8 Central Pain

Central pain has been defined as “*spontaneous and/or evoked, anomalous, painful or non-painful, sensations projected in a body area congruent with a clearly imaged lesion impairing –transitorily or permanently- the function of the spinothalamoparietal pathway*” (Canavero and Bonicalzi 2011). It follows cerebrovascular accidents, spinal cord injury, multiple sclerosis and other neurologic conditions affecting the CNS. There are approximately 7 million patients worldwide.

In 1991, Tsubokawa et al introduced Motor Cortex Stimulation as a treatment of central pain. In 1995, Canavero and Bonicalzi reported the first case of effective somatosensory cortex stimulation. Since then, the most positive results have been seen when the stimulating poles overlies parts of cortex corresponding to painful body parts (generally face, arm, chest, leg singly or in combination), although data suggest that precise, “millimetric,” somatotopic localization of the electrode may not be required. In addition, the leg area often extends, at least partially, on the convexity.

8.1 Efficacy

Globally, more than half of all reported patients with CP originating from the brain were relieved more than 40% on a VAS scale during the long term. Pain in patients with CCP was also relieved, although the number of treated cases (about 20) is too small for any definite conclusions to be drawn (Table 8.1). Concurrent drugs can be reduced or even stopped in many cases. A suggestion of greater response of evoked versus spontaneous pains is not confirmed in most series and M1 ICS does not relieve nonpainful paresthesias.

What is rather puzzling is the observation that some groups report both good short- and long-term results, some have excellent initial results with a loss of benefit within weeks or months, and that some have scarce or no results at all. In practically all papers, the failure rates have ranged between 12% and 84%. However, the majority of these reports list as treatment failures cases improving by <30-40%, but there are several patients who are actually satisfied with 20-40% relief, at least for a time, due to improved functional ability and quality of life. Conversely, other patients may report high levels of pain reduction, yet fail to demonstrate any functional improvement. Accordingly, changes in VAS scores alone do not always accurately reflect the true effectiveness of a particular therapy, and clearly are inadequate for determining benefits with regard to functional capacity, quality of life, and so on. Nonetheless, explaining such variable results is not easy. Localization of stimulation target can be ruled out. Groups that meticulously explored the whole target cortex

with intraoperative stimulation and used sophisticated localization technology (neuro-navigation, evoked potentials...) achieved either excellent or poor results in the same proportion. Inadequate (too short or too few contact combinations tried) neurostimulator programming is certainly a reason in some cases, and so is a team's lack of experience with neuromodulatory techniques and, above all, chronic pain management. A few groups ascribe their success to elimination of nonresponders to subacute therapeutic stimulation from those receiving long-term stimulation, which amounts to a sizable population. Accordingly, some neurosurgeons are enthusiastic about the technique, whereas others are rather cold or downright negative. It may be that ICS is performed at many more centers than those which publish and most of the failures go unreported, with only series with good results being published. This spurred the search for prognostic markers. Some have been proposed:

1. An intact or nearly-intact corticospinal motor function has been touted as a favorable prognostic sign, with about 75% of patients without major motor deficits getting benefit, but several exceptions are on record ([Table 8.1](#)).
2. Severe sensory changes not modified by M1 ICS represent a predictor of unfavorable outcome, whereas improvement in sensory deficits that appears during the subacute therapeutic trial is followed by a favorable outcome (Drouot et al 2002, Velasco et al 2008). Exceptions to the rule exist, and at least 3 cases of CP improved by ICS in spite of almost total lack of sensory cortex are on record (e.g. Peyron et al 1995; Nguyen et al 1999). Normal or near-normal sensory thresholds are not necessarily predictive of favorable outcome.
3. Response to noninvasive stimulation (e.g. rTMS) may identify patients who will get successful stimulation, but this is not an iron-cast criterion (see [Box 8.1](#)).
4. Drug dissection protocols may help identify responders. The first was proposed by Tsubokawa's group ([Table 1](#)): doses of 3 mg of morphine are injected every 5' up to 18 mg followed by naloxone 0.2 mg bid, followed by thiopental 50 mg IV bolus every 5' up to 250 mg and ketamine 5 mg IV bolus up to 25 mg. Canavero and Bonicalzi (2002, 2007, 2007b) developed the subhypnotic propofol test, in which the patient is injected in a single blind fashion with 1.5 mg of Intralipid or similar white fat solution and after 20' with 0.2 mg/Kg IV bolus of propofol.
5. Canavero and Bonicalzi (1995) introduced parietal cortex stimulation on the basis of neuroimaging data, the first report of neuroimaging-directed brain stimulation. However, functional neuroimaging has not yet been evaluated in a clinically meaningful fashion.
6. Successful ICS may be impossible in patients with a large surface of the cortex destroyed (e.g. stroke) and in those with a cortex distant from the dural surface (subdural hygroma, post-stroke atrophy...). However, Canavero has made a strong case for ipsilateral (to pain) ICS (Canavero 2009).

Table 8.1: Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Tsubokawa's group <i>Pain</i> 1990; <i>Suppl</i> 5:5491 (abs.952)	CP (thalamic) (7 pts)	Excellent (5: no drugs needed) or good (2: some drugs needed) pain relief (abstract: effective in 75% of cases (>7 mos))	First report of MCS for CP (1988) MCS vs. thalamic stimulation. MCS is more effective than thalamic stimulation. Improvement of motor function in some pts MCS improved movements of the painful limbs. Pain subsided within a few minutes. 5'–10' ON, 4–5 h relief 5–6 times daily, then 2–3 times daily
Tsubokawa et al. (1991) Also see : <i>Acta Neurochir Suppl (Wien)</i> 1991; 52:137–9	CPSP (12 pts; thalamic lesion: 6 pts; putaminal lesion: 3 pts; pontine hemorrhage: 1 pt; other lesions: 2 pts)	Complete pain relief in 5/12 pts (1 yr), considerable pain reduction in 3/12 pts (1 yr). Long-term benefit in 8/12 pts (>1 yr)	Intermittent stimulation effective in 5/12 pts. No seizures; pain relief at stimulus intensities below movements threshold. Paresis improvement. Pain improvement in barbiturate-sensitive, morphine-resistant pts. Disappearance of the analgesic effect in 3 pts, with reappearance after revision of electrode placement
Tsubokawa et al. (1993) Also see : <i>Tsubokawa et al. Pain</i> 1993; 58 (Suppl.):150	CPSP (11 pts; thalamic stroke: 8 pts; putaminal hemorrhage (+ small lesion in the posterior limb of the internal capsule): 3 pts)	Pain relief: Immediate: Excellent (>80%): 6/11 (54%) Good (60–79%): 2/11 (18%) Fair (40–59%): 1/11 (9%) Poor (<40%): 2/11 (18%) Long-lasting: Excellent (>80%): 5/11 (45%) Good (60–79%): 0/8 Fair (40–59%): 0/8 Poor (<40%): 3/8 (37%) (2 yrs)	Barbiturate-sensitive pts: 5 (+3?)/11; morphine-resistant pts: 10 (+1?)/11. Stimulation of area 4 ipsilateral to the inciting lesion. One week test period. Fair and poor responders not implanted. Satisfactory immediate pain relief in 8/11 pts (73%). Gradual effect reduction over several months in 3/8 pts. Long-term response in barbiturate-sensitive and morphine-resistant pts (also for Vc DBS). No pain-relieving effect by high-frequency postcentral stimulation (11/11 pts): in 2, worsening of pain, similar to their spontaneous ones. In 3 pts, areas rostral to MI stimulated without relief. Nonpainful paresthesias unrelieved. 5'–10' 'ON' at a time – no stimulation at night 50 – 120 Hz 100–500 µs
Katayama et al. (1994) <i>Stereotact Funct Neurosurg</i> 1994; 62:295–9	CPSP (6 pts; lateral medullary infarct)	MCS in 3 pts. Pain relief: 2/3 > 60%; 1/3 > 40% (4 mos)	Pain relief > 40% in 1 pt previously unsuccessfully treated by Vc DBS. No satisfactory pain control by thalamic stimulation in any pts

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Yamamoto <i>et al.</i> (1997)	CPSP (39 pts; thalamic stroke: 25 cases; supratheralamic stroke: 14 pts)	28 MCS. Excellent/good (50–100%) pain relief: Thalamic pts: 10/19 (53%) Suprathal. pts: 3/9 (33%) (difference not significant) T+ or K+ & M+: 2/4 (50%) T+ or K+ & M-: 10/14 (71%) T- & K- & M+: 0/2 (0%) T- & K- & M-: 1/8 (13%) Overall: 13/28 (46%) (12 mos)	Supratheralamic stroke = infarct or hemorrhage of the posterior limb of internal capsule, or parietal lobe, sparing the thalamus. No pts with midbrain or medullary lesions. MCS test period: 1 wk. 8/39: morphine responsive 22/39: thiamylal responsive 11/23: ketamine responsive Thiamylal+ketamine sensitivity + morphine resistance may predict a positive effect of MCS
Katayama <i>et al.</i> (1998) (Also includes: Katayama <i>et al. Stereotact Funct Neurosurg</i> 1997; 69:73–9 & Tsubokawa <i>et al. In: Abst. 3rd Int Congress INS. Orlando, 1996, p. 123</i>) includes all pts from previous publications!	CPSP (31 pts. Thalamic stroke: 20 pts; putaminal hemorrhage: 8 pts; lateral medullary infarction: 3 pts)	Early satisfactory (>60%) pain relief: 23/31 pts (74%). Long-term efficacy (≥ 2 yrs): 15/31 pts (48%)	Damage of the posterior limb of the internal capsule in pts with putaminal hemorrhage. Previous ineffective SCS. Pain relief >60%: 13/18 pts (73%) with no or mild motor weakness (70% of pts with inducible muscle contraction); 2/13 pts (15%) with moderate or severe motor weakness (difference statistically significant). Satisfactory pain control in 14/20 pts (70%) with inducible muscle contraction but in only 1/11 pts (9%) without inducible motor contractions ($p < 0.01$). No relationship between pain control and presence of hypesthesia, dysesthesia, hyperpathia, allodynia or disappearance of SSEP N20 wave plus stimulation-induced paresthesias, or motor performance improvement. 3 pts with MCS or DBS became pain-free without stimulation for years (all 3 getting initial excellent relief at progressively longer stimulation intervals during intermittent stimulation). 1 subcutaneous infection, 3 seizures during testing at intensities higher than muscle threshold. 10'-20'ON at a time 20-50 Hz 100-500, most at 200 μ s 2-8 V

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Yamamoto <i>et al.</i> (2000)	Small thalamic stroke, then action tremor, then Vim DBS, then cardioversion, then CPSP	50% relief over 2 years	Thiamylal/ketamine responsive, morphine resistant
Katayama <i>et al.</i> (2001)	CPSP (45 pts)	Satisfactory pain control: SCS: 7% of pts; DBS: 25% of pts; MCS: 48% of pts	DBS and MCS in 4 pts: better result: MCS 1/4 pts; DBS 2/4
Fukaya <i>et al.</i> (2003) Also includes: Katayama <i>et al.</i> <i>Acta Neurochir Suppl.</i> 2003; 87:121–3	CPSP (31 pts)	Unsuccessful MCS in 2 CPSP pts reporting abnormal pain sensation after stimulation of the motor cortex (see text)	Experimental study on conscious somatosensory response during surgery for electrode placement
Paris group : Nguyen <i>et al.</i> (2009) Also includes : Nguyen <i>et al.</i> 1997 <i>Acta Neurochir Suppl.</i> 1997; 68:54–60 Nguyen <i>et al.</i> (1999) Nguyen <i>et al.</i> <i>Arch Med Res</i> 2000; 31:263–5 Nguyen <i>et al.</i> <i>Neurochirurgie</i> 2000; 46:483–91 Drouot <i>et al.</i> 2002	CPSP (32 pts) BCP (thalamic abscess) (1 pt) BCP (head injury) (2 pts) SCI (9 pts) 1993–2004	>60% relief: 13 40–60% relief: 15 <40% relief: 7 mean improvement on VAS: 53%, on MPQ: 56.7%, on WBPQ: 62.7%, on MQS: 32.9% NA (in a previous series of 4: <40% in a paraplegic pt (18 mos); 100% (visceral pain + substantial reduction of diffuse pain) in a tetraplegic pt (22 mos), another improved >40%, one failure) f-up (global): 29–170 mos	Progressive loss of effect in some pts reversed in most by correct repositioning of paddle. 3 hours 'ON' and 3 hours 'OFF' (12 h die) 40 Hz (25 Hz – 55 Hz) 82.5 (60 –180) μ s

Table 8.1: Invasive cortical stimulation

continued

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Nguyen <i>et al</i> (2008) (with Velasco's group in Mexico)	3 CPSP	Pt 1: -16% Pt 2: -38% (both hemisoma CP) Pt3 (face CP): -80% f-up: 1 year (stable benefit)	Benefit NOT due to placebo effect. MCS decreased MPQ affective subscore Drugs down 55% (pt 3) Improved QoL
Lyon group:			
Nuti <i>et al.</i> (2005)	CP (27 pts) -Ischemic	Follow-up: 2-104 mos (mean 49 mos).	Parameters: 0.5-5V (mean 1.5V), 30-80 Hz (mean 45.5 Hz), 60-330 μ s (mean 140 μ s), ON 30-120 min, OFF 15min-24 hours.
<i>Includes all previous publications:</i>	lesions 11 pts (3 thalamic (Vc), 4 medulla, 2 cortical parietal, 1 parietal/insula/ACC, 1 parietal/insula)	Pain relief: BCP: Excellent (>70%): 3 Good (40-69%): 8 Poor (10-39%): 8 Negligible (0-9%): 4 CCP:	5 – 6 hours of stimulation each day Prospective evaluation of MCS. Long-term outcome evaluated by means of: 1) %pain relief 2) VAS 3) postoperative VAS decrease 4) reduction in drugs intake 5) yes/no response for being operated again.
<i>Larrea <i>et al.</i> Stereotact Funct Neurosurg 1997; 68:141–8</i>	-Haemorrhagic lesions 11 pts (1 thalamic (Vc), 1 thalamus/ midbrain, 5 capsulothalamic, 1 capsulolenticular/insula, 3 cortical parietal)	Excellent: 0 Good: 3 Poor: 1 Negligible: 0 Decreased analgesic intake: 52% of pts (complete withdrawal 36%); unchanged: 45% of pts, unavailable data: 3%. Decrease/withdrawal of analgesic in 10/11 poor responders	<u>MCS efficacy not predictable by motor status</u> , pain characteristics, lesion type, QST, SSEP/LEPs, pain duration, BCP vs CCP, presence of evoked pain.
<i>Garcia-Larrea <i>et al.</i> (1999)</i>	-Frontoparietal trauma, 1 pt	(! Contradictory results as noted by Authors)	No subjective sensations during active stimulation.
<i>Funct Neurosurg 1999; 73:122</i>	SCI (discal hernia-associated myelopathy): 3 pts	Favour re-intervention: 70% of pts	Partial epileptic seizures in 3 pts in the early postoperative stage or during trials for increasing intensity.
<i>Sindou <i>et al.</i> 9th World Congress on Pain, Book of abstracts, IASP Press, 1999</i>	AVM: 1 pt		1 speech disorders and 1 motor deficit resolved spontaneously Long term relief predictable from early pain relief.
<i>Montes <i>et al.</i> Neurophysiol Clin 2002; 32:313–25</i>	1992-2003		1-2 paddles. 3 subdural MCS may have adverse cognitive effects. The risk may increase with age (>50 yrs)

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Maarrawi et al. (2013)	CPSP 10 pts (capsular/thalamic/lenticular: 6 pts; brainstem: 3 pts; insular: 1 pt) SCl (1 pt) 2002-2009	Pain relief: Excellent (>70%): 2 Good (40-69%): 6 Poor (10-39%): 2 SCl pt: 20% relief	Drug therapy: clonazepam (2.5-3 mg/d); Gabapentin (2400-3200 mg/die); Paracetamol (1500 mg/d) (!!!), Oxcarbazepine (1200 mg/d), Carbamazepine (1000 mg/d), Clomipramine (125-150 mg/d), All patients either unresponsive/intolerant to oral opioids (7 pts) or only mild relief (8 pts). 0.5-5V, 180µs, 35-45Hz, cyclic (30'-60'ON, 2 Hrs OFF)
Turin Advanced Neuromodulation Group (TANG) Canavero and Bonicalzi. (1995)	CP (2 pts; CPSP: 1 pt; syringomyelia: 1 pt)	Pain relief: 30-50% in syringomyelia pt (2 yrs); no relief in CPSP	Syringomyelia pt: parietal somatosensory stimulation. Spreading of pain to contralateral side and vanishing of analgesia at 2 yrs. Modest propofol response CPSP pt: propofol unresponsive
Canavero et al. (1999)	CPSP (1 pt; thalamocapsular stroke)	Effective short-term pain relief (allodynia disappearance and 50% reduction of burning pain) (5 wks)	Propofol-responsive pt. Painful supernumerary phantom arm during MCS and lasting 6 mos after stimulator switch-off. Pain relapse after 5 wks
Canavero and Bonicalzi (2002, 2007) Includes: Canavero et al.: In: <i>Proc 4th Int Congress of INS, Luzern, 1998</i> Canavero et al. <i>Neurol Res</i> 2003; 25:118-22	CP (CPSP 5 pts; SC pain: 2 pts) + 1 (algodystonia) 1993-2003	Effective (30-100%) pain relief with MCS/PCS in 2/7 pts. Long-term efficacy (4 yrs) in 2 pt (BCP and MS CP). Ineffective MCS in 4/7	Effective SI stimulation in 1, then resubmitted to MCS with same benefit plus 50% opioid reduction (however, patient unsatisfied and explanted). Overall efficacy: 3/7 CP pts, all propofol-responsive. Ineffective MCS in 4/7 CP pts, all propofol-unresponsive, but 1 who could not be assessed due to intermittent nature of pain. Algodystonia: temporary benefit

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Saitoh's group: Hosomi et al (2008) Includes all previous publications including Tani et al JNS 2004 ; 101 :687-689	CPSP (thalamic) (10 pts) [+1 pt relieved without stimulation]	4: no initial relief 6: 21-90% initial relief (mean: 55.6%) [late relief at 14-75 mos: 10-80% (mean: 31.6%); 1 explant due to enduring benefit from CS manipulation -all 3 relieved initially 60-75% (mean: 65.3%) [late relief at 13-88 mos: 15-60% (mean: 41.6%); 1 explant (15% relief pt) 1: no relief	Pharmacological test with phentolamine, lidocaine, ketamine, thiopental, morphine, placebo. Ketamine-sensitive pts seem to be good candidates for MCS <u>Some pain reduction by SI stimulation.</u> Ineffective prefrontal stimulation. First report of bilateral cortical stimulation for SCI pain. 4 mos interval between implants. 2 serious ICH, with 1 vegetative. 2 infections
<i>Saitoh et al. Neurosurg Focus 11(3), article 1, 2001</i> Includes <i>Saitoh et al. J Neurosurg 2000; 92:150-5</i> <i>Tani et al. J Neurosurg 2004; 101:687-9</i>	CP (brainstem: stroke 3pts, injury 1pt) CPSP (temporo-parietal) (1 pt) CCP (SCI) (2 pts) 1996-2005	3: 25-63% initial relief (mean : 42.6%) [late relief at 33-73 mos: 15-50% (mean: 35%) 30% initial relief, then 10% at 72 mos 50-89% initial pain relief (60-65% late relief at 27-75 months); 1 explant	subdural approach, 1-2 plate electrodes within central sulcus, in 9 pts 1 plate in interhemispheric fissure, extradural ECS in only 2 pts. MCS within central sulcus more effective than surface MCS. Globally: initial VAS score reduction in BCP: 42%; late relief: 26% at 1+ year 3-4 periods ON (30' each) a day, followed by 5-6 h benefit in OFF. 25-50 Hz 200 μ s 0.9 to 5 volts
Other groups:			
Tasker et al (1994)	CPSP (1 pt, large supratthalamic infarct) CPSP (2 pts) (1 pt with AVM)	Substantial pain relief with <i>ipsilateral to pain MCS</i> ; gradual abatement over 6 yrs; relief with <u>subdural</u> stimulation over a few months. 1 relief, 1 failure	Contralateral MCS due to a lack of sufficient MI on the affected side. Stimulation-induced ipsilateral paresthesias

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Hosobuchi (1993) Also includes: <i>Stereotact Funct Neurosurg</i> 1992; 59:76–83 <i>Abstr. IASP congress</i> 1993	CPSP (5 pts; post-removal of parietal cortical AVM: 1 pt; brainstem infarction: 1 pt; thalamic lesion: 3 pts)	Pain relief: Initial: 5/5 excellent. At 2–3 mos: 4/5 excellent (>50%); 1 fair. At 9–30 mos: 3/5 excellent (thalamic, parietal, brainstem)	Efficacy dramatically reduced in 2 thalamic pain pts, to 0% in 1 pt and 30% in 1 pt 2–6 mos after implantation 1h ON/6h OFF 20–30 Hz, 180–260 μ s, 3–5V
Meyerson <i>et al.</i> (1993) <i>Acta Neurochir Suppl (Wien)</i> 1993; 58:150–3	CPSP (3 pts; thalamic hemorrhage: 2 pts; brainstem infarction: 1 pt)	Pain relief: CPSP: none: 3/3	In spite of multipolar electrode grid in 1 and relocation of paddle in another. Most patients had one or two seizures during test stimulation. Painful sensations at the electrode site in 2 pts. 1 epidural clot leading to aphasia. 20'–30' ON 5 times a day; 50 Hz, 300 μ s, amplitude 20 to 30% below motor threshold
Dario <i>et al.</i> Long-term results of chronic MCS for CP. <i>Abstr. 9th World Congress on Pain, IASP Press, 1999, A185.</i> Also includes Dario <i>et al. Riv Neurobiol</i> 1997; 43:625–9	CPSP (thal. stroke: 2 pts; brainstem stroke: 1 pt)	70% pain relief in 1 thal. pt. (3 yrs) Gradual abatement of pain relief over 2 yrs. 60–90% relief. Then 50–70%, then 20–30% at 3–41 mos (ave: 27 mos)	All pts propofol-responsive. 2–2.5 V, 50–75 Hz, 120–210 ms, continuous mode.

Table 8.1: Invasive cortical stimulation

continued

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Franzini <i>et al.</i> (2003) Also includes: <i>Franzini et al. In: Abstr. XLVIII Congresso SINCH, Coppinello, 1999</i> <i>Franzini et al. J Neurosurg</i> 2000; 93:873–5	CPSP (3 pts, A, B, C)	Satisfactory (30–50%) pain relief: Pts A (>4 yrs) and B (>2yrs). Short-term pain relief (6 mos): pt C	2 responders propofol-sensitive. Pain abolition after a second stroke in pt B. Unsatisfactory pain relief (30%) by further stimulation in pt C. Complete abolition of thalamic hand
Herregodts <i>et al.</i> (1995)	CP (thalamic) (2 pts)	Immediate pain relief: >50% in both pts Long-lasting: 1/2 (full relapse in one at 4 mos). 1h ON every 6 hrs	
Migita <i>et al.</i> (1995)	CPSP (2 pts; putaminal hemorrhage: pt A; post-20 mos stereotactic thalamotomy; pt B)	Pain relief: 70–80% in pt A (1 yr) No relief in pt B	Pt A: morphine and barbiturate unresponsive. 30% pain relief with TMS Pt B: previous 6 month effective Vc DBS. Barbiturate responsive, morphine and TMS unresponsive
Fuji <i>et al.</i> (1997)	CPSP (thal. infarction: 2 pts; thal. hemorrhage: 5 pts)	Satisfactory pain relief: 6/7 pts (1 mo) Unsatisfactory pain relief: 5/7 pts (3 mos).	Lesions included internal capsule, Vc and pulvinar (MRI confirmed, 5 pts). Early electrode removal in 1 pt after unsatisfactory test stimulation. 30' ON 10 – 100 Hz 200 μ s 3-8V
Barraquer-Bordas <i>et al.</i> (1999)	CPSP (1 pt: capsuloincular hemorrhage)	MCS trial ineffective (motor response elicited)	Hemisoma burning pain, + evoked pains. DBS reduced CP for 5 mos and evoked pains, until glioma displaced electrode with relapse and death
Roux <i>et al.</i> (2001)	CPSP (2 pt) SCI (1 pt) Myelopathic pain (1 pt)	-both >80% relief -60% relief -90% relief f-up: 6-14 months	

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Mogilner and Rezai (2001)	SCI (1 pt)	Relief (not broken down) (mean follow-up 6 mos)	30'-2h ON 5-10 times die, 110 Hz, 210 μ s 2-8V
Rodriguez and Contreras (2002)	SCI (post-cervical ependymoma removal) CP (1 pt)	Evoked pain dramatically improved. Steady burning pain moderately relieved (2 mos)	3rd party analysis of results. Tremor improvement. No reduction of analgesic intake after MCS. 7.1 V, 5 Hz, 450 ms, ON 2 h, OFF 3 h, 0-/2+
Nandi <i>et al.</i> (2002) <i>Includes all pts reported in Carroll et al. Pain 2000; 84:431-7</i> <i>Smith et al. Neurosurg Focus 2001; 11(3):article 2</i>	CPSP 7 pts (cortic. stroke 1 pt; thal. stroke: 3 pts; brainstem stroke: 2 pts). Gunshot brainstem injury (1 pt)	Appreciable pain relief: 1 pt, cortical (4 yrs); 2 pts (weeks to months) No relief: 4 pts (thalamic, brainstem) Brainstem injury: 50-60% (31 mos): 1 pt	The only pt where it was tried: propofol-sensitive. Pain disappearance for 5 mos after stimulator switched off in the responder. Enduring benefit in 1 pt only
Frighetto <i>et al.</i> (2004)	CPSP (1 pt)	Relief (no details given)	Previous ineffective thalamotomy
Henderson <i>et al.</i> (2004)	CPSP (1 pt)	Relief, then loss, then new relief (?) after intensive reprogramming	

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Brown and Pilitsis (2005)	CPSP, Wallenberg (1 pt) CPSP, thalamic (1 pt)	0% VAS 10 to 8; McGill Quest. Index from 65 to 32 (both sensory and affective scores)	Follow-up max. in whole series (PNP and CP): 10 months. <u>Contrary to Nguyen, they conclude that precise, somatotopic localization of the electrode may not be required, because the optimal inter-electrode distance determined during cortical mapping and afterwards with subjective patient evaluation of pain control was fully 3 cm.</u> Intraoperative neuronavigation and cortical mapping for stimulation site targeting. Strength and discriminative sensation improvement from MCS in 3 pts with facial weakness and sensory loss. Dysarthria improvement in 1 pt More than 50% reduction in pain medication dose. <u>Continuous stimulation</u> 40 Hz, 90-240 μ s 2-8V
Slawek <i>et al.</i> (2005)	CPSP, brainstem (1 pt)	20% VAS reduction; withdrawal of narcotic and decrease of non-narcotic medications, ability to introduce rehabilitation and improvement of sleep	Follow-up: 4 mos. No side effects
Savas and Kanpolat (2005)	CP (1 pt)	0% relief during test stimulation	
Gharabaghi <i>et al.</i> (2005) <i>Also includes Tirakotai et al. Min. Invas. Neurosurg 2004; 47:273-7</i>	CPSP (hemorrhage) (3 pts) CP, insular (1 pt)	70-100% relief (follow-up: 6-18 mos) 90% relief (follow-up: 24 mos)	Frameless neuronavigation. <u>Single burr hole and vacuum headrest.</u> Awake patient. No complications 3rd party evaluation Volumetric 3-D MR with superimposed fMR data plus intraoperative electrical stimulation

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Pirotte <i>et al.</i> (2005) <i>Also includes Pirotte et al. Neurosurg Focus 2001; 11(3)</i>	CPSP : subcortical: 3 pts; capsular: 2 pts; brainstem: 1 pt; MS pain: 1 pt; cervical syrinx: 1 pt; SC ependy- moma: 1 pt 1998–2003	Pain relief (%) 100%/50%/worsening 83%/failure (both plegic) 87.5% 100% 70% Failure	50–75% drug dosage reduction among responders 3rd party evaluation. <u>Plegia not an unfavorable prognostic factor.</u> 1h ON every 4 hrs 40 Hz, 100 μ s 1–5V
Rasche <i>et al.</i> (2006) <i>Includes : Tronnier VM. Schmerz 2001; 15 : 278–279</i>	CPSP (thalamic): 7 pts 1994–2005	3 responders (-31%, -41%, -62%) 2/7 pts placebo responder. Duration of positive effect: 2, 4, 1.5 years Relief of dysesthesia, allodynia and hyperpathy in 2 CPSP pts (pts were able to touch the painful area without having painful sensations).	4.5–6.0 V, 50–85 Hz 210–250 μ s, <u>continuous stimulation, then intermittent.</u> Double-blind test trial. VAS evaluation. <u>Single burr hole</u> , neuronavigation. Paddle parallel to central sulcus No sensation evoked by stimulation. Minor changes of parameters during f-up. Immediate or almost immediate (30'–60') pain reduction after turning the MCS on. After-effect: 30'-hours
Tronnier and Rasche (2009)	CPSP (11 pts)	4 pts:>50% relief f-up: up to 15 years	
Son <i>et al</i> (2006)	BCP (traumatic): 1 pt	90–95% relief of spontaneous burning pain in arm and lower trunk, 70–80% relief of burning pain, heaviness and deep pressure-like pain in leg, 50% relief of heaviness and deep pressure allodynia in foot follow-up: 1 year	Severe motor deficit in distal arm and leg. Subdural electrode for arm pain; extradural paddle for leg pain parallel to the course of the superior sagittal sulcus 21 Hz, 210 μ s, 0.8–2.5V 0-/3+, <u>continuous stimulation</u> (arm electrode) 30Hz, 210 μ s, 2–2.5V 0-/2+ continuous stimulation (leg electrode) After-effect: 5'
Sokal <i>et al</i> (2006)	CP (thalamic) (1 pt)	Decrease of pain	

Table 8.1: Invasive cortical stimulation

continued

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Cioni <i>et al</i> (2007)	CPSP (4 pts, thalamic) SCI (2 pts)	Pain relief (50–60%): 1/4 pts, but unsatisfactory relief at 1 yr 1 >40% relief, 1 failure	Extradural multipolar (16–20) grid in all plus electrophysiologic mapping; several combinations assessed over 12 h
Molet <i>et al</i> (2007)	CPSP (thalamic) (3 pts) CCP(paraplegia) (1 pt)	Benefit in some	CP and PNP series: results not broken down
Arle <i>et al</i> (2008)	2 poststroke pain (PSP) pts (P5, 58 yrs; P7, 64 yrs) 3 mixed pain and movement disorders (PSM) pts (but according to their table 2: P1 64 yrs, P2 61 yrs, P4 64 yrs, P6 49 yrs = 4 pts)	1 CPSP < 20% at 17 mos 1 CPSP >60% at 30 mos PSM: good result: P2, 36 mos follow-up; fair results: P1, 39 mos follow up, P4, 34 mos follow-up; poor result: P6, 23 mos follow-up P5: good pain control in her upper extremities and face, but less pain control in her leg region, minimal control of a third-limb sensation. 5 benefits >50% (f-up: up to 9 years)	2 intraoperative seizures 1 post-operative programming seizure. No further seizure with voltage <4.0 V. <u>Continuous stimulation</u> 60-130 Hz, 60-400 μ s, 2-7 V
Arle (2014, personal communication)			
	CPSP (8 pts)		
Velasco <i>et al</i> (2008)	CPSP (thalamic) (1 pt)	60% relief (allodynia disappeared; hyperalgesia decreased) at 1 year follow-up	Double-blind randomized trial Hypesthesia unchanged. 40-130 Hz, 2-3.5V, 90 μ s
Shabalov <i>et al</i> (2008)	SCI (cervical) (1 pt)	VAS reduced >50%	V 1-5.5 ; 20-50 Hz, 60-210 μ s (whole group)
Mondani <i>et al</i> (2008)	CPSP (2 pts) MS (2 pts)	50-80% benefit at 3 months.	Subdural strips

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Delavallee <i>et al</i> (2008)	CPSP (3 pts) 1 thalamic ischemia 1 MCA hemo. 1 MCA ischemia	Poor result (pain relief <40%): P2 (VAS 9 vs 6) Excellent result (pain relief 100-80%): P4: (VAS 8 vs 1), P6: (VAS 9 vs 1) F-up: mean 54 mos (range, 19–69 mos) for whole group (CP + PNP)	Subdural strips. Octopolar electrode. <u>One severe motor deficit was satisfactorily relieved</u> P2: Initial satisfactory pain relief, rapidly diminished to poor relief. System dysfunction/lead mobilization ruled out Parameters of stimulation: P2: 3.0 V, 210 μ s, 80 Hz, 30 min, several times/d; P4: 2.1 V, 210 μ s, 50 Hz 60 min, 1 time/d; P6: 2.0 V, 210 μ s, 60 Hz 30 min, 1 time/d.
Finet and Raftopoulos (2009)	CPSP (1 pt)	Initial satisfactory analgesia, rapid loss of effect (poor result).	Subdural octrode in interhemispheric fissure in front of CS.
Vesper (2010)	CPSP (1 pt) CP (post AVM irradiation) (1 pt)	>50% relief 100% relief f-up: 1-4 years	rTMS predictive
Tanei <i>et al</i> (2010)	MS CP (1 pt)	Test: >50% VAS relief 60% relief f-up: 6 mos	ON 1 h OFF 2 h 0/1+ 2/3- 6.5V >100Hz Reduction of pre-op drugs (+ketamine stopped)
Fagundes-Pereyra <i>et al</i> (2010)	(1) CPSP (5) (2) Traumatic BCP (2) (3) MS (1) (4) Tumoral BCP (1) (5) SCI (1) 1994-2002	(1) Relief 30%, 35%, 50%, 50%, 70% (2) Relief: 50%, 80% (3) Relief: 32% (4) Relief: 50% (5) Not available Follow-up: 12 months	First 7 patients: single burr hole; 3 later patients: craniotomy and Robotic Neuro-navigation with 3D MRI reconstruction Paddle perpendicular to central sulcus. Presence of motor deficit duration of pain: insignificant factors Better results with robotic neuronavigation. Decrease of effects in some patients. CP group; VAS preop, 7.8, postop.: 3.82 ($p < 0.00001$) 45-130 HZ. 45-210 μ s. 2-5.3V, monopolar or bipolar stimulation. Pts with <40% relief intolerant of MCS interruption!

continued **Table 8.1: Invasive cortical stimulation**

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Tanei <i>et al.</i> (2011)	CPSP(8) CCP (tumor) (1) brainstem CP (MS, Chiari I) (2) 1999-2009	CPSP: 80-100% relief (2 patients) 60-79% relief (4 patients) < 40% relief (2 patients) other CP: 60-79% relief (3 patients)	Single burr hole. 1 week trial. VAS assessment. ON 1 h, OFF 2 h Statistically significant Thalamic (55 Hz) and brainstem-cord CP (106 Hz) (3.04 vs. 6.68 V; 180 vs. 308 μ s) <u>DBS + MCS in 2 cord CP patients: additive effect</u>
Lefaucheur <i>et al.</i> (2011)	CPSP (6)	VAS scores were 0,0,0,2,4,5, and 8 (Initial: all > 7) at 1 year	Postoperative stimulation OFF for 1 month followed by a single-blind randomised phase (1 month) with stim OFF (3 patients) or ON (3 patients), then 10 months of open label. No crossover. Safety, not efficacy study. <u>Octopolar round paddle</u> (surgery: average length <u>320 minutes!</u>). 2 pts had IPG explanted for infection and then reimplanted 6 months later. Assessment: VAS, BPI, MPQ, SIP, MQS, PGIC Final parameters: 40-50Hz, 60 μ s, 2-6V. Continuous in 4 patients, cyclic in 2, in the randomized, blinded arm, only 1/3 patients with stim ON reported > 50% VAS relief. Open label: improvement increased over time but significant only after 6 months.
Sakas <i>et al.</i> (2011)	CPSP, thalamic (1 pt)	MI CS : 40% VAS reduction SI CS: 0% MI+SI: 90% VAS relief (face) 70% (arm) <10% (leg) f-up : 2 yrs	2 eight-polar paddles in direct contact with MI and SI. Interdural positioning, subdural interface
Ito <i>et al.</i> (2011) <i>Also includes :</i> Ito <i>et al.</i> (2006)	CPSP (thalamo-capsular/basal ganglia) (6 pts) 2005-2008	100%, 100%, 54%, 50%, 2 failures during test period MCS ineffective. Later SI/SII CS effective for 4 yrs	Follow-up: 46-60 mos 25-50Hz, 2.5-6V, 210-450 μ s, 3+/1-, 0+/3-, 1+/4-, 0+/3-, cyclical (15-30' ON, OFF?) Paddle parallel to MI Minimal motor deficit in 4 responders
Kuroda <i>et al.</i> (2000)	CPSP (evacuated putaminal hematoma) (1 pt)		

continued **Table 8.1:** Invasive cortical stimulation

Author(s)	Type of pain (no. of patients)	Results (follow-up) Parameters	Notes
Mandat <i>et al</i> (2012)	? (possibly 8 with hemibody pain, others possible) in a group of 23 patients with neuropathic/deafferentation pain	Improvement in the whole group of patients ($p < 0.001$). Best results in the neuropathic facial pain group ($p < 0.001$) while the worst ones were noted in the deafferentation pain group ($p = 0.04$).	16 out of 23 patients treated with rTMS with a positive response in 10 cases. VAS assessment 1 month before and 3 months after MCS. Pain duration positively correlated with outcome. 1 post-infection explantation.
Reyns <i>et al</i> (2013)	CPSP (thalamo-capsular/basal ganglia) (4 pts) CPSP (insula) (1 pt) CPSP (brainstem) (1 pt) CCP (syrinx) (1 pt)	-0%, 15%, 25%, 40% -80% -15% -75%	45Hz, 60 μ s, 1.5-3V, bipolar, continuous stimulation
Vargas-Lopes <i>et al</i> (2014)	SCI (1)	VAS reduction from 10 to 4	Use of neuronavigation. Subdural, interhemispheric. 50Hz, 200 μ s, 5V

Noninvasive cortical stimulation (rTMS, tDCS) is known to offer less pain relief than ICS, and for a short time only. A review of all studies shows that several patients did not deviate from baseline Visual Analog Scale (VAS) ratings. In some TMS studies, reductions in pain ratings were also noted among patients in the sham conditions, and, in some trials, did not differ significantly from pain-rating reductions noted with active treatment (Canavero and Bonicalzi 2011). There is no uniformly effective frequency of stimulation, and both high (10-20 Hz) and low (0.2-0.5 Hz) frequencies can be effective. The effect of TMS may start within minutes, but the duration of analgesia after a single session is usually brief (5'-8 days). Some authors emphasize how repeated sessions on consecutive days may lead to cumulative effects lasting beyond the time of stimulation, which might be exploited clinically in patients awaiting surgical implantation. Unfortunately, differences in mean VAS ratings reported in all studies before and after treatment can be misleading, influenced by a large change in only a small subset of patients. Furthermore, significant differences were obtained even with small reductions in the VAS after rTMS treatment. In a sample series, Ohn et al (2012) found rTMS only modestly analgesic for CP in 64% of the patients for two weeks. Thus, noninvasive cortical stimulation cannot be recommended for chronic treatment at the present time, except in an unpredictable fashion in some highly responsive patients. TDCS does not appear to offer superior efficacy over rTMS.

The first to suggest that a trial of TMS could predict analgesia following ECS were Migita et al (1995). Canavero et al (1998, 2002, 2002b, 2003) first confirmed this finding. Other reports followed (Saitoh et al 2007, Lefaucheur et al 2011, André-Obadia et al 2006, 2014). While there is a consensus on the relation between a positive effect after TMS and subsequent analgesia with ECS, a negative TMS trial should not necessarily rule it out. We found a relation between TMS and propofol, and suggested that the propofol test may predict analgesia with ICS (Canavero et al 1998, 2002, 2002b, 2003, Canavero and Bonicalzi 2005, 2011).

Box 8.1: Can TMS help select patients for Invasive Stimulation?

There is no significant statistical difference between results obtained in thalamic or cortico-subcortical brain CP patients. Coverage of restricted painful territories (e.g. chest) should not be taken as contraindicating ECS, even though no sensori-motor phenomena are elicited during test stimulation. Paddles have been placed parallel to the rolandic fissure or perpendicular, with similar results. What is clear is that, despite some claims to the contrary, subdural implantation does not seem to improve results and may actually be less effective than extradural implantation: for CP, benefit at 1 year was 26% only in the largest series (Hosomi et al 2008). Pain relief is not associated with age, sex, presence or absence of cerebral lesion, treated painful region or pain laterality. Some authors offer ICS if the mean VAS score is 6 or more, but this is moot.

Therapeutic ICS does not generally induce any motor activation, even at a high voltage, or any sensory phenomena in a majority of patients. Thus blinded controlled studies are feasible. All studies performed up to now (e.g. Rasche et al 2006, Velasco et al 2008, Nguyen et al 2008) exclude a placebo effect as the primary basis of analgesia.

Absolute exclusion criteria from ICS include: suicidal thoughts or gestures, major psychosocial stressors (job dissatisfaction, marital problems...), major personality disorders, alcoholism and drug addiction. Hemisoma pains do not represent a contraindication, as these can be managed with two strip electrodes combined.

Programming includes a wide range of stimulation parameters (each patient is different and no indications are possible) with voltage varying from 0.5 volts to 6V up to 10.5V (mean 3.8V), pulse width varying from 60 μ s up to 500 μ s (mean: 251.2 μ s), and frequency varying from 5 Hz to 60Hz (often 25-50Hz, mean: 51.1Hz) up to 80Hz and 130 Hz. Chronic stimulation can be cyclical (battery sparing) or continuous. When cyclical, the duration of each stimulating session varies anywhere from 5' to 9 hours 1-to-10 times a day. The choice of stimulation parameters also depends on the presence of the so-called post-effect. Many, but not all patients, have their pain relieved or improved immediately or within 5'-60' during intra-operative stimulation for periods ranging from several minutes to hours or several days without further stimulation. This effect has a tendency to abate over time and by the second month may stabilize at several minutes to a few hours.

Analgesia also can fade over time. Repositioning of the electrode or intensive reprogramming may restore benefit in some cases, although at a lower level than before. Tolerance and fatigue are proposed mechanisms of such effects. Granulations and fibrosis around the contacts have been found in some failures (e.g. Hosomi et al 2008, Canavero and Bonicalzi 2002): surgical curettage may restore benefit.

8.2 Adverse and unusual effect

Permanent disabling morbidity (including epilepsy and intracerebral hemorrhage) and mortality have not been reported for the extradural approach, while there is a small such risk for the subdural approach. The most common adverse effect reported in the literature consists of short generalized seizures, all of which were observed during the initial testing phases. The literature does not reveal cases of epileptic seizures during chronic treatment for CP (Canavero and Bonicalzi 2002). Anti-epileptic medications are -or are not- administered for 1 to 6 months. Caution is however to be exercised when adjusting parameters even long after stimulation has been instituted. Infections are possible (but not meningitis/ encephalitis) and so are hardware failures. Extradural hematomas in need of evacuation are possible, but very rare. Worsening of original pain via ipsi- or contralateral stimulation of MI/ SI has been observed sporadically and one of our CP patients developed a painful supernumerary phantom arm after MCS (see Canavero et al 1999).

Analgesia via ipsilateral stimulation is on record. No major modification of cortical somatotopy is seen in these patients, but bilateral benefit from unilateral stimulation is possible and focal stimulation of the hand area also relieved hemisoma pain in one case (see in Canavero 2009).

A handful of patients with excellent initial analgesia and increasing periods of post-effect have not relapsed for years after switching off the stimulating apparatus, a sign of neuroplastic phenomena induced by M1 ICS in SI.

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