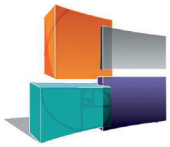
Annales Françaises d'Anesthésie et de Réanimation 33 (2014) 88–97



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Electrical modulation of neuronal networks in brain-injured patients with disorders of consciousness: A systematic review☆,☆☆

Modulation électrique de réseaux neuronaux de patients cérébro-lésés avec trouble de la conscience : revue de la littérature

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ARTICLE INFO

Keywords:
Deep brain stimulation
Consciousness
Thalamus
Neuromodulation
Brain injury

ABSTRACT

Six clinical studies of chronic electrical modulation of deep brain circuits published between 1968 and 2010 have reported effects in 55 vegetative or minimally conscious patients. The rationale stimulation was to activate the cortex through the reticular-thalamic complex, comprising the tegmental ascending reticular activating system and its thalamic targets. The most frequent intended target was the central intralaminar zone and adjacent nuclei. Hassler et al. also proposed to modulate the pallidum as part of the arousal and wakefulness system. Stimulation frequency varied from 8 Hz to 250 Hz. Most patients improved, although in a limited way. Schiff et al. found correlations between central thalamus stimulation and arousal and conscious behaviours. Other treatments that have offered some clinical benefit include drugs, repetitive magnetic transcranial stimulation, median nerve stimulation, stimulation of dorsal column of the upper cervical spinal cord, and stimulation of the fronto-parietal cortex. No one treatment has emerged as a gold standard for practice, which is why clinical trials are still on-going. Further clinical studies are needed to decipher the altered dynamics of neuronal network circuits in patients suffering from severe disorders of consciousness as a step towards novel therapeutic strategies.

Mots clés :
Stimulation cérébrale
Conscience
Thalamus
Neuromodulation
Dommage cérébral

RÉSUMÉ

Six études cliniques de modulation électrique chronique de circuits cérébraux profonds, publiées entre 1968 et 2010, ont rapporté des effets chez 55 patients, végétatifs ou en état de conscience minimale. Le rationnel de stimulation était d'activer le cortex par le complexe réticulo-thalamique comprenant le système réticulaire activateur ascendant tegmental et ses cibles thalamiques. La cible la plus fréquemment visée était la zone centrale intra laminaire du thalamus et les noyaux adjacents. Hassler et al. ont aussi proposé de moduler le pallidum, partie du système d'éveil et de vigilance. La fréquence de

☆ French NeuroAnesthesia and Intensive Care society Meeting, Paris, November 2013, 21st and 22nd: "The acutely brain-injured patient: consciousness and neuroethic".
☆☆ This article is published under the responsibility of the Scientific Committee of the "35e Journée de l'Association des neuro-anesthésistes réanimateurs de langue françaises" de la SFAR. The editorial board of the *Annales françaises d'anesthésie et de réanimation* was not involved in the conception and validation of its content.

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0750-7658/$ – see front matter
http://dx.doi.org/10.1016/j.annfar.2013.11.007

stimulation variait de 8 Hz à 250 Hz. La plupart des patients se sont améliorés, bien que de manière limitée. Schiff et al. ont démontré un lien entre l'apparition de comportements d'éveil et conscients et stimulation du thalamus central. D'autres traitements ont pu améliorer cliniquement le patient : médicaments, stimulation magnétique transcrânienne répétée, stimulation du nerf médian, stimulation des cordons postérieurs de la moelle cervicale et stimulation du cortex frontopariétal. Aucun traitement n'a été validé pour la clinique courante, d'où la réalisation d'études cliniques, enregistrées, en cours. De nouvelles études sont nécessaires pour décrypter les altérations de la dynamique des circuits neuronaux chez des patients souffrant de troubles de la conscience sévères, permettant ainsi de proposer de nouvelles stratégies thérapeutiques.

Deep brain stimulation (DBS) is a validated treatment for severe symptoms refractory to optimal drug trials. It involves modulating altered neuronal brain circuits by chronic electric stimulation, placing electrodes in the brain, in thalamic nuclei or basal ganglia. The DBS story highlights the tortuous route taken by the medical community to assimilate the technique [1]. Be that as it may, DBS is now proposed as a way to alleviate extrapyramidal motor disorders such as tremor, dyskinesia, rigidity and dystonia [2–4], and research is on-going to explore or validate further indications such as depression, obsessive compulsive disorder, pain, obesity, anorexia and epilepsy [5–7].

The aim of DBS in patients with severe post-brain injury disorders of consciousness is to restore communication and goal-directed behaviour. However, DBS brings a number of challenges: we do not yet master all the aspects of the brain networks engaged in consciousness processing, and there is the hypothesis that DBS could overdrive neuron activity promoting plasticity within residual, partially damaged, and also undamaged but dysfunctional, circuits. Injury involves multiple mechanisms that are often combined, such as trauma, haemorrhage, ischemia, epilepsy, hydrocephalus and anoxia, and so prospective patients liable to benefit from DBS for severe, chronic or sometimes long-term disorders of consciousness fall into a wide range of individual phenotypes. Consciousness disorders follow a clinical progression of recovery: coma, where the eyes remain closed; vegetative state, where the eyes open but there is no observable conscious goal-directed behaviour; and minimally conscious state (MCS), where the patient shows inconsistent but discernible evidence of consciousness [8]. Emergence from MCS is achieved when the patient fully communicates, whatever the severity of the remaining disability [9]. The European Task Force on Disorders of Consciousness recently passed a proposal rename persistent vegetative state as *unresponsive wakefulness syndrome* [10]. The Liège group, which participates actively in defining these clinical states, has proposed two MCS subcategories [11]: MCS+, patients following commands, intelligible verbalization and gestural or verbal yes/no responses, and MCS−, patients demonstrating pursuit eye movement, ability to localize (and orient) noxious stimuli, and appropriate movements or affective behaviours. There is also a growing body of evidence that we can learn more about consciousness-related brain function from functional magnetic resonance imaging (fMRI) than from clinical observation (see [12] for a review). This new ability to explore covert behaviours combined with recent advances in neural correlates is expected to yield further insight into the phenomenology of consciousness applied to clinical phenotypes [13]. On-going research hopes to decipher the intimate mechanisms and circuits supporting the emergence of consciousness.

The goal of this systematic review is to summarize key data from all the clinical DBS trials that aimed to alleviate post-brain injury disorders of consciousness – three case reports [14–16], two observational series [17–21] and one crossover study [22] published between 1968 and 2010. The thalamus, tegmentum and pallidum were targeted for electrode implantation (Table 1) as the thalamus and tegmentum belong to the reticular-thalamic activating complex involved in arousal and consciousness [23–25] and as pallidum stimulation provokes arousal in cats and human [15,26]. Methodology and results are given for each series, and discussion is consolidated in an attempt to propose realistic medical perspectives.

1. The literature from 1968 to 2010

McLardy et al. [14] reported the very first case of DBS in 1968, in a vegetative 19-year-old male, implanted about 8 months after head injury. They intended to place one electrode in the intralaminar thalamic nuclei and the reticular formation of the midbrain, in the left hemisphere. Stimulation frequency was 250 Hz. Only the effects of the midbrain contacts were reported: left orientation of the head, movements of the left hand, and slight modifications of the electroencephalogram (EEG). The electrode was removed one month later. The patient died of infectious disease two years later, and the autopsy showed that the electrode went through the thalamus, crossing the rostral nucleus *reticularis*, ventral anterior nucleus, paracentral nucleus and centromedian parafascicular nucleus complex (CMPf), then through the red nucleus to reach the reticular formation of the lower midbrain and terminating in the raphe tegmental area (Table 1). The lesions predominated within the right-hemisphere cortex and the left and right thalamus.

Hasler et al. [15] then published a DBS case in 1969 of a 26-year-old male implanted about 5 months after head injury. The patient was in vegetative state, and sleep-waking cycles were clinically observed. The terms apallic patient, coma vigil and akinetic mutism were used due to the apparent loss of neocortical function, no reproducible evidence of intentional behaviour, and the fact the patient did not speak [27]. He was stimulated bilaterally – the intention was to place the left electrode in the anterior thalamus and the right electrode in the pallidum. Unilateral-acute, low-frequency (left electrode, 50 Hz; right electrode, 8 Hz), 15-minute stimulations 3 to 4 times per day provoked eyelid and eye movements with a post effect up to 20 sec. Stimulation of the right pallidum was associated with sporadic contralateral arm movements, and bilateral acute stimulations provoked stronger effects plus head movements following the eyes. Convulsive seizures sometimes occurred during thalamic stimulations up to 100 Hz. The patient improved during the 19-day follow-up, showing apparently purposeful gaze and mimics, left arm and leg movements, head movements sometimes oriented toward relatives and unintelligible vocalization after tracheotomy removal. EEG frequencies increased during acute thalamic stimulation, especially under thalamic and pallidal bilateral acute stimulation. The electrodes were removed when broken. At the end of the 19-day follow-up, EEGs showed a reduction of right-left asymmetry and an abolished left delta focus.