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13 Chronic Disorders of Consciousness

In Section 1 of this chapter, we will examine the use of nonimplantable brain stimulation (ie, transcranial magnetic stimulation - TMS and transcranial direct current stimulation - tDCS) to improve the recovery of patients with Disorders of Consciousness (DOC) (see Box 13.1-2). For details on this technology, the reader is referred to a comprehensive review (Canavero 2009). Whereas TMS is more focal and may reach up to 3 cm depth, tDCS stimulates a wider area more superficially. TDCS is simpler and appears safer in this context; it is also possible to conduct double-blind and sham-controlled trials, since both subjects and operators can be easily blinded. In section 2, we will examine the use of invasive CS. This allows for more continuous, multi-site stimulation and a much wider choice of stimulating parameters.

13.1 Non-Implantable Cortical Stimulation

13.1.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

Pape et al (2009) delivered rTMS over 30 sessions (F8,300 trains per session, 100 ms interpulse interval, 5-second intertrain interval, 110% of motor threshold, 5 days per week for 6 weeks) onto the right dorsolateral prefrontal (DLPF) cortex in a 26 year old patient, who was initially in post-traumatic PVS/UWS (287 days after a TBI, SSEPs absent bilaterally). He improved to MCS after 15 sessions (+8 DOC points), with further improvements up to the 25th session. However, between the 25th rTMS session and the follow-up, there was a decline of functioning of 10 points. No side effects were reported. The same authors (Pape et al 2014) assessed the safety of rTMS in 2 other PVS/UWS patients (6 months and 9 years) targeting the right and left DLPFC respectively (110% MT, 30 sessions, 300 paired pulse trains per session, the rest as above). As a result, patient 1 showed purposeful vocalizations and obeyed simple commands, patient 2 turned the head towards speakers.

Piccione et al (2011) submitted a patient in a MCS for 5 years to an ABA design alternating between rTMS and peripheral nerve stimulation. rTMS (condition A) involved the delivery of 10 trains of 100 stimuli at 20 Hz using a stimulator with a 70-mm fig.-of-eight coil to elicit a contraction of the abductor pollicis brevis. Condition B used median nerve electrical stimulation. After peripheral stimulation, the patient did not exhibit clinical, behavioral, or electroencephalographic (EEG) changes. The frequency of specific and meaningful behaviors increased after rTMS, along with the absolute and relative power of the EEG δ, β, and α bands. These same authors (Manganotti et al 2013) studied 3 PVS and 3 MCS patients >12 months post-

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The *vegetative state* (VS; other recent terms: *Unresponsive Wakefulness Syndrome* (UWS), and, for patients with clear imaging signs of responsiveness, *Non-Behavioral* or *Functional Minimally Conscious State* (NBMCS/FMCS) or *Functional Locked-In Syndrome* (FLIS)), an artifact of intensive care units introduced in the 1960's, was described by Jennett and Plum in 1972. The VS is diagnosed when, after some days to weeks of brain injury, comatose patients open their eyes, but there is no apparent intentional interaction with the environment. VS may be permanent or a transition to the minimally conscious state (MCS), a conscious disabled state or full recovery. Traumatic VS has an incidence of 1-10/100000, with a prevalence lying between 56 and 140 per million: in the USA, at least 4200 new cases of VS and 29000 MCS cases are diagnosed yearly (Giacino et al 2014). Anoxic VS is always more severe than post-traumatic or post-hemorrhagic cases. The widely held notion that preserved consciousness does not occur in patients who have survived for many years after TBI is incorrect (Fernandez-Espejo and Owen 2013). Emergence from the VS later than 1 year is possible - although no better than a severely disabled fully dependent state of living (about 10 cases reviewed by Wijdicks and Cranford 2005), sometimes even 5 years after brain injury (Dyer 1997). Actually, many VS patients evolve to the MCS. A patient emerged from traumatic VS 20 months after the event: beginning from the sixth month, event related potentials (ERPs) to complex sensory and verbal stimulation started to improve, although the clinical examinations remained unchanged (Faran et al 2006). Sarà et al (2007) reported on a 44 year-old man with recovery of consciousness and severe diability 19 months after a nontraumatic brain trauma. Sancisi et al (2009) reported on a 22 year old male who recovered consciousness 19 months after brain injury, with further improvement over 7 years, attaining a condition of independent living. In Estraneo et al (2010)'s series, out of 50 pts, 6 patients in VS improved to MCS (though in a severely disabled state) beyond the 12-month mark. In 1 anoxic VS case, this happened 22 months later. Age younger than 39 years and post-traumatic VS were positive prognostic factors. In Luautè et al (2010)'s series, over 5 years, no VS patient improved, whereas one third of those in MCS improved after 12 months. Yet, it must be recognized that recovery mechanisms from VS and MCS remain poorly understood. Several experimental therapies, both pharmacological (LevoDopa. amantadine, zolpidem, baclofen), and stimulative (deep brain stimulation, DBS; spinal cord and peripheral nerve stimulation), have been attempted over the decades, occasionally successfully, but never with consistent, across-the-board results (Georgiopoulos et al 2010, Lemaire et al 2014), and without a real understanding of the mechanisms underlying their efficacy. Failures in large series have been reported (e.g. Thonnard et al 2014: zolpidem 10 mg ineffective in 28 VS and 32 MCS cases). Yet, the need to restore stable awareness to these patients has become vital, with the advent of virtual reality (VR) and brain-computer interfacing (BCI) and the possibility to eventually control exoskeletons and robotic motor actuators (Naci et al 2012, Rao 2013). BCI can only be applied in the presence of non-fluctuating, stable levels of arousal, awareness and cognition, and these vary dramatically between patients.

Box 13.1: Overview of Docs

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Assessing the presence of intentionality and thus consciousness in the single patient is a daunting task. Consciousness may be present in more patients than previously thought, with qualitatively different levels thereof, although the existence of low level consciousness cannot be proven. Conscious and unconscious processing of verbal material employs largely overlapping brain structures, with conscious processing probably involving more cell assemblies of the same type simultaneously: the continuum is fluid, *no exact borders can be drawn* (Kotchoubey B, et al. News Physiol Sci 2002;17:38-42). Thus, clinical differentiation between VS and MCS is very difficult. Estimation of the presence of consciousness requires expert clinical interpretation of "motor responsiveness": VS patients can move extensively and differentiating reflex or automatic from voluntary or willed movements is thus hard. According to Laureys (Trends Cogn Sci 2005; 9:556-9), up to 40% of patients in apparent VS have some signs of consciousness. MCS is now classified as *MCS+ (obeys simple commands)* or *MCS- (visual pursuit, orientation to pain, smiling to family but not strangers),* recognizing that smiling and crying, in certain contexts, might be the only means of communication available to patients (i.e. volitional) (Owen AM and Coleman MR. Nature Rev Neurosci 2008; 9: 235-243) and that previous criteria to diagnose MCS (correct responses to 6 of 6 orientation questions on 2 consecutive examinations) were too stringent (Nakase-Richardson R et al. Neurology 2009; 73:1120-1126). Blinking to threat, when present, predicts recovery in 30% of the cases. Up to 43% of PVS patients (and 10% of MCS cases) are reclassified as MCS by specialized operators, using such scales as the CRS-R (Schnakers C et al. BMC Neurol 2009; 9:35; see also: Andrews K et al. BMJ 1996; 313: 13-16; Childs NL and Merger WN. BMJ 1996; 334: 13-16), yet even in the best hands some patients will likely remain erroneously diagnosed. The need to know the level of awareness of the subject is key, since emotional harm may come from bedside discussions of condition and prognosis and such knowledge would help customize treatment. fMR and EEG studies (Fernandez-Espejo and Owen 2013) have revealed a subset of VS patients who are aware (command following), but entirely physically unresponsive *(at least 17-19%),* even in the long-term, and some even communicated via these means. Activity in higher level associative cortices provides important positive prognostic information. Up to now, a*ll (but one) the reported patients shown to be covertly aware are post-traumatic.* Performing fMR in PVS patients remains exceptionally challenging and many patients may not be detected (negative studies) by these techniques, because of subclinical seizure activity, aphasia, motor deficit, pain, fatigue, lack of motivation or will, sensory or perceptual impairment, fluctuating arousal with sleep bouts, lack of the cognitive resources (sustained attention, language comprehension, response selection, working memory) required to understand and execute the study tasks. Moreover, patients are generally on several medications and this can alter neurovascular coupling. Also, a patient may not show a response in one modality, but can to another type. More simply, neuroimaging may be insensitive to small changes in brain activity in some patients. *No conclusions or claims about the preservation or loss of residual awareness in patients can be drawn on the basis of a negative finding. False negatives in functional neuroimaging are common even in healthy volunteers and MCS+.* Stender et al (Lancet, 2014, 384: 514-522) reported that ^{18}F-FDG PET has high sensitivity for identification of patients in MCS and high congruence with behavioral CRS–R scores, unlike fMRI. ^{18}F-FDG PET correctly predicted outcome in 74% of the cases and fMRI in 56%. 32% of the behaviorally unresponsive patients (ie, diagnosed as unresponsive with CRS–R) showed brain activity compatible with (minimal) consciousness on at least one neuroimaging test; 69% of these patients subsequently recovered consciousness. Event related potentials (ERPs), such as MMN, P300 and others, are another means to assess VS patients: it is important to remember, though, that these too are biased to underestimate patients'cognitive abilities. *ERP test data should be treated as the lowest limit of the patients' capabilities*. This means that one to two thirds of VS patients are capable of cortical differentiation of physical stimulus features and *at least 20%* of these patients can differentiate semantic stimuli (i.e. understood language) (Kotchoubey et al 2002). Similar figures (*25%* have nP300, *ca 20%* evince a MMN) have been reported by others (Fischer C et al. Clin Neurophysiol 2010; 121: 1032-1042). Within the first year, many patients show an intact P300 and several also an N400, indicating considerable residual information processing: at follow-up, about 25% recover (Steppacher I et al. Ann Neurol 2013; 73: 594-602). One of 8 VS and both MCS patients showed an increased hand EMG signal specifically linked to a verbal command (Bekinschtein TA et al. JNNP 2008; 79: 826-828).

Box 13.2: Assessing Consciousness Pre- and Post-treatment

A Perturbational Complexity Index (PCI) has been developed to classify the level of consciousness of patients or healthy subjects, by combining TMS and high-density EEG (Casali AG et al. Sci Transl Med 2013;5:198ra05, Gosseries O et al. Ann Rev Neurosci 2014; 37: 457-478). The PCI estimates brain complexity, including both the information content and the integration (long-range cortical effective connectivity) of brain activations, through algorithmic compressibility, with good spatio-temporal resolution. For example, the PCI is invariably above 0.31 in healthy awake subjects, in patients in MCS or patients in locked-in syndrome, as well as in healthy subjects in REM sleep. In contrast, the PCI is always below a 0.31 threshold during deep sleep, in both UWS patients and in those under general anesthesia using midazolam, propofol or xenon (Fig. 5). Unfortunately, TMS-compatible EEG sets are not commonly found and hundreds of TMS pulses needed to compute a single PCI value, which can be a problem where consciousness fluctuates.

Several caveats are in order, that question recent efforts to characterize "markers" of conscious awareness. In too many studies, comparison has been made with healthy subjects, whereas the appropriate control should have been brain damaged patients with intact consciousness. Also, the choice of the resting condition (eyes closed vs eyes open) must be considered carefully, e.g. when comparing PVS with control subjects, because it fundamentally differs in network recruitment (exteroceptive vs interoceptive) on fMRI (Xu P et al. Neuroimage 2014; 90C:246-255). The sense of self is not the same as self-awareness and a state of consciousness that has no content is conceivable (e.g. certain kinds of epileptic states or meditative states). Nonconscious stimuli can evoke emotional states. In a study (Yu T et al. Neurology 2013; 80: 1-8), 5 of 44 VS patients showed consistent fMR responses to cognitive imagery instructions and 24 showed pain matrix activation by pain cries (sensory in 34% and affective in 30%). Thus, affective consciousness can remain in VS cases, even in the absence of cognition. There is much recent discussion about the importance of the default mode network and of binding synchrony of frontoparietal connectivity as markers of conscious awareness. Actually, while this is rather fashionable, there is ample evidence that casts a pall on any overenthusiastic acceptance of these imaging-driven constructs. In human studies, neither gamma power per se, nor synchrony per se correlated with consciousness (Pockett S, Holmes MD. Consciousness and Cognition 2009;18:1049-55) and there are no compelling reasons to assign functional cognitive roles to oscillatory synchrony in the gamma range beyond its generic functions at the level of infrastructural (activation) neural control (Merker B. Neurosci Biobehav Rev 2013;37:401-17). Reemergence from anesthesia (propofol) is not accompanied by large changes in neocortical function (i.e. comes before full recovery of neocortical processing) and what seems to count most is the midline thalamus, the hypothalamus and the brainstem (locus coeruleus / parabrachial area) (Langsjo JW, et al. J Neurosci 2012; 34: 4935-4943; see also Castaigne P et al. Ann Neurol 1981; 10: 127-148). This is in line with cases of hydranencephalia -where the thalamus and brainstem are intact-who appear conscious, although with deficits in rich contents (Merker B. Behav Brain Sci 2007; 30: 63-81). It has been shown how the insular cortex, anterior cingulate and medial prefrontal cortex are not required for most aspects of self-awareness; the thalamus and brainstem are relevant (along with the post cingulate / precuneus / retrosplenial cortex: Philippi CL, et al. PloS One 2012; 7: e38413; see also Silva S et al. Neurology 2010; 74: 313-320 and Fernandez-Espejo D et al Ann Neurol 2012 ; 72 : 335-343). A patient submitted to direct intraoperative stimulation of the posterior parietal cortex showed behavioral unresponsiveness with loss of external connectedness; upon reawakening the patient described himself as in dream, outside the operating room (Herbet et al. Neuropsychologia 2014; 56: 239–244). It should also be borne in mind that -arousal-wise – extrathalamic input from the brainstem can compensate for damaged thalamocortical transmission.

Finally, to further compound the problem, many (including this author) believe that consciousness is not generated by the brain, but merely filtered through it, a position variously expressed by Penfield, Eccles and many others.

continued**Box 13.2:** Assessing Consciousness Pre- and Post-treatment

injury. R-TMS (1 session of 1000 stimuli in 10 trains of 20 Hz at motor threshold; F8 coil, PosteroAnterior orientation; earplugs on) of the MI (left or right depending on presence of MEPs; C3/4 and P3/4) achieved no clinical benefit, except in one MCS (post-hemorrhagic) patient (JFK CRS-R: auditory: from 2 to 4, visual from 2 to 4, motor from 3 to 6, arousal from 2 to 3, verbal axis and communication unchanged).

Giovannelli et al (2013) conducted a randomized, double-blind, sham-controlled, cross-over study on 11 patients classified as PVS (9 post-anoxic, 2 post-traumatic). RTMS (20 Hz, left MI, for 5 consecutive days, 10 min stimulation or 1000 pulses at 60% of maximum stimulator output). Slight changes in JFK CRS-R did not significantly differ between real and sham conditions. Also, there was disagreement on Clinical Global Impression changes between clinicians and patients'relatives.
Globally, the risk of seizure is very low. There was an atypical seizure that required lower intensity of stimulation in one patient of Pape et al (2014).

13.1.2 Transcranial Direct Current Stimulation (tDCS)

Two studies tested tDCS over the motor and the prefrontal areas of patients in PVS/UWS and MCS. Angelakis et al (2014) tested 5 days of anodal tDCS (25 cm2 rectangular sponge saturated with saline; cathode: rectangular sponge 35 cm2 over right orbit) at 1-2 mA for 20 minutes per day, 5 days per week, for 3 weeks in 10 patients (7 UWS and 3 MCS-). The authors stimulated the left primary sensorimotor cortex (C3 on the 10/20 EEG international system) (n= 5) or the left dorsolateral prefrontal cortex (F3) (n= 5). Follow-up was 1 year. Sham stimulation achieved no effects in all patients. Results were assessed with the JFK CRS-R scale. No patient in PVS improved, although one went from 8 to 9 points. Two patients in MCS- (posttraumatic and postoperative brain damage) went from 10 to 22 (conscious) and from 9 to 19 (conscious), respectively: the latter was submitted to two cycles of stimulation at a 3 month interval and effects were additive. Both these two patients were stimulated on C3. These authors concluded that more cycles may lead to additional benefit. Thibaut et al (2014) explored the effect of a single session of anodal tDCS during 20 minutes over the left prefrontal dorsolateral cortex (F3 on 10/20 EEG international system) on 55 patients with DOC (30 MCS, 25 UWS, 25 post-TBI, 35 chronic – more than 3months post insult). Two stimulations were performed, one anodal and one sham, in a randomized order, preceded and followed by a behavioral assessment with the Coma Recovery Scale-Revised. 13 (43%) patients in MCS and 2 (8%) patients in UWS further showed post-anodal tDCS related signs of consciousness, which were neither observed during the pre-tDCS evaluation nor during the pre- or post-sham evaluation (i.e., tDCS responder). Out of the 13 MCS responders, 5 were included more than 12 months after injury. One patient in UWS became MCS- and the other one became MCS+ and 4 patients in MCS- became MCS+. Clinical improvement of the tDCS responders are reported in Table 13.1.

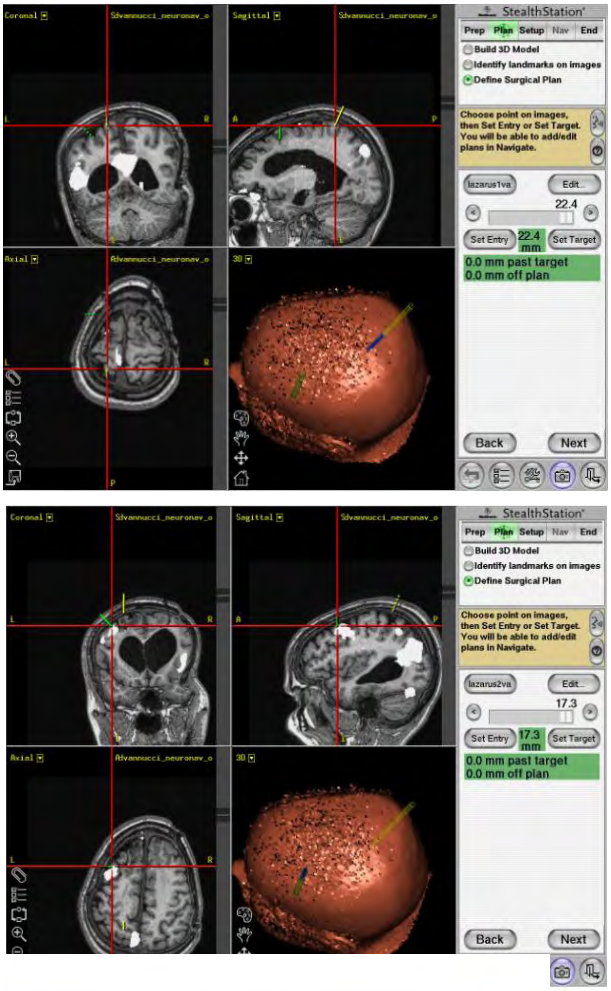
Table 13.1: Clinical improvement of tDCS responders (n=15)

CRS-R SUBSCALES	RECOVERY	NUMBER OF PATIENTS
Auditory	Systematic command following	1
	Reproducible command following	4
	Localization to sounds	1
	Auditory startle	0
Visual	Object recognition	2
	Object localization	1
	Visual pursuit	5
	Blinking to threat	0
Motor	Functional use of object	1
	Automatic motor reaction	2
	Object manipulation	3
	Localisation to noxious stimulation	0
	Flexion withdrawal	1
	Abnormal posturing	0
Oromotor/Verbal	Intelligible vocalisation	0
	Vocalisation	3
	Oral reflexive movement	0
Communication	Functional communication	2

13.2 Implantable Cortical Stimulation

Canavero et al (2009a, 2009b) performed extradural bifocal cortical stimulation in two VS patients 20 months following traumatic brain injury (for which decompressive hemicraniectomy was performed in the female case). The N20/P25 components of the SSEPs were absent bilaterally in both cases. The female (born 1988) was scored 25 on the Disability Rating Scale/DRS (Category 9) and the male (born 1985) 23 (category 8). The male patient had been on intrathecal baclofen for severe spasticity for several months. His defensive blink reflex was present and brisk, whereas it was completely absent in the female patient. While the male could be fed regularly, the female only with great difficulty. The parietal gyri P1 and P2 and the middle frontal sulcus (F2), including Brodmann's areas 8 and 46, were targeted for ICS in order to functionally reconnect a widespread network connected via the superior longitudinal fasciculus

and exploit remaining corticothalamocortical reentrant loops. Stimulation of DLPFC, via its connections with the supplementary motor area (SMA), was also expected to influence swallowing and axial tone. The female was stimulated on the left side and the male on the right to confirm the role of laterality in possible consciousness recovery. After induction of general anesthesia, a double sigmoid incision of the skin overlying the target areas was performed. Specifically, the left superior parietal lobule and dorsolateral prefrontal cortex were targeted (Fig.13.1-2). Four burr holes were fashioned and two stimulating paddles were inserted extradurally (Lamitrode 4, MOD. 3240, ANS, Plano, Texas). The paddles were linked via a dual extension to a subclavearly pocketed pulse generator (Genesis, MOD. 3608, ANS, Plano, Texas). Stimulation was started at a low power and then gradually increased (8-12 mA). It consisted of daily stimulation with switching off at night. Parameters were determined empirically, on the basis of our previous experience with MCS for other disorders (Canavero 2009). Low frequency stimulation was elected (6-16 Hz) with pulse widths trials ranging between 52 and 455 μs in the female patient. In the male patient, assessed parameters were 6-100 Hz, 65-455 μs, 8-13 mA, 0+1-2-3+ /0+1-2-3+. Clinical progression was evaluated over the following 10 months on 9 occasions by means of the Coma Recovery Scale-Revised and the Levels of Cognitive Functioning Scale. Within 48 hours of switching the stimulator on, a few days after surgery, both showed increased arousal during follow-up. On changing parameters during follow-up, it was observed that arousal, spasticity and other vegetative parameters could dramatically change (improve or worsen) within 12 hours. High frequency (100 Hz) stimulation was not tolerated (spasticity increased) in the male patient. Best parameters were 50-60 Hz, 65-208 μs, 8-10 mA. In the female, best parameters were 8-10 Hz, 65 μs, 11 mA, ++--/--++. Intensity was higher than reported in DBS studies (2-3 mA versus 8-13 mA). Effects emerged immediately, but strengthened in time. The female showed increased vigilance with clear improvements of swallowing and self-management of oral secretions. Oral feeding with both solids and liquids became possible and episodes of aspiration were not reported; weight increased by 4 Kg. Axial tone too increased dramatically. Most importantly, occasionally after the first month and on a more repeatable basis at study end, she could lift her left arm and hand on command, a clear sign of consciousness. On several occasions, the physiotherapists had the clear impression of the patient being “conscious and cooperative”. The male could respond to emotionally charged stimuli with appropriate facial expressions. Consistent interaction with family was the most important change cited by family members. Resting state fMR (Cauda et al 2009), explored as a potential “marker” of self-consciousness, showed a clear improvement, with a pattern towards normalization in both cases (Fig.13.3a,b,c,d). Diffusion tensor imaging (DTI) did not show signs of fiber regrowth (Table 13.2). In the male, Magnetic Resonance Spectroscopy (MRS) showed signs of altered neuronal metabolism (Table 13.3). Importantly, at the end of study, stimulators were deactivated: the benefits persisted, a sign of neuroplastic effects seen also in Parkinson Disease and Central Pain, so-called *after-effect* (Canavero 2009).



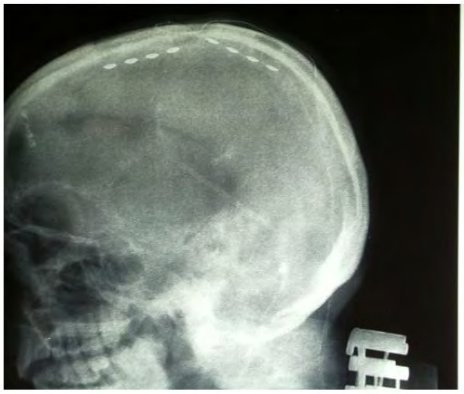


Fig. 13.1: case 1 (female). Neuronavigation images showing the parietal (a) and frontal (b) targets. Lateral skull x-rays showing the position of the two stimulating strips (c).

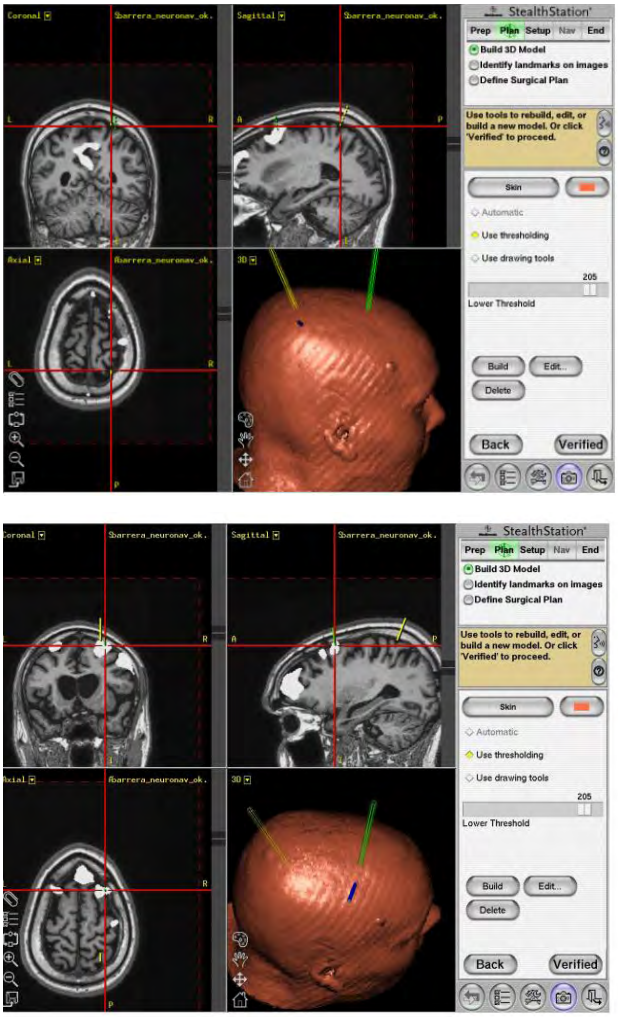
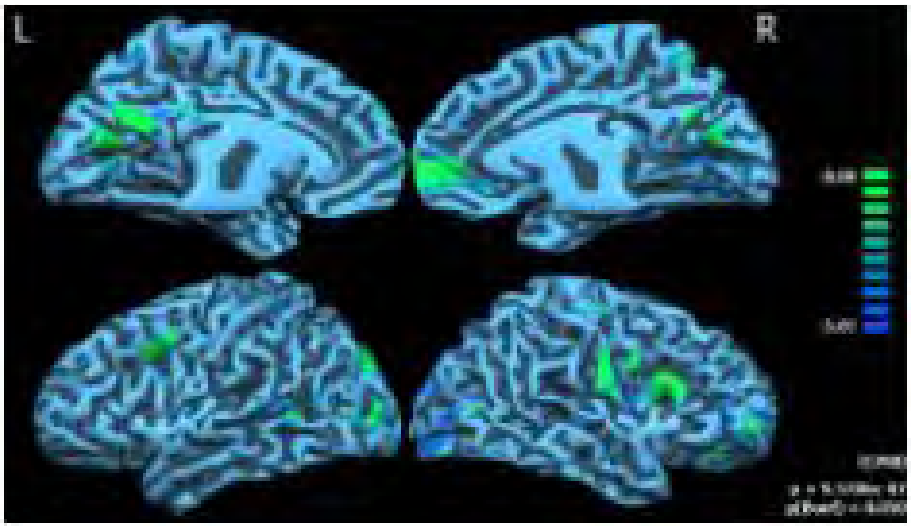


Fig. 13.2: case 2 (male). Neuronavigation images showing the parietal (a) and frontal (b) targets. Lateral skull x-rays showing the position of the two stimulating strips (c).

A



B

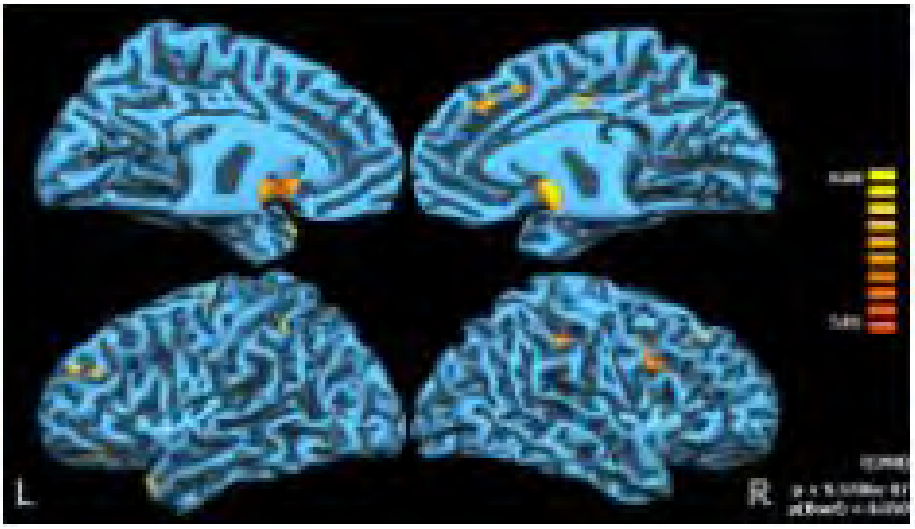
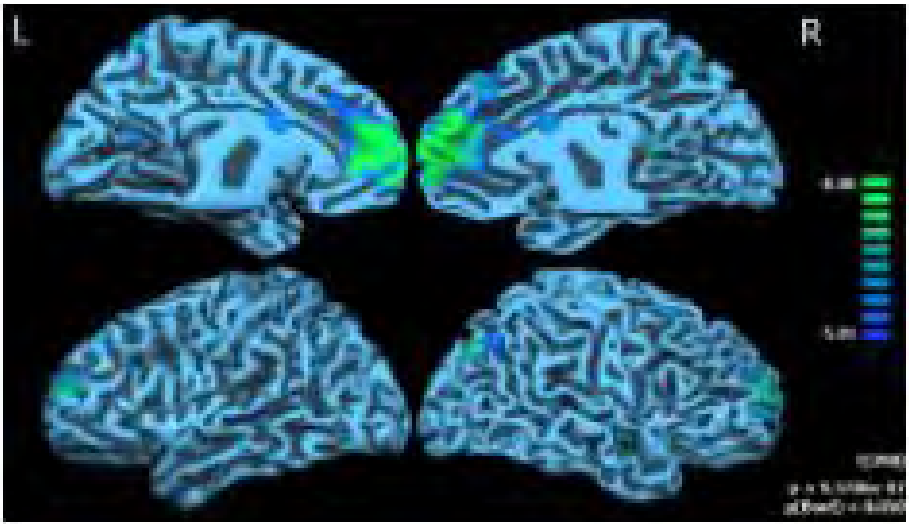


Fig. 13.3: Default Mode Network changes in the 2 patients. Female: increases (A) and decreases (B).

C



D

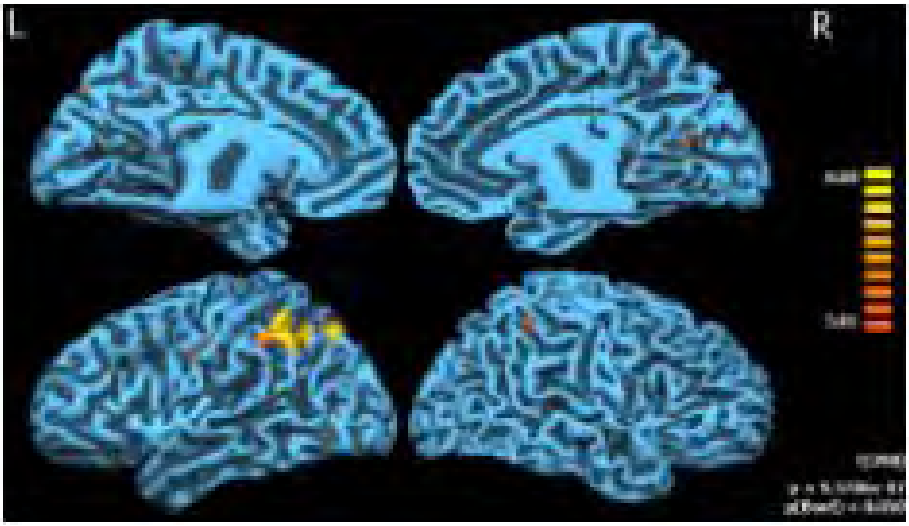


Fig. 13.3: Default Mode Network changes in the 2 patients. Male: increases (C) and decreases (D).

Chance recovery can be dismissed. Their level of functioning had been static for a significant amount of time before initiating therapy and there was a clear temporal relationship between the provision of stimulation and neurobehavioral gains. The girl died 4 years after implantation following antibiotic-resistant pneumonia.

Table 13.2A: Female patient. Bundle of interest statistics (mean and standard deviation): FA (Fractional Anisotropy), l (length), r (fibers density) for Cortico-Spinal Tract (CST), Corpus Callosum (CC) Superior Longitudinal Fasciculus (SLF) at pre and post treatment condition.

CST LEFT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.46	0.17	0.48	0.16
l [mm]	61	6	100	25
r [fibers/mm3]	0.010		0.008	
CST RIGHT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.44	0.17	0.44	0.18
l [mm]	63	17	60	14
r [fibers/mm3]	0.026		0.027	
CC	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.37	0.26	0.40	0.16
l [mm]	28	18	40	27
r [fibers/mm3]	0.044		0.037	
SLF LEFT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.43	0.16	0.42	0.15
l [mm]	29	15	35	18
r [fibers/mm3]	0.033		0.040	
SLF RIGHT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.38	0.14	0.38	0.14
l [mm]	25	9	29	16
r [fibers/mm3]	0.038		0.032	

Table 13.2B: Male patient. Bundle of interest statistics (mean and standard deviation): FA (Fractional Anisotropy), l (length), r (fibers density) for Cortico-Spinal Tract (CST), Corpus Callosum (CC) Superior Longitudinal Fasciculus (SLF) at pre and post treatment condition.

CST LEFT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.47	0.17	0.49	0.17
l [mm]	105	15	110	12
r [fibers/mm3]	0.005		0.019	
CST RIGHT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.45	0.15	0.47	0.15
l [mm]	97	10	83	12
r [fibers/mm3]	0.006		0.011	
CC	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.41	0.17	0.40	0.18
l [mm]	24	11	27	13
r [fibers/mm3]	0.044		0.053	
SLF LEFT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.39	0.15	0.40	0.15
l [mm]	28	13	28	17
r [fibers/mm3]	0.034		0.026	
SLF RIGHT	**Pre mean**	**Pre SD**	**Post mean**	**Post SD**
FA	0.44	0.15	0.43	0.15
l [mm]	40	21	49	23
r [fibers/mm3]	0.029		0.027	

Table 13.3: Magnetic Resonance Spectroscopy * data (male patient)

PREOPERATIVE MRS	**POSTOPERATIVE MRS (6 weeks after surgery)**
NAA/Cr 1.28	NAA/Cr 1.94
NAA/Cr(h) 1.32	NAA/Cr(h) 1.83
Cho/Cr 0.75	Cho/Cr 0.69
Cho/Cr(h) 0.69	Cho/Cr(h) 0.80
NAA/Cho 1.72	NAA/Cho 2.82
NAA/Cho(h) 1.92	NAA/Cho(h) 2.28
Cho/NAA 0.58	Cho/NAA 0.35
Cho/NAA(h) 0.52	Cho/NAA(h) 0.44

*posterior frontal white matter

13.3 Editor's Conclusion

The data reviewed in this chapter indicate that the severely injured brain has a capacity for recovery that exceeds current expectations and highlights the need for continuation of treatment efforts even years following injury.

CS might be combined with other stimulatory and pharmacologic therapies, and in the future, stem cells. CS can trigger neuroplastic changes (see Chapter 12). Despite a suggestion that fiber regrowth might be at work in the recovery of consciousness (Voss et al 2006), DTI data in two patients do not support this view. This is compatible with the "fast" improvement of level of consciousness in patients submitted to CS, both invasive and non. CS can force into resynchronization –"rebind"- (Slewa-Younan et al 2002) and rebalance activity across wide swaths of damaged hemispheres bilaterally (see Chapter 10), by altering thalamocortical transmission ipsilaterally and contralaterally via the corpus callosum and other deep structures. Cortico-cortical coherence between distant brain areas has been selectively enhanced by simultaneous bifocal 10Hz rTMS (Plewnia et al 2008). CS may also compensate for a loss of arousal regulation that is normally controlled by the frontal lobe in the intact brain.

The advantage of cortical stimulation over deep brain stimulation (DBS) is evident: DBS is more invasive and exposes the patient to more risks than CS (including death and further disability: Canavero 2010). CS can activate cortico-thalamo-cortical connectivity from the cortical side. Thalamic DBS is dependent on preserved metabolism in the thalamus, and thus is probably best reserved to MCS cases (Le Maire et al 2014).

As per the most appropriate targets of stimulation, three such targets have emerged: the prefrontal cortex (BA 9/46, possibly BA10), the posterior parietal cortex (BA 5/7) and M1, this latter being densely interconnected with both the prefrontal cortex and the thalamus, basal ganglia and brainstem. Areas BA 39/40 are another possible target, since they have been linked to the "will to move" (Desmurget and Sirigu 2012). Patients who survive a few months in PVS show gradual enlargement of the ventricular system: this may complicate targeting and affect electric conduction through the brain.

In sum, a VS patient may be submitted to tDCS/rTMS (also H-coil rTMS: Zangen et al 2005) of DLPFC, PPC and MI, on both sides, sequentially. If no benefit accrues or the benefit is limited, neurosurgical implantation of stimulating paddles centered on these same areas is possible (bifocal CS: M1 and PPC, MI and DLPFC, DLPFC and PPC), even on both sides (although this adds to overall cost). The search for effective parameters requires months and after-effects must be factored in. Finally, given recent speculation about the role of the claustrum in "binding" consciousness (Smythies et al 2014), this could become the focus of future neurostimulation studies.

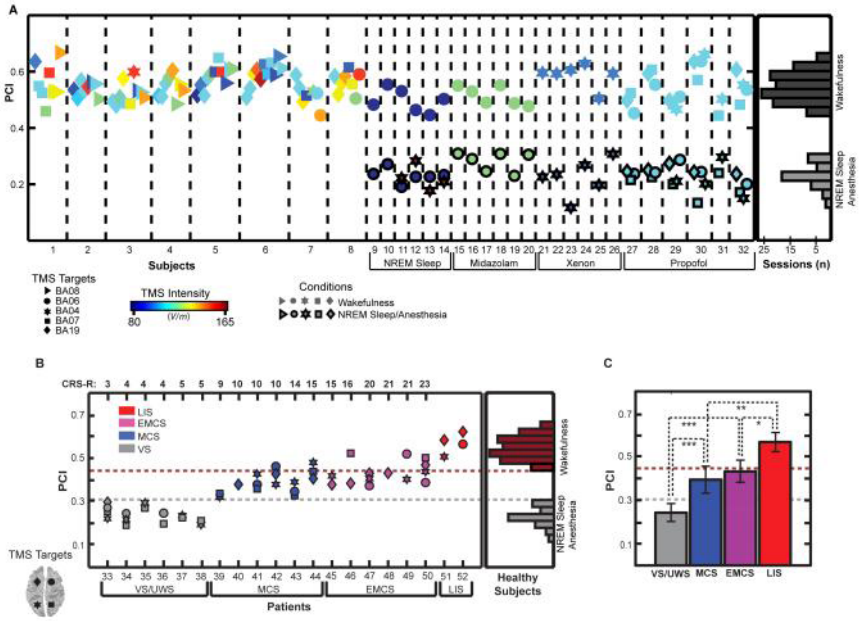


Fig. Box 13.1: PCI values in severely brain-injured patients. PCI progressively increases from VS/UWS to MCS and to recovery of functional communication (EMCS). PCI attains levels of healthy awake subjects in LIS patients (Coma Science Study Group, Liege, Belgium)

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