it evokes later I-waves than PA-oriented TMS, at least in some patients (Di Lazzaro et al 2009). The conclusions of this study are weakened by observing that the descending volleys generated by M1 ICS were not compared to those in patients in whom M1 ICS failed, and the effects recorded could have thus been purely unspecific. Moreover, nothing could be said about possible influences of M1 ICS on the brainstem or cord, since recordings were effected in response to single pulses, whereas M1 ICS for pain relief is performed at 40 Hz.

18.3 Modelization Studies

Several attempts at modelizing the effects of ICS have been made (see Chapters 19-20 for detailed discussion). However, their limits are immediately apparent if one considers the daunting task of simultaneously factoring in the multitude of parameters that are at work in the living human brain, many of which are unknown.

The belief that only a cathode can activate cortical neural tissue and that the anode placed over the cortex is indifferent seems to be wrong (Manola and Holsheimer 2009). Although the stimulation of nervous tissue generally occurs in the vicinity of the cathode, this is not true in ICS due to the different orientations of cortical nerve fibers (parallel and perpendicular to the laminae) and to the large size of the epidural lead electrodes: thus various populations of axons can be activated under either the cathode or the anode (horizontal fibers vs perpendicular fibers), making bipolar stimulation bifocal (thus, in M1 ICS with a perpendicular position of the paddle, S1 is engaged). A large motor response is evoked when either anodal stimulation is applied on M1 or cathodal stimulation is applied on the central sulcus, according to the orientation of cortical nerve fibers in the stimulus-induced electric field. When the MEP amplitude is high in anodal stimulation, it will be lower in cathodal stimulation and viceversa. When the electrode covers the lip of CS, anodally and cathodally evoked MEPs may have similar amplitudes. Also, despite the large center-to-center distance of the cathode and the anode in a quadripolar strip (=/> 10
mm), some overlap of the corresponding stimulus-evoked field is still present: due to this overlap, the electrical fields in the cortex below the cathode and the anode are different from real monopolar fields, and elicited neural activities will most likely differ from monopolar ones. In other words, when M1 ICS is applied bipolarly, the neural activity evoked near the cathode may affect the activity near the anode - and vice versa - via their intracortical connections (likely an inhibitory interaction).

According to Arle et al. (2008)’s model of ICS for pain control, ‘subthreshold’ M1 ICS only excites the horizontal inhibitory fibers coursing horizontally within the exposed parts of the M1 gyrus, and these in turn lead to local inhibition, and subsequent lack of layer 5 excitation, of S1 (thus inhibiting S1 by providing less excitation as well)(see also Drouot et al 2002): in particular, during stimulation, the mean firing rate in S1 is decreased by 40.5% (Shils et al 2008). Many of the horizontal fibers are from the predominantly inhibitory layer 1-3 stellate interneurons. The significant change in activity is centered only within the topographically oriented region which is coding for the ‘painful’ stimulus coming from sensory thalamus. In other words, the computational representation of a ‘painful’ stimulus arising through sensory thalamic cells and carried on to S1 is inhibited by M1 ICS acting on just the inhibitory interneurons of M1. This is in line with Manola and Holsheimer (2009)’s studies, in which the neural elements most likely stimulated by M1 ICS were superficial horizontal fibers of the largest diameter. Higher amplitudes would also stimulate excitatory layer V pyramidal cells (for instance) in M1, in addition to the inhibitory interneurons: this increased activity would override the inhibition and lead to motor unit driving, which indeed does occur clinically, through vertically oriented fibers. M1 ICS stimulates both horizontal and vertically oriented fibers, rather than directly hyperpolarizing them, as has been reported (Hanajima et al 2002).

According to Wongsarnpigoon and Grill (2009, 2012)’s modelization studies of (now defunct) NorthStar Neuroscience’s stimulating array, bipolar stimulation increases thresholds compared to monopolar stimulation for neurons beyond the stimulating electrode, with thresholds lowest beneath the electrodes (i.e. focuses injection of charge). Although current passes through the region of the cortex between the electrodes as it travels from the anode to the cathode, thresholds for excitation of neurons directly between the two electrodes are greater than beneath the electrodes. This is the case also when the electrodes straddle M1, with thresholds lowest beneath the electrodes, and not in the crown of M1 between the electrodes. The two electrodes stimulate two distinct populations of neurons, but it is unclear if and how activation of one population affects the other. The conclusion is that monopolar stimulation would be more prudent. Importantly, if the electrode is placed perpendicularly to the central sulcus to straddle two gyri, as done by some groups, this configuration leads to substantially lower thresholds in the adjacent gyrus compared to stimulation with the lead oriented over and parallel to M1 and this could have clinically relevant effects beyond what is intended. Thus, these authors advise against perpendicular positioning across the rolandic fissure (or any other) unless one is sure ICS of the
adjacent gyrus is innocuous (which is arduous to guarantee anywhere in the cortex).
In other words, the counter-electrode during bipolar ICS does more than simply return the current to the stimulator and bipolar ICS can produce different outcomes from monopolar stimulation singly for the anode or the cathode. Selective stimulation (straddling electrodes) of neurons located deep within a sulcus appears exceedingly difficult with ICS: this means that, while the hand area is generally targeted in many ICS procedures, sulcal neurons cannot be directly activated without co-activation of neurons on the crowns and lips of M1 and S1. However, in TMS, despite the gyral crown of the cortex being subjected to a larger magnetic field magnitude, the sulcal bank of M1 has larger cerebral CBF responses (Krieg et al 2013). However, the importance of localization is not well understood. In certain disorders, stimulating a wide area of the cortex may be more beneficial than targeting a small area, a fact confirmed by ICS cases in which focal stimulation benefited widespread body pain or in PD where benefit is pansomatic. Another important observation is that thresholds beneath the electrode are directly related to electrode diameter, i.e. larger electrodes reduce the spatial selectivity of stimulation beneath the electrode. Spatial selectivity is also influenced by inter-electrode spacing: reducing the spacing (7 mm vs 10 mm) increases thresholds (larger amplitudes are needed to produce an effect) throughout most of the cortex for bipolar stimulation. This affects the ability to perform current steering, a technique where stimulation is delivered through multiple independent sources to direct the flow of current and focus stimulation on a specific region between the electrodes.

18.4 Conclusion

In sum, ICS directly engages the underlying stimulated cortex and only thereafter other brain regions (including the thalamus) connected anatomically. The effects of ICS appear to be produced by activation of horizontal fibers located in the superficial layers of the cortex and in the vicinity of the origin of the pyramidal tract corresponding to the targeted region, but not by direct activation of the pyramidal tract in case of M1 ICS. Both the cathode and the anode have effects.

References

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