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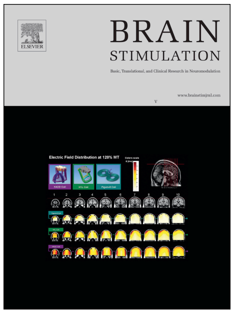

Deep brain stimulation for disorders of consciousness: Systematic review of cases and ethics

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Deep Brain Stimulation for Disorders of Consciousness: systematic review of cases and ethics

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Abstract

Background: A treatment for patients suffering from prolonged severely altered consciousness is not available. The success of Deep Brain Stimulation (DBS) in diseases such as Parkinson's, dystonia and essential tremor provided a renewed impetus for its application in Disorders of Consciousness (DoC).

Objective: To evaluate the rationale for DBS in patients with DoC, through systematic review of literature containing clinical data and ethical considerations.

Methods: Articles from PubMed, Embase, Medline and Web of Science were systematically reviewed.

Results: The outcomes of 78 individual patients reported in 19 articles from 1968 onwards were pooled and elements of ethical discussions were compared. There is no clear clinical evidence that DBS is a treatment for DoC that can restore both consciousness and the ability to communicate. In patients who benefitted, the outcome of DBS is often confounded by the time frame of spontaneous recovery from DoC. Difficult ethical considerations remain, such as the risk of increasing self-awareness of own limitations, without improving overall wellbeing, and the issues of proxy consent.

Conclusion: DBS is far from being evident as a possible future therapeutic avenue for patients with DoC. Double-blind studies are lacking, and many clinical and ethical issues have to be addressed. In the rare cases when DBS for patients with DoC is considered, this needs to be evaluated meticulously on a case by case basis, with comprehensive overall outcome measures including psychological and quality-of-life assessments, and with the guidance of an ethical and interdisciplinary panel, especially in relation to proxy consent.

Keywords

Deep Brain Stimulation; Disorders of Consciousness; Minimally Conscious State; Vegetative State; Coma; Neuroethics; Neuromodulation.

CRS-R: JFK Coma Recovery Scale-Revised, CT-DBS: "Central Thalamic" Deep Brain Stimulation, DBS: Deep Brain Stimulation, DoC: Disorders of Consciousness, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, MCS: Minimally Conscious State, PCS: Prolonged Coma Scale, PVS: Persistent Vegetative State, TBI: Traumatic Brain Injury, UWS: Unresponsive Wakefulness Syndrome, VS: Vegetative State.

Introduction

What would one do in case a patient survives a severe brain injury, but remains in a chronic altered state of consciousness? Some patients seem to be awake, without apparent awareness. Other patients seem to be awake as well as slightly aware, but still lack a normal consciousness.

In the concept of consciousness a difference is made between wakefulness and awareness. To be awake means to be receptive for stimuli (for instance the eyes are open), while being aware means that one is somehow responsive to stimuli (for instance one reacts to a visual cue). The state that defines how responsive one is to a stimulus is called arousal. Both wakefulness and awareness are needed in order to be conscious. Disorders of Consciousness (DoC) translate into different conditions [1] of which some chronic conditions are explained below.

A clarification of definitions of DoC applied in this review is necessary because various distinctions of DoC have been made throughout the literature and over time.

In the definition of coma, both awareness and wakefulness are absent, though basic physiological functions, such as heart rhythm and respiratory function, are maintained. Eyes are normally closed and only specific reflexive behavior to stimuli can be observed [1,2].

In Vegetative State (VS) awareness of the self and environment is absent, but the eyes are open and closed in alternating periods [2]. This intermittent wakefulness was thought to be a manifestation of a sleep-wake cycle and a relevant diagnostic criterion [3,4], but actigraphy and electrophysiological assessments have demonstrated that the nature of circadian sleep-wake cycle in VS patients is absent [5,6], while sleep wake patterns are preserved [5]. The reduced ability of being awake is a key difference to coma. Responses to stimuli are only reflexive and not driven by a conscious behavior. As “Vegetative State” tends to have a bad connotation, the label “Unresponsive Wakefulness Syndrome” (UWS) has been suggested instead [7].

A Persistent Vegetative State (PVS) denotes a prolonged VS for over 3 months in case of an anoxic injury or for ≥1 year after trauma [8,9]. PVS and VS/UWS have the same clinical presentation, but differ in duration. Throughout the literature, this difference is not always consistently made, partly because the original definition of PVS [2] was not different from VS.

In Minimally Conscious State (MCS), both wakefulness and awareness are to some degree present. The key difference compared to VS is the ability of a patient in MCS to respond meaningfully, though inconsistently, to a stimulus. There may be some communication (verbal or gestural), or simple commands may be performed [1]. For example, a patient in MCS without any motor dysfunction would be able to squeeze the hand when prompted.

The terms “Coma vigil” (= awake coma), “prolonged coma” and “apallic syndrome” (= lack of cortical function) are outdated terms that referred to a condition other than coma, as wakefulness is maintained, but these terms lacked specificity [2,10]. They could be equivalent to (P)VS or MCS.

In the literature, various scales have been used for scoring the level of DoC. The JFK Coma Recovery Scale-Revised (CRS-R) has been developed to help in the diagnosis of VS and MCS. It measures repeatedly behavioral responses to standardized stimuli, in six categories: auditory, visual, motor, verbal, communication and arousal [11]. The CRS-R was developed to address shortcomings of the Glasgow Coma Scale (GCS) [11]. Analogous to CRS-R, the GCS classifies responses to stimuli [12], but it consists of only 3 subscales, and is not reliable to discriminate between VS and MCS. The Prolonged Coma Scale (PCS) does not use subscales, but is an attempt to represent 10 subsequent behavioral changes when a person gradually emerges from coma [13]. The Glasgow Outcome Scale (GOS) has a different approach, because it describes the grade of disability of the patient. GOS is based on 4 categories, from “vegetative state” to “good recovery” [14,15].

Since the 1960s researchers have investigated whether DBS could improve DoC. However, attempts to obtain a consensus about the use of DBS for chronic DoC have remained in vain. Issues concerning safety and effectiveness of the technique, as well as ethical considerations have been debated. To the best of our knowledge, there is no systematic review of both patient cases and ethical considerations of DBS for DoC. As these aspects are highly intertwined, we conducted a systematic review of the literature to clarify whether DBS contributes to improvement of patients with DoC, and to examine the ethical issues surrounding DBS in these conditions.

Methods

A search was performed in 4 databases (PubMed, Embase, Medline and Web of Science), using two key concepts: coma in broad sense and DBS. Search words included: ("DBS" OR "Deep Brain Stimulation") AND ("disorder of consciousness" OR "consciousness disorder" OR "Minimally Conscious State" OR "coma" OR "Vegetative State" OR "Persistent Vegetative State" OR "apallic syndrome" OR "Unresponsive Wakefulness Syndrome" OR "coma vigil"), see Fig. 1. Inclusion criteria were articles in English or French that reported treatment with DBS of human patients in a state of MCS, PVS, VS, DoC, coma or related prolonged condition affecting consciousness. Additionally, publications concerning ethical discussions of DBS for DoC were included. Review articles are screened for any additional reference to patient reports of DBS in DoC.

Excluding criteria were articles published in languages other than English or French and articles that did not report nor discuss DBS as treatment for humans with DoC. A first selection is made based on titles and abstracts, and a second selection by reading full articles. The included papers were classified in two groups: Papers reporting patient data and papers dealing with ethical issues.

Results

Articles published between 1968 and March 2017 were pooled and duplications were removed. Of the 120 unique articles meeting the search criteria, 89 were excluded because although they met the search criteria, they did not meet the inclusion criteria (Fig. 1). Four additional references concerning patient reports of DBS in DoC were retrieved from screening review articles that met search criteria (McLardy *et al.* [16], Hassler *et al.* [17], Sturm *et al.* [18], Hosobuchi *et al.* [19]). The included articles for the present systematic review were then classified in two groups: articles reporting patient data (n=19, see Table 1) and articles dealing with ethical issues (n=16, see Table 2).

Clinical characteristics

Table 1 shows details of the clinical features of patients with DoC who had received DBS. There are 19 articles, published from 1968 onwards, and reporting on 78 unique patients. These articles are summarized below.

Etiology of Disorders of Consciousness and Diagnosis

The etiology is very different across the 78 patients: traumatic brain injury (TBI) is mentioned most (26 cases), followed by anoxic causes (15 cases), vascular causes (11 cases) and other (1 case). The study of Cohadon & Richer with 25 cases did not provide details on the etiology [20]. Throughout the literature, it is not clear whether etiology may predict outcome.

Time frame

The represented time frame consists of two components: the interval (between the injury and the DBS implant), and the length of follow-up after surgery. The reported intervals in the literature varied from 17 days [18] up to 21 years [21]. The follow-up in the majority of the cases was reported to be one year or longer, as long as 10 years in a cohort reported by Yamamoto *et al.* [22] and 12 years in some of the 25 patients reported by Cohadon & Richer [20]. One exception is the patient reported by Wojtecki *et al.* [23] for whom no follow-up is available. In most reports it is not mentioned whether DBS was applied during the entire follow-up. The exception is the patient reported by Schiff *et al.* [24] where DBS was alternated during follow-up using a crossover paradigm.

Brain targets

The various brain targets for DBS were: the mesencephalic reticular formation (cuneiform nucleus) [13,25], the pallidum [17] and in many cases various areas of the thalamus, including the centromedian parafascicular nucleus, the thalamic reticular nucleus, the intralaminar nuclei, the central lateral nucleus and paralaminar region.

Outcome and outcome measures

Throughout the literature, the evaluation of the outcome of DBS for DoC has been variable. McLardy in 1968 gave a descriptive view of the patient's level of consciousness and EEG was recorded before and after DBS, indicating small changes in activity compared to baseline [16].

In 1969, Hassler *et al.* stated that they had improved consciousness in one male [17]. They started DBS treatment 17 days after injury and the outcome was "unintelligible vocalization" and "spontaneous movements of left limbs". In 1993, Hosobuchi & Yingling [19] mentioned improvements in one male, but without restoring consistent communication.

In the same year, Cohadon & Richer [20] reported "improvements" of 11 patients: one patient improved to a condition with moderate disability (GOS) and 10 patients to a severe disability (GOS). An outcome of severe disability based on evaluation with the GOS was also mentioned by Yamamoto *et al.* [13].

In 2007, Schiff *et al.* reported improvements after DBS in one patient who had been in MCS for 6 years [24]. The patient´s communication was restored and various behavioral improvements using CRS-R subscales were obtained. However, whether the patient remained disabled or not, is not specified. A second patient in MCS from this series of 3 single-subject studies did not show improvement, scored using CRS-R, while changes in sleep-like patterns assessed via EEG were reported after DBS [21]. Two patients in PVS and one in MCS were treated with DBS by Magrassi *et al.* and each improved according to the CRS-R score, but consciousness or consistent communication were not restored [26]. In 2017, Chudy *et al.* reported that 3 out of 14 patients regained consciousness after DBS [27]. These three patients were diagnosed with MCS and were treated within 1 year of injury. One patient in VS improved to MCS, and the remaining 10 other patients did not recover.

Ethical considerations

Table 2 shows details from reviewed papers discussing ethical considerations of DBS for DoC. The different perspectives and main ethical issues presented in the 16 articles are summarized further below.

Standardized health care and "therapeutic nihilism"

The papers state that one key driver to explore the therapeutic potential of DBS in patients with DoC stems from the fact that the care of these patients is often reported to be severely neglected [28]. The neglect of patients in DoC is partly translated into a lack of standardized healthcare that is specific for them [29–31], such as in-patient rehabilitation [31]. As these patients cannot communicate whether they are "in pain or emotional distress" [30], they are considered to be vulnerable [29,32], and a denial of their needs has been called "therapeutic nihilism" [28,30] or "societal neglect syndrome" [33].

Proxy consent

Patuzzo and Manganotti stated that "DBS for PVS does not require informed consent", but rather a type of start consent, because DBS could be seen as a "necessary" treatment [34]. Bouncing to ethical limits, they seem to be alone in their view, compared with the broad consensus in the literature that there is a need for an informed consent by means of surrogate [29,35–38]. In order to deal with the vulnerability of the patients, the literature agrees that there is a need for an interdisciplinary panel consisting of researchers, specialized physicians, as well as family members, to guide in the ethical decisions [28,39,40]. However, it is commonly stated that, assuming DBS could restore consciousness, it is still not a treatment for disabilities [32].

To convey the risks and benefits of an intervention in the consciousness of a person could be "ineffable" [41], i.e., something inexplicable "in any ordinary meaning of the term". This does not mean that there is no possibility to consent, but it emphasizes the highly personal approach to assess whether the given consent is thoroughly to protect the patient's best interest [41], especially given the medical nature of DoC [36].

Self-awareness of disability and overall outcome

Emerging from VS and MCS gradually to normal conscious state, could be accompanied by restoring self-awareness of own disabilities [42], whereby psychological harm cannot be excluded [35]. This could be called the paradox of recovery [33] or the self-awareness paradox. However, it has been claimed that the reversibility of DBS [40] could be seen as a "mitigating factor" [42] for the self-awareness paradox, because the stimulation can be deactivated at any time. Moreover, some authors has been called into question whether patients in MCS are always unaware of their situation [33]. Conversely, the true reversibility of long term DBS is not yet known [43]. The fact that patients in MCS could be aware of their predicament is not further discussed in the literature.

Discussion

In this review of DBS for DoC, the authors attempted to provide a comprehensive summary of published patient reports and of related ethical considerations. Several issues were highlighted by this review: there is a disparity among authors in the terminology and definitions of states of DoC that hampers interpretation of the role of DBS in these conditions; the outcome measures used have been variable and difficult to interpret, and none of them did capture aspects of quality-of-life and psychological well-being of the patients; several of the patients reported to have improved by DBS did so within a time frame of likely spontaneous recovery; DBS in DoC raises many difficult ethical questions, probably more than in any other condition in which DBS has been trialed.

Etiology of Disorders of Consciousness and Diagnosis

Despite the fact that various authors had hoped to predict the outcome of DBS based on the etiology, no correlation was found. Nevertheless, from a theoretical perspective, the suggestion has been made to focus on patients with TBI, because the glucose consumption in the brain would be better and because patients in MCS with TBI are more likely to recover compared to patients with other etiologies of DoC [28,37].

Historically, the terminology used in diagnosis of DoC often lacked specificity. In the oldest publications, such as those of Hassler *et al.* in 1968 and McLardy *et al.* in 1969, the terms "apallic syndrome" or "coma vigil" are used [16,17]. After the introduction of the term PVS in 1972 and the call to carefully distinguish between different prolonged conditions affecting consciousness [2], some diagnoses were still labeled as "subcoma with unconsciousness" by Sturm *et al.* in 1979 [18], or "apallic state" by Hosobuchi & Yingling as late as 1993 [19]. While the terminology used for various DoC is currently more specific, the diagnosis of MCS, VS and similar states (such as Locked In-Syndrome, which is not a DoC) is still an issue. Because the diagnosis relies on subtleties, it is often inaccurate [32]: according to some authors, diagnostic errors amount to up to 40% of cases [8,31]. Some of the patients that were diagnosed with PVS by Yamamoto *et al.* were later reclassified by other authors as MCS [44,45]. It has also been suggested that diagnosis was sometimes altered on purpose, because the patient would have better access to healthcare facilities [30]. Alternatively, the CRS-R could be seen as a good standard tool for the diagnosis of (P)VS and MCS [11,31]. To distinguish between (P)VS and MCS is important when assessing the potential effect of DBS treatment, because in these two conditions the likelihood on a spontaneous recovery differs, as discussed below.

Time frame

The interval (between the injury and the DBS implant) is important to take into consideration in order to avoid ambiguity between a spontaneous recovery and the effect of DBS. The Multi-Society Task Force on PVS reported that (spontaneous) recovery from VS lasting longer than one month occurs in 30% of patients at 6 months and in 43% at 12 months [3,4,46]. Giacino & Kalmar reported a spontaneous recovery rate in 51% of patients by 6 months for VS, and this percentage increased marginally only at 12 months [47]. If the etiology is TBI, the chance of recovery is approximately twice as high compared to non-TBI

[3,4,31,47]. The prognosis for MCS is much better compared to that of VS [47]. For example, according to Lammi *et al.*, 83% of the patients (15/18) emerged from MCS by 6 months [48]. Giacino *et al.* [31] stated that recovery from MCS was significantly more favorable than assumed, with considerable recovery even at long-term (5 years).

Schiff *et al.* state that DBS should not be offered within the interval of spontaneous recovery from DoC, i.e., certainly not before six months for VS, and not before one year in case of MCS [33,36,37]. The reports by Yamamoto *et al.* [49–51] have been heavily criticized because the DBS was performed between 3-6 months after injury [36,44], which is a confounding factor for the outcome [8]. Equally, improvements following DBS, that were reported in other historical reports, by Cohadon & Richer [20], Hassler *et al.* [17], and Sturm *et al.* [18], may not be specifically attributed to the DBS. Nonetheless, Chudy *et al.* [27] reported recently on three patients in MCS who had regained consciousness following DBS: two of them had received DBS 2 months after cardiac arrest and the third patient 11 months after TBI. In these patients, spontaneous recovery cannot be excluded, even if the different prognosis for TBI and non-TBI etiology is taken into account [31,36,44,47,48].

Brain targets

According to Schiff, the so-called "Central Thalamus" (CT) is of interest as a target for DBS (CT-DBS). The rationale to target the central thalamus is that it is connected to the brainstem and frontal cortex, and it is a hub for "arousal systems" and "executive functions" [1,52]. Some of these connections are selectively vulnerable to cell death in VS patients [53] and although some researchers believe that DBS could reverse this massive thalamic cell death, but this has been questioned by others [53,54]. The target "Central Thalamus" is said to be different from historical thalamic targets such as CMPf because researchers think it is better placed to support an integrated "long range network interactions" instead of the arousal system itself [28]. However, even within targeted thalamic parts, the nuclei have different properties and connections, and are therefore distinct [37]. Thus, it is challenging to provide a rationale for the choice of a brain target, as long as a precise verification of which subnucleus of the thalamus is being stimulated is not available.

Outcome and outcome measures

The first outcome that was convincingly shown to be due to DBS, was reported in the patient of Schiff *et al.* [24], thanks to the study design itself: the alternating crossover experiment using CRS-R subscales, discriminated between effects of the DBS when it was switched on compared to carryover effects and to DBS switched off. However, in the same series of case studies [37], Adams *et al.* [21] failed to obtain a good outcome, although the experimental design was adapted from the study of Schiff *et al.* [24]. A possible reason could be that in Schiff´s study, an "intact language networks" had been shown with fMRI before DBS application [24], which is important to consider in interpreting the outcome. Indeed, after applying well-described patient selection criteria, Magrassi *et al.* 2016, suggested that the majority of patients with DoC would not meet "minimal criteria of brain connectivity" before trailing with DBS [26]. Yet, they reported 3 patients who had improved with several points on the CRS-R scale, but the patients were not able to communicate consistently. The authors stated that, rather than improvements on the CRS-R, it is "restoration of consistent communication" that is the aim of DBS for DoC [24], and therefore one could reflect on how exceptional the single case study of Schiff *et al.* was.

Standardized health care and "therapeutic nihilism"

It has been stated that because clinicians assume that patients with DoC have a poor prognosis, the care of these patients is sometimes withdrawn too quickly [9]: the dilemma of whether to continue care or to let the hope for recovery go has been described as ethically very difficult. However, it has been shown that the prognosis of DoC seems to be better than generally assumed [31]. In any case, some ethicists do point out that while research for new treatments is needed, the patient must be protected from futile research [29].

Proxy consent

Although there is a consensus for proxy consent in the literature, it is also recognized as problematic since the surrogate is prone to advocacy [29]. A frequent problem underlying this issue is that there is a lack of accurate information to the surrogate on the prospect of what DBS would entail for the patient [8,28,29,35], especially since the prognosis is often not clear and may be incorrectly labelled as poor [31]. There is also a risk that the intervention generates “unreasonable expectations” [43]. Furthermore, the family is often under pressure to decide whether to withhold life-sustaining therapy or not, before a clinical observation spanning several months is performed [8]. For instance, family members may consent to an investigational trial of DBS, in order to ensure more rehabilitation services to the patient [29]. On the other hand, a trial of DBS research might limit other treatment alternatives, and consequently, families are rather unwilling to consent [31]. It is evident that proxy consent is needed, but the circumstances of how it is obtained may raise still ethical questions.

Self-awareness of disability and overall outcome

The clinical condition of the patient depends on the specific etiology of a severe brain injury [38], and whether it is combined with injury to the spinal cord or other organs (such as in multi-trauma patients). The patient may have significant brain damage resulting in cognitive impairment, paralysis or a range of disabilities in addition to altered consciousness. Therefore, it has been stated that an outcome in terms of physical and cognitive functions is of no value without a careful psychological assessment [35,54], which was not performed in any of the patient reports reviewed here. While Magrassi *et al.* [26] suggested that restoring consistent communication is the most important clinical target of DBS, it seems at the same time that this is the only possibility to enable a psychological assessment in order to address the “self-awareness paradox”. By the specific nature of treatment of DoC, there is the potential of increasing patients’ self-awareness of their own limitations and handicap, and thus the risk of affecting negatively the patient’s psychological well-being.

Improvements of risk-benefit ratio

Another clinical and ethical issue concerns the study design. Poor study design in many previous studies has led to very confusing clinical conclusions. It has been claimed that in many DBS experiments, the risks involved were unnecessary due to lack of a scientific rationale [36]. To expose patients to the risks of an unproven technique is only ethical if a fair attempt is made to provide more scientific rationale for the potential of the technique.

One way to improve the risk-benefit ratio is to clarify the study design. In contrast to research done before, the study case of Schiff *et al.* in 2007 [24] was more stringent, and the clinical conclusion was less biased, thanks to the double-blind design, the extensive baseline assessments, the tests for carryover effects, and the exclusion of spontaneous recovery. However, in addition to performing behavioral assessments, a psychological evaluation of the patient would have been desirable. In an attempt to address the self-awareness paradox, an overall outcome should be carefully assessed to reflect the quality-of-life and psychological well-being [35,54], in addition to mere physical or behavioral outcome. Selection criteria need to reflect on how likely a patient is to benefit from the DBS treatment, but should also consider if the patient has had reasonable access to other (experimental) less invasive treatments [55]. Last but not least, an interdisciplinary approach to guide informed consent is mandatory [28,39,40]. On one hand this would prevent that the surrogate is seen as a "passive spokesperson" [29]. On the other hand the interdisciplinary panel can contribute to avoid misconception [29]. There is no clarification in the literature so far how this should be done.

Limits to the risk-benefit ratio

If more research in DBS for DoC would be reasonable to conduct, there is as yet no experimental set-up thinkable that could identify the optimal brain target for DBS, or the optimal stimulation parameters. Also, it has been said that understanding the molecular basis of consciousness or DoC could be very important for further investigation of DBS [52]. Moreover, the mode of action of DBS itself is not well understood. Currently, assumptions are made that there must be integrity of neuronal tissue that enables connectivity between cortex, thalamus and brainstem. On this issue, the findings of Magrassi *et al.* 2016 were rather pessimistic: even if the assumptions are true, DBS would only be applicable in few patients [26]. This puts limits on patient selection strategies. Additionally, the idea of "healing" consciousness by mere stimulation of a particular brain region itself is potentially confounding. Although not based on any evidence, the concept that the nature of consciousness is more holistic than localized, reveals a potential pitfall in the approach of DBS for DoC [32].

The rationale behind Deep Brain Stimulation for Disorders of Consciousness

The most publicized report by Schiff et al. published in 2007 in Nature [24] raised expectations about the potential of DBS for DoC, however, their unique experience did not lead to any breakthrough in this field.

Nevertheless, while DBS for DoC has not yet any proven potential, there is a belief that it is worthwhile investigating. A key driver for this is the recognition of the neglect of patients with DoC by healthcare, and that there is no other treatment available. Though the goal of trying to find a treatment for these patients is per se ethical, this does not as such *a priori* justify the use of DBS. Important and conflictual ethical considerations remain.

However, assuming a proper diagnosis of the DoC, judicious selection criteria of patients, a respect for the time frame of possible spontaneous recovery, a multidisciplinary panel including ethicists, a scientific choice of brain target for DBS and a comprehensive evaluation of outcome, one may consider a trial whereby patients are implanted with DBS with a blinded randomized cross-over design, or a design by which half the operated patients are stimulated immediately and the other half serve as control, with possibility to turn on stimulation at a later time point.

Conclusions

In conclusion, the reports in the literature on DBS for DoC are not satisfying in terms of providing clues as to the validity of using DBS in these conditions. The ethical issues are multifaceted and far from agreed upon. Further investigation of the technique has to be based on the mere assumption that it could provide more evidence for the eventual potential of DBS in selected cases of DoC. This ethical challenge is on top of the lack of evidence that DBS for DoC can restore both consciousness and communication, even though absence of evidence may not mean evidence of absence. Until comprehensive double-blind studies are performed, DBS for DoC must be evaluated meticulously on a case per case basis.

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References

[1] Schiff ND. Recovery of consciousness after severe brain injury: the role of arousal regulation mechanisms and some speculation on the heart-brain interface. Cleve Clin J Med 2010;77 Suppl 3:S27-33. doi:10.3949/ccjm.77.s3.05.

[2] Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet (London, England) 1972;1:734–7.

[3] Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. N Engl J Med 1994;330:1499–508. doi:10.1056/NEJM199405263302107.

[4] Medical aspects of the persistent vegetative state (2). The Multi-Society Task Force on PVS. N Engl J Med 1994;330:1572–9. doi:10.1056/NEJM199406023302206.

[5] Landsness E, Bruno MA, Noirhomme Q, Riedner B, Gosseries O, Schnakers C, et al.

Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain 2011;134:2222–32. doi:10.1093/brain/awr152.

[6] Cruse D, Thibaut A, Demertzi A, Nantes JC, Bruno M-A, Gosseries O, et al. Actigraphy assessments of circadian sleep-wake cycles in the Vegetative and Minimally Conscious States. BMC Med 2013;11:18. doi:10.1186/1741-7015-11-18.

[7] Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 2010;8:68. doi:10.1186/1741-7015-8-68.

[8] Sen AN, Campbell PG, Yadla S, Jallo J, Sharan AD. Deep brain stimulation in the management of disorders of consciousness: a review of physiology, previous reports, and ethical considerations. Neurosurg Focus 2010;29:E14. doi:10.3171/2010.4.FOCUS1096.

[9] Fins JJ. Rethinking disorders of consciousness: new research and its implications. Hastings Cent Rep 2005;35:22–4.

[10] Machado C, Korein J. Persistent Vegetative and Minimally Conscious States. Rev Neurosci 2009;20:203–20.

[11] Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85:2020–9.

[12] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet (London, England) 1974;2:81–4.

[13] Yamamoto T, Katayama Y, Obuchi T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation and spinal cord stimulation for vegetative state and minimally conscious state. World Neurosurg 2013;80:S30.e1-9. doi:10.1016/j.wneu.2012.04.010.

[14] Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet (London, England) 1975;1:480–4.

[15] Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury:

observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 1981;44:285–93.

[16] McLardy T, Ervin F, Mark V, Scoville W, Sweet W. Attempted inset-electrodes-arousal from traumatic coma: neuropathological findings. Trans Am Neurol Assoc 1968;93:25–30.

[17] Hassler R, Ore GD, Bricolo A, Dieckmann G, Dolce G. EEG and clinical arousal induced by bilateral long-term stimulation of pallidal systems in traumatic vigil coma. Electroencephalogr Clin Neurophysiol 1969;27:689–90.

[18] Sturm V, Kuhner A, Schmitt HP, Assmus H, Stock G. Chronic electrical stimulation of the thalamic unspecific activating system in a patient with coma due to midbrain and upper brain stem infarction. Acta Neurochir (Wien) 1979;47:235–44.

[19] Hosobuchi Y, Yingling C. The treatment of prolonged coma with neurostimulation. Adv Neurol 1993;63:247–51.

[20] Cohadon F, Richer E. [Deep cerebral stimulation in patients with post-traumatic vegetative state. 25 cases]. Neurochirurgie 1993;39:281–92.

[21] Adams ZM, Forgacs PB, Conte MM, Nauvel TJ, Drover JD, Schiff ND, et al. Late and progressive alterations of sleep dynamics following central thalamic deep brain stimulation (CT-DBS) in chronic minimally conscious state. Clin Neurophysiol 2016;127:3086–92. doi:10.1016/j.clinph.2016.06.028.

[22] Yamamoto T, Katayama Y, Kobayashi K, Kasai M, Oshima H, Fukaya C. DBS therapy for a persistent vegetative state: ten years follow-up results. Acta Neurochir Suppl 2003;87:15–8.

[23] Wojtecki L, Petri D, Elben S, Hirschmann J, Yelnik J, Eickhoff S, et al. Modulation of central thalamic oscillations during emotional-cognitive processing in chronic disorder of consciousness. Cortex 2014;60:94–102. doi:10.1016/j.cortex.2014.09.007.

[24] Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature

2007;448:600–3. doi:10.1038/nature06041.

[25] Tsubokawa T, Yamamoto T, Katayama Y, Hirayama T, Maejima S, Moriya T. Deep-brain stimulation in a persistent vegetative state: follow-up results and criteria for selection of candidates. Brain Inj 1990;4:315–27.

[26] Magrassi L, Maggioni G, Pistarini C, Di Perri C, Bastianello S, Zippo AG, et al. Results of a prospective study (CATS) on the effects of thalamic stimulation in minimally conscious and vegetative state patients. J Neurosurg 2016;125:972–81. doi:10.3171/2015.7.JNS15700.

[27] Chudy D, Deletis V, Almahariq F, Mar?inkovi? P, ?krlin J, Parad?ik V. Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: experience in 14 patients. J Neurosurg 2017:1–10. doi:10.3171/2016.10.JNS161071.

[28] Fins JJ. A proposed ethical framework for interventional cognitive neuroscience: A consideration of deep brain stimulation in impaired consciousness. Neurol Res 2000;22:273–8. doi:10.1080/01616412.2000.11740670.

[29] Lanoix M. Where angels fear to tread: Proxy consent and novel technologies. Brain Inj 2010;24:1336–42. doi:10.3109/02699052.2010.504524.

[30] Fins JJ. Giving Voice to Consciousness. Camb Q Healthc Ethics 2016;25:583–99. doi:10.1017/S0963180116000323.

[31] Giacino JT, Katz DI, Whyte J. Neurorehabilitation in disorders of consciousness. Semin Neurol 2013;33:142–56. doi:10.1055/s-0033-1348960.

[32] Gillett G. The Gold-Plated Leucotomy Standard and Deep Brain Stimulation. J Bioeth Inq 2011;8:35–44. doi:10.1007/s11673-010-9281-z.

[33] Schiff ND, Giacino JT, Fins JJ. Deep brain stimulation, neuroethics, and the minimally conscious state: moving beyond proof of principle. Arch Neurol 2009;66:697–702. doi:10.1001/archneurol.2009.79.

[34] Patuzzo S, Manganotti P. Deep brain stimulation in persistent vegetative States: ethical

issues governing decision making. Behav Neurol 2014;2014:641213. doi:10.1155/2014/641213.

[35] Glannon W. Neurostimulation and the minimally conscious state. Bioethics 2008;22:337–45. doi:10.1111/j.1467-8519.2008.00645.x.

[36] Schiff ND, Fins JJ. Deep brain stimulation and cognition: moving from animal to patient. Curr Opin Neurol 2007;20:638–42.

[37] Giacino J, Fins JJ, Machado A, Schiff ND. Central thalamic deep brain stimulation to promote recovery from chronic posttraumatic minimally conscious state: challenges and opportunities. Neuromodulation 2012;15:339–49. doi:10.1111/j.1525-1403.2012.00458.x.

[38] Fins JJ. Neuroethics and Disorders of Consciousness: Discerning Brain States in Clinical Practice and Research. AMA J Ethics 2016;18:1182–91. doi:10.1001/journalofethics.2016.18.12.ecas2-1612.

[39] Fukushi T, Sakura O. Ethical challenges and clinical implications of molecular imaging of human consciousness. Am J Bioeth 2008;8:23–4. doi:10.1080/15265160802412510.

[40] Schiff ND, Plum F, Rezai AR. Developing prosthetics to treat cognitive disabilities resulting from acquired brain injuries. Neurol Res 2002;24:116–24. doi:10.1179/016164102101199576.

[41] Dagi TF. Consenting to the ineffable: the problem of neuromodulation and altered consciousness. J Clin Ethics 2010;21:140–2.

[42] Schiff ND, Rezai AR, Plum F. A neuromodulation strategy for rational therapy of complex brain injury states. Neurol Res 2000;22:267–72. doi:10.1080/01616412.2000.11740669 To.

[43] Glannon W. Consent to deep brain stimulation for neurological and psychiatric disorders. J Clin Ethics 2010;21:104–11.

[44] Shah SA, Schiff ND. Central thalamic deep brain stimulation for cognitive neuromodulation - a review of proposed mechanisms and investigational studies. Eur J

Neurosci 2010;32:1135–44. doi:10.1111/j.1460-9568.2010.07420.x.

[45] Yamamoto T, Katayama Y. Deep brain stimulation therapy for the vegetative state. Neuropsychol Rehabil 2005;15:406–13. doi:10.1080/09602010443000353.

[46] Jennett B. The vegetative state. J Neurol Neurosurg Psychiatry 2002;73:355–7. doi:10.1136/jnnp.73.4.355.

[47] Giacino JT, Kalmar K. The Vegetative and Minimally Conscious States: A Comparison of Clinical Features and Functional Outcome. J Head Trauma Rehabil 1997;12.

[48] Lammi MH, Smith VH, Tate RL, Taylor CM. The minimally conscious state and recovery potential: a follow-up study 2 to 5 years after traumatic brain injury. Arch Phys Med Rehabil 2005;86:746–54. doi:10.1016/j.apmr.2004.11.004.

[49] Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Tsubokawa T. Deep brain stimulation for the treatment of vegetative state. Eur J Neurosci 2010;32:1145–51. doi:10.1111/j.1460-9568.2010.07412.x.

[50] Yamamoto T, Katayama Y, Oshima H, Fukaya C, Kawamata T, Tsubokawa T. Deep brain stimulation therapy for a persistent vegetative state. Acta Neurochir Suppl 2002;79:79–82.

[51] Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C, Katayama Y. DBS therapy for the vegetative state and minimally conscious state. Acta Neurochir Suppl 2005;93:101–4.

[52] Schiff ND. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Mol Biophys Mech Arousal Alertness Atten 2008;1129:105–18. doi:10.1196/annals.1417.029.

[53] Schiff ND. Central thalamic deep-brain stimulation in the severely injured brain: rationale and proposed mechanisms of action. Ann N Y Acad Sci 2009;1157:101–16. doi:10.1111/j.1749-6632.2008.04123.x.

[54] Glannon W. Ethical issues in neuroprosthetics. J Neural Eng 2016;13. doi:10.1088/1741-2560/13/2/021002.

[55] Georgiopoulos M, Katsakiori P, Kefalopoulou Z, Ellul J, Chroni E, Constantoyannis C. Vegetative state and minimally conscious state: a review of the therapeutic interventions. Stereotact Funct Neurosurg 2010;88:199–207. doi:10.1159/000314354.

[56] Katayama Y, Tsubokawa T, Yamamoto T, Hirayama T, Miyazaki S, Koyama S. Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: pain-related late positive component of cerebral evoked potential. Pacing Clin Electrophysiol 1991;14:116–21.

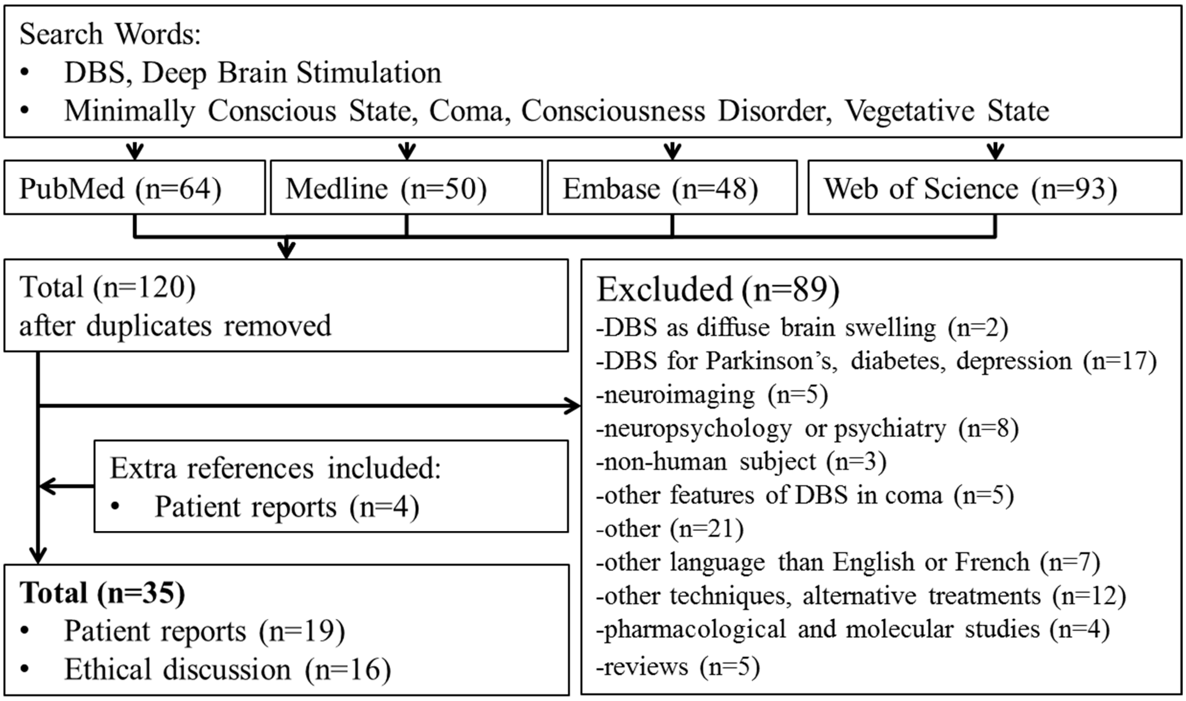

Figure 1: Flowchart of systematic review strategy.

n: number of publications. DBS: Deep Brain Stimulation

Table 1: Overview of patient reports of DBS for DoC

Authors	No. of patients, sex, age	Etiology	Interval injury to DBS implant (months)	Diagnosis	Follow-up after surgery (months)	Outcome	Brain targets	Stimulation parameters	Comments Mode of stimulation
Chudy *et al.* 2017 [27]	One male, 17	Anoxic (CA)	2	MCS	60	-Regained consciousness -Largely independent			
	One male, 23	Anoxic (CA)	2	MCS	57	-Regained consciousness -Largely independent, -"still experiences short term memory impairment and emotional regression"			
	One female, 15	TBI	11	MCS	51	-Regained consciousness - "has a severe left side hemiparesis and needs assistance in everyday life". -Needs wheelchair	CMPf (preferentially on left side, but, if too damaged right side)	Monopolar, 25 Hz, 90 μs, 2.5-3.5 V	Stim Int 0.5/2 DT
	Seven male, 17, 17, 20, 25, 34, 43, 59 Four female: 16, 28, 39, 49	3 TBI 8 anoxic (CA)	3-138	1 MCS 10 VS	38-59	-1 VS improved to MCS -3 died -7 no recovery			
Adams *et al.* 2016 [21]	One male, 38	TBI	252	MCS	58	Variable CRS-R of 11-14	Same as Schiff *et al.* 2007	Same as Schiff *et al.* 2007	-Change in sleep pattern recorded via EEG -Stim 12/12 DT

Magrassi *et al.* 2016 [26]	One male, 58	TBI	28	MCS (CRS-R 14)	18	CRS-R 15	Bilateral, anterior intralaminar thalamic nuclei and adjacent paralaminar regions	1 unipolar 2 bipolar, 80-110 Hz (median 100 Hz)	-The method used is called CATS: Cortical Activation by Thalamic Stimulation. -Stim 14/10 DT
	One male, 23	TBI	34	VS/UWS (CRS-R 8)	60	CRS-R 11			
	One male, 29	TBI	96	VS/UWS (CRS-R 6)	59	CRS-R 9			
Wojtecki *et al.* 2014 [23]	One female, 45	TBI (closed head injury)	84	DoC (GCS 4)	na	-No recovery (yet) -Patient had increased brain activity on response to her children	CT (internal medullary lamina and the nuclei reticularis thalami)	70-250 Hz, other parameters same as Schiff *et al.* 2007	-The aim of the study was to record EEG and "field potentials from the central thalamus" 2 days after DBS implantation and prior to internalization
Schiff *et al.* 2007 [24] (see also Giacino *et al.* [37])	One male, 38	TBI (closed head injury)	78	MCS	24	CRS-R subscales, various improvements (arousal, motor and communication as primary measures) -Restoration of communication ("interact consistently and meaningfully")	Bilateral, anterior intralaminar thalamic nuclei and adjacent paralaminar regions	Left monopolar, right bipolar, 100 Hz, 4 V	-Parameter optimization 70-250 Hz and 0-5 V -6 months double-blind crossover study -3 times 30 subsequent days on, 30 days off -Side-effect: vomiting -patient had intact language networks -Adams *et al.* mention for this case that if DBS is on, Stim 12/12 DT
Yamamoto *et al.* 2002-2013 [13,22,45,49–51]	5 patients, 18-47 (mean= 33.5 ±14.3)	3 TBI 2 vascular	3-6	MCS	120	All 5 recovered, live at home with family -Severe disabled condition (GOS) -Need wheelchair, 4/5 patients "could not operate wheelchair by themselves"	5 CMPf, unilateral, less injured side	Bipolar, mostly 25 Hz, various intensities	Stim Int 0.5/3 DT

(continued) Yamamoto *et al.*	Four female, 19, 41, 58, 59 Three male, 30, 43, 75 One person, (na)	6 vascular 2 TBI	3-6*	PVS (PCS 2-5)	120	-All 8 recovered: -7 are bedridden (PCS 8-10) -1 is “able to live in a wheelchair” -Able to communicate “with some speech or other responses” -Need assistance for everyday life in bed -Severe disabled condition (GOS)	-19 CMPf -2 mesencephalic reticular formation -Unilateral, less injured side	Bipolar, mostly 25 Hz, various intensities	-4/21 patients survived 10 years after DBS -Stim Int 0.5/3 DT -Included 8 patients overlap with Tsubokawa *et al.*
	Seven male, 29, 30, 42, 44, 48, 49, 56 Six female: 30, 39, 41, 44, 61, 74	7 TBI 3 vascular 3 anoxic	3-6*	PVS (PCS 2-5)	120	-All 13 no recovery (PCS 3-7)			
Cohadon & Richer 1993 [20]	25 patients, (na)	na	>3	VS	12-144	-1 improvement to moderate disability (GOS) -10 improvement to severe disability (GOS) -2 died -12 no recovery	CMPf	2 monopolar and 23 bipolar 50 Hz, 5-10 mV [sic], 5 msec.	-Improvement measured with score task system: from 0-10% to 30-60% -Stim 12/12 DT
Hosobuchi & Yingling 1993 [19]	One male, 23	Anoxic (ischemia)	8	Apallic state, GCS < 6	10	Improvement -Oral feeding possible -Could respond to verbal commands -Could not shake or nod the head on yes/no questions	na	na (amplitude increased till “30% of the arousal threshold”)	-Blind study -Stim 12/12 DT
	Two male, 35, 35 One female, 27	2 TBI 1 anoxic (ischemia)	10-36	apallic state, GCS < 6	12-18	-All 3 no recovery			

Tsubokawa *et al.* 1990 [25] (see also Katayama *et al.* [56])	Five male, 24, 43, 44, 48, 75 Three female, 41, 41, 74	4 TBI 3 vascular 1 anoxic	>6*	PVS (PCS 2-4)	12	-3 "full recovery" (PCS 8-9) -1 incomplete recovery (PCS 7) -3 no recovery (PCS 3-5)	-6 non-specific thalamic nucleus (CMPf) -2 Nucleus cuneiformis in mesencephalic reticular formation -Unilateral	50 Hz, 0-10 V	-Stim 2/22 DT (4 times 30 min) -See Yamamoto *et al.* for precise information about the outcome (overlapping patients).
Sturm *et al.* 1979 [18]	One male, 68	Outcome of operation for aneurysm, probably ischemia of the brain stem	<1	"subcoma with uncon-sciousness"	2	-Partial and temporary limited improvement -After 2 months the patient died from pneumonia	-Right rostral part of the lamella medialis thalami -Left nucleus reticulatus polaris thalami	Bipolar 6-10 V, 50 Hz, 0.5 msec	-After 4 days, the right side electrode was removed. -Stim 10/12 DT Int 0,16/1 (10 min each hour)
Hassler *et al.* 1969 [17]	One male, 26	TBI	5	"apallic syndrome" or "coma vigil"	<1	-Improvement of consciousness -Spontaneous movements of the left limbs -Unintelligible vocalization	-Basal portion of the left lateropolar nucleus of the thalamus -Basal part of the right pallidum	Left: 25-50 Hz, 20 V Right: 8 Hz, 30 V 1-3 msec	-After 19 days the electrodes were removed. There was no further gain of either consciousness or vocalization. -Stim Int 0,25/6 or 0,25/8 (3-4 times/day)
McLardy *et al.* 1968 [16]	One male, 19	TBI	7	"coma vigilans"	24	-Could move left hand -No change in consciousness -Died 24 months after surgery	Left thalamus and left midbrain for intralaminar nuclei and reticular formation	250 Hz, 1 msec	
Total	**78 patients**								

CA: Cardiac arrest; CT: "Central Thalamus"; CMPf: Centre Median Parafascicular complex; CRS-R: JFK Coma Recovery Scale Revised; DBS: Deep Brain Stimulation; DoC: Disorders of Consciousness; DT: stimulation during Day Time; MCS: Minimally Conscious State; na: not available; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; PCS: Prolonged Coma Scale; PVS: Persistent Vegetative State; Stim: Stimulation cycle of DBS in hours ON/ hours OFF; Stim Int: Intermittent Stimulation in hours ON/total period in hours; TBI: Traumatic Brain Injury; UWS: Unresponsive Wakefulness Syndrome; VS: Vegetative State. *in one of the 21 patients the interval from injury to DBS implant was 8 months, but the etiology of the DoC was not specified. There were inconsistencies regarding this patients between different reports (reference 22 vs. reference 28).

Table 2: Overview of ethical considerations of DBS for DoC

Authors	Patient issues -Self-determination -Awareness of disability	Patient's surrogate -Informed consent by proxy	DBS as technique -Risks and limitations -Side-effects -Potential -Alternatives	Care -Diagnosis -Health care	Scientific research -Selection of patients -Application	Society -Patients with DoC through eyes of society.
Dagi 2010 [41]		To convey the risks and benefits of DBS is sometimes not possible: the intervention in the consciousness of a person may be "ineffable". DBS requires a highly personal approach to assess whether the given consent is thoroughly to protect the patient's needs.				
Fins 2000 [28]	Patients with TBI are often neglected in care. TBI is too quickly seen as immutable, this is called "therapeutic nihilism". Self-awareness of patient's disability is problematic, but we need to consider that DBS is reversible.	Next-of-kin should be recognized as legal surrogate. There is a lack of accurate information to the surrogate on the prospect of the patient.	Although one cannot harm PVS patients more than MCS, the risk-benefit of DBS in MCS patients is better and more ethical.		Research on humans is justified. Focus trials -on MCS patients. -TBI as etiology -comprehensive baseline assessment prior to selection "responsible and responsive research agenda"	
Fins 2016 [38]		Informed consent can be assessed different for a patient, when the target is to restore communication.	DBS has been proven safe for drug-resistant Parkinson's.	When the diagnosis is other than MCS and TBI, misconception is fostered, e.g. a patient with anoxic injury.	Participants should be enrolled in a clinical study, with a plausible hypothesis and with surrogate consent.	There is an ethical framework, distinct from "the dark legacy of psychosurgery".
Fins 2016 [30]				We need "medical parity": a medical care for DoC patients.		We need "to view consciousness, when it is present, as a civil right."

Georgiopoulus *et al.* 2010 [55]			In a systematic review on treatment of DoC one cannot yet conclude which approach (DBS, nerve stimulation, SCS drugs) is most appropriate.		We need double-blind research.	
Giacino *et al.* 2013 [31]	Patients that possibly could benefit from intensive care for long term, do often not remain in treatment.	Trials sometimes limit treatment options, and as a result “families are reluctant to consent”. This is not beneficial for control groups in research.	There is not yet a conclusion on rehabilitation strategy, but we “should center on mobilization strategies” as there is “no evidence that they are unsafe”	There is “no standardized evaluation” for patients with DoC. Misdiagnosis range “from 37-43%”.	There is a suggestion that rTMS might be useful for patient selection for DBS.	The “beliefs of poor outcome in this patient population are incorrect”.
Gillett 2011 [32]	-There is a risk that the patient’s well-being would be severely corroded. “Risk of Unacceptable Badness” -There is a risk that the real needs of the patients are neglected.		DBS application should be carefully reflected to prevent that the ethical justification would be the same as the “Gold plated leucotomy standard”. i.e., the justification used by Walter Freeman to perform leucotomy, biased by his own collection of evidence and clinical judgement.	The uncertainty on the diagnosis of VS or MCS is significant.		We should not reduce a comatose human to a mere dysfunction of some nuclei. DBS and psychosurgery must be considered within a holistic approach.
Glannon 2016 [54]	The overall experience of the patient in the outcome of DBS has to be assessed rather than only symptoms.		General adverse effects of DBS are to be considered		So far, “there is no definitive evidence” that DBS in DoC can restore higher cognitive functions.	

Glannon 2010 [43]		There is a chance that DBS generates “unreasonable expectations”.	The “quality of life” should be carefully assessed with and without DBS. It is ethical to use DBS only if there is “a high probability that the technique will benefit the patient” and there is no alternative.		There is insufficient evidence to know whether side-effects are “temporary or permanent”.	
Glannon 2008 [35]	The patient’s psychological condition is as much as important as the physical and cognitive condition.	-Proxy consent is possible, but after thoroughly discussion. -The consent depends on the cognitive and physical outcome, however, too often the pitfall is made to overlook the psychological condition if the patients become aware of their impairment.	A better investigation of the benefits and risks is needed, such as the long-term outcomes, in order to inform the surrogate.		DBS as an innovative technique can be ethically justified, if the quality-of-life of the patients is carefully assessed.	
Lanoix 2010 [29]	Refers to Fins: comatose patients are “vulnerable to being denied” and hence research in DBS in those patients is an “ethical obligation”.	The judgement of the surrogate cannot be made thoroughly as there is no standardized health care for patients with DoC. Hence, the surrogate might overestimate the benefits of participation in research for the patient (misconception)	The minimizing risk of DBS cannot be seen independent of optimizing care.	There is no standardized health care for DoC.	The researchers should carefully support the surrogate in making a decision, to ensure the best interest of the patient.	
Patuzzo & Manganotti 2014 [34]		“DBS for PVS does not require informed consent” but a “start-informed consent”, because DBS can be seen as a necessary treatment or “ordinary medical intervention” of PVS.	In PVS patients, there is no risk of DBS to damage “mental integrity, since in PVS the human brain is already severely damaged”.			
Schiff *et al.* 2002 [40]		Participation in research should rely on an interdisciplinary dialogue.	The risk is limited as it is adjustable and reversible.		DBS research is justifiable because there are no good alternatives.	Research for treatment of DoC must be seen as “a societal imperative”

Schiff & Fins 2007 [36]		The specific etiology of PVS and MCS does not justify the “categorical exclusion” of these patients based on their decisional incapacity. Surrogate consent is needed and ethical.			Schiff and Fins raise strong criticism on former DBS study design. Some errors frequently made are: -DBS applied within the “time frame for spontaneous recovery” -no blinding -no good baseline assessment, or linkage DBS/behavior -poor diagnosis or bad criteria VS/MCS -no assessment of carry-over effects	
Schiff *et al.* 2009 [33]	The assumption “that the patient in MCS would forever remain permanently unware of his or her predicament is called into question”. Hence, there is a change in the risk-benefit ratio.		DBS for MCS could become a “halfway technology”, an important treatment for MCS, but not solving the core of the problem.			The patients are suffering from a “societal neglect syndrome”.
Sen *et al.* 2010 [8]	Suicidal ideation is reported in patients with TBI (3%-33%).	The family has to decide very quickly whether to withhold life-sustaining therapy or not, while normally an observation of 12 months is needed to assess the recovery of the patient.	The research of DBS is very limited so far and therefore “no definitive conclusions can be made”.	Diagnostic errors are very problematic (up to 40%). The communication and responsiveness of the patients have to be examined very carefully.	The early researches on DBS in coma states are confounded by the actual meaning of coma (PVS or MCS) and also by “the window of spontaneous recovery”.	

DBS: Deep Brain Stimulation, DoC: Disorders of Consciousness, MCS: Minimally Conscious State, PVS: Persistent Vegetative State. SCS: Spinal Cord Stimulation. rTMS: repetitive Transcranial Magnetic Stimulation, TBI: Traumatic Brain Injury, VS: vegetative state. Note: Arguments that are mentioned in several publications by the same author(s) are not repeated.

Deep Brain Stimulation for Disorders of Consciousness

Highlights

- Spontaneous recovery can often not be excluded in outcomes of DBS for DoC
- Proxy consent and patients' self-awareness of own limitations are main ethical issues
- There is no satisfying clinical evidence for a meaningful effect of DBS for DoC
- DBS for DoC must be evaluated case by case, including a psychological assessment