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J C I C M JOURNAL OF CLINICAL INTENSIVE CARE AND MEDICINE
ISSN 2639-6653

Review Article

The continued relevance of Deep Brain Stimulation for chronic pain

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Abstract

For the millions of patients experiencing chronic pain despite pharmacotherapy, deep brain stimulation (DBS) provides a beacon of hope. Over the past decade the field has shifted away from DBS towards other forms of neuromodulation, particularly spinal cord stimulation (SCS). DBS for pain is still performed, albeit off-label in US and UK, and experiences variable success rates.

SCS is an extremely useful tool for the modulation of pain but is limited in its application to specific pain aetiologies. We advocate use of DBS for pain, for patients for whom pharmacology has failed and for whom spinal cord stimulation is inadequate. DBS for chronic pain is at risk of premature neglect. Here we outline how this has come to pass, and in the process argue for the untapped potential for this procedure.

More Information

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Submitted: June 26, 2021
Approved: July 26, 2021
Published: July 27, 2021

How to cite this article: Farrell SM, Aziz T. The continued relevance of Deep Brain Stimulation for chronic pain. J Clin Intensive Care Med. 2021; 6: 009-014.

DOI: 10.29328/journal.jcicm.1001034

Introduction

Chronic pain, pain extending beyond the time of injury and healing, is debilitating. A serious and pervasive problem, systematic reviews have shown between 1/3 and ½ of the adult population in the UK are affected. This corresponds to just under 28 million adults, of whom 14.3% were categorized as moderate- to-severe [1]. In the US, as many as 20% (50.0 million) of adults have chronic pain with 19.6 million of these classified as high-impact chronic pain [2,3]. The US estimates a cost of $500 billion a year in medical treatment and loss in productivity [4].

Pharmacotherapy often fails these patients, with 5% of the population suffering chronic pain despite medication [5]. Even when effective, side effects such as nausea and vomiting are frequent due to the nonspecific nature of the medication; opioids, in particular, suffer from reduced long-term efficacy due to receptor downregulation [6]. The opioid epidemic in the US has provided additional encouragement for the medical industry to seek alternative solutions for managing chronic pain.

For the past 50 years, neurosurgeons have been building a toolbox of surgical techniques for the neuromodulation of pain. Public consciousness is generally more at ease with less invasive approaches; but whilst noninvasive neuromodulatory strategies are available these show modest results. Repetitive transcranial magnetic stimulation (rTMS) [7-9] and transcranial direct current stimulation (tDCS) [10-12] show some efficacy in reducing pain, but the mixed outcomes and short-term nature of the effects are limiting factors.

Spinal cord stimulation (SCS) is the most demonstrably successful neurostimulation method used for chronic pain, largely due to the upsurge of patients with Failed Back Surgery Syndrome (FBSS), present in 10% - 40% of patients after lumbar spine surgery [13,14]. Whilst the efficacy level is classed as 'moderate', a 2005 systematic review showed the procedure to be safe with no major adverse events [15].

Further success is promised with higher frequency versions of the conventional treatment (10000Hz compared to 1200Hz) [16]. Burst Dorsal root ganglion stimulation, where stimulation is delivered directly to nerve roots, enjoys additional success. Initial studies demonstrate positive results with regions not usually successful in SCS, such as Complex Regional Pain Syndrome (CRPS) and groin pain. The United States Food and Drug Administration (FDA) has approved DRG thanks to a prospective RCT comparing DRG and SCS [17].

Despite the tantalising suggestions of success from other forms of neuromodulation, DBS has not been usurped

or rendered superfluous. Its relevance lies in providing solutions for patients where SCS cannot. If SCS fails, or if the pain aetiology is central (e.g. post stroke pain and atypical facial pain), a surgeon may try either DBS, or motor cortex stimulation (MCS), largely depending on their skillset and familiarity, as has been shown to be the case in several studies [18,19].

A brief overview of DBS targets

Three main target sites have been used for DBS in chronic pain patients:

The thalamus- ventral posterolateral nucleus and ventral posteromedial nucleus (VPL/VPM) – stimulation in this region induces a phenomenon of purportedly "pleasant" paraesthesia.

Regions surrounding the third ventricle and aqueduct of sylvius, including the periventricular grey and periaqueductal grey (PVG/PAG). Pain relief following PAG/PVG stimulation has been attributed to the release of endogenous opioids; evidenced by nullification of efficacy following naloxone [20].

The more recent target of the rostral anterior cingulate cortex (ACC) posterior to the anterior horns of the lateral ventricle. Here the affective component of pain relief plays a role; patients describe that although pain was present, it was 'less bothersome' or 'separate from them'.

Other regions of interest include:

Posterior hypothalamus; for cluster headaches in those for whom occipital nerve stimulation has failed [21].

Insular cortex; mounting evidence suggests stimulation here may yield success. This is yet to be trialled specifically in chronic pain patients proper [22].

Neuromodulation in historical context

The first DBS to alleviate pain was performed in 1950s [23], shortly followed by the use of a septal target to relieve cancer pain [24]. These trials were spurred on by a mix of incidental findings of targets from ablative procedures [25,26], animal studies [27], and a sensible overarching theory - Melzack and Wall's gate theory of pain [28]- thus legitimizing the use of electrodes to reduce pain. Initial trials predominantly centred around the thalamus [29,25], then periaqueductal grey/ periventricular grey (PAG/PVG) [30,31], before later using ACC [32-35]). A more complete history of DBS has been outlined elsewhere [36], demonstrating mixed results throughout history. This ranges from a Randomized Control Trial (RCT) by Marchland showing placebo, but not thalamic stimulation, improved pain intensity [37], to Boccard, et al. reporting successful long term outcomes for 37/59 patients with a variety of pain aetiologies, stimulated in either the PAG or Thalamus, experiencing a pain reduction of at least 50% [33].

The importance of contextualizing DBS in its piecemeal history, is to understand the issues that led to a misrepresentation of its usefulness. Not least, two ill-fated industry open label studies combining Ventral posterolateral nucleus (VPL) and PAG stimulation, experiencing high levels of follow up losses, under powering and lack of accrual [38]. This led to FDA bestowing only 'off-label' status [39]. Few clinical trials have since been reported.

The literature boasts more success than these infamous 'failed' studies would suggest. Particularly amongst the Oxford group, regarding stimulation in the anterior cingulate cortex (ACC) [33,34,40] More comprehensive accounts of these studies can be found in Farrell et al 2018 [36], with the conclusions confirmed by a recent systematic review incorporating 22 articles and 228 patients. Whilst more research is needed to be confident of its efficacy, the ACC is a promising target [41].

Current studies do not reveal the true potential of DBS for chronic pain

Studies often fail to capture the merits of DBS for chronic pain. Through examining why, we hope to reignite interest in a modality that has been unfairly deprioritized and seek to generate data that fully reflects the potential for DBS.

Unsurprisingly, a multitude of factors are at play. It is often discussed how randomized control trials (RCTs) are difficult to perform, this is particularly true for neurosurgery in chronic pain patients-marred by low patient numbers, difficulties of blinding, the ethics of sham surgery and logistical difficulties surrounding patient follow up. Additionally, the patients selected have heterogenous pain aetiologies, different target locations, and different pain profiles; and surgeons have varying levels of expertise and knowledge regarding deep brain stimulation. Any given patient undergoing a given procedure may achieve varying success depending on the stimulation parameters programmed. Adding to this, the types of patients undergoing DBS are biased towards failure: DBS tends to be a treatment that takes place once SCS has failed- its less targeted and more invasive approach means that SCS may be trialled first- suggesting the patient population who receive DBS are filtered to be those more difficult to treat, skewing the results unfavorably against DBS. In addition to this, poor patient selection is a factor producing lower efficacy than the procedures capability.

Specific issues with the outcome measures used to detect successful results also hamper results of chronic pain research. The subjective ratings of the visual analogue scale (VAS) are in frequent use, only sometimes with more holistic quality of life questionnaires added. Subjective rating of pain can be flawed by the self-fulfilling prophecy of pain anticipation, modulated by attention, mood, depression, anxiety and wider sociocultural factors. It is also worth noting that successfully removing pain may not necessarily translate

to a reduction in VAS scores. For example, the removal of a particular component of pain, such as burning hyperaesthesia, may unmask another type, such as muscular allodynia, as has been described after stroke [42]. Thus, neuromodulation may have achieved its intended specific role, but the patient is left with another form of pain. This illustrates the need to combine objective measures with wider measures of patient satisfaction. In the future, a score capturing objective changes in analgesia would be more informative, for example, heart rate variability or BP monitoring may correlate to analgesia [43,44]. Indeed, some brain regions may provide useful biomarkers for objective assessment and effective treatment [45].

Thresholds typically used for a therapy to be 'successful' in the trials of first-line therapies or pharmacotherapy are less relevant for, yet still applied to, our chronic pain patients. Patients are tested against a standard that may not be achievable and indeed may not be necessary for the patient to deem an outcome satisfactory. In the literature for chronic pain this has typically been 50% of patients having 50% pain relief. These values may be unhelpful, and are somewhat arbitrary considering other cut-offs exist within the pain literature- for example one paradigm posits a 12 point improvement on the 100 point visual analogue scale is a marker of 'clinically significant improvement' [46]. Testimonials suggest that even partial reduction in pain has resulted in a greatly increased quality of life. It is fair to say, patients who have reduced pain and improved subjective quality of life are represented as a 'failed' DBS procedure in the literature. Reductions in VAS have been poorly correlated with patient satisfaction of disability. For example, one study showed five out of nine patients would have the surgery all over again if they knew the results it would produce [47].

More generally, RCTs examining population statistics, looking at mean changes, may not be the best way to examine efficacy of a treatment for an individual with refractory pain who has already used up the limited treatment options available. For a given individual we must consider risk vs benefit, for example, an individual may be weighing up a 20% chance of success with a 1:500 risk of stroke. An individual should have the opportunity to take this reasonable risk. We would argue that, as long as the surgery is safe and patient selection is considered, given that parameters can be optimized by the team in conjunction with the patient to create a satisfactory pain relief, this 'n of 1' study, i.e. outcomes measures for a given individual assessed on a case by case basis, is sufficient to suggest its use [48].

Furthermore, efficacy will increase as we improve our understanding of the neural signature of chronic pain. Firstly, this will allow us to better predict who will respond. We are currently far from the patient pre-selection ability, but evidence from LFP recording shows chronic pain patients with DBS 'off' have characteristically enhanced low frequency (8-14hz) power spectra of both PAG and VP (thalamus) local field potentials when in pain [49]. The exploration of non-invasive functional neuroimaging and interventions, including single-photon emission computed tomography (SPECT) positron emission tomography (PET), magnetoencephalography (MEG), may find further correlates of pain to target [42,50-53]. TMS, currently limited to short term analgesic effects, may even be a modality by which we can 'test' a patient's suitability of more invasive approaches.

Secondly, once we are able to select patients with clear biomarkers of chronic pain, we can then ameliorate this pain with personalized neurostimulation. DBS is currently applied 'open loop' without consideration of moment to moment underlying physiology. However, the potential to create a system that accommodates patient-specific dynamics of pain processing with feedback mechanisms producing a 'closed-loop system' is imminent. Using neural biomarkers of pain to selectively control stimulation only when needed may also provide longer term efficacy in a system where the effect is known to peter out. There are currently two listed trials from Shirvalkar's group at the University of California, testing feasibility of personalized targeting, aiming to develop closed loop technology. Electrodes will be placed bilaterally in thalamus, anterior cingulate, prefrontal cortex, insula and amygdala. A trial period will identify candidate biomarkers of pain and optimal stimulation parameters for each individual (estimated for completion 2024). Neural targeting has already been suggested for movement disorder patients where it is thought that predominant beta-activity may serve as an electrophysiologically determined target for the optimal outcome in the subthalamic nucleus for Parkinson disease [54]. There are some issues in the transposition of this research to chronic pain. The majority of studies detecting pain biomarkers to date focus on stimulation-related pain relief, rather than spontaneous pain, the latter of which will be more accurate to the pain states requiring modulation in chronic pain patients. TMS has high levels of stimulation artefact and can be painful (confounding interpretation). Shirvalkar, et al. champion the more invasive option of SteroEEG (SEEG) trials with the aim to identify optimal brain regions in candidates likely to respond. This method has been used in refractory epilepsy, and can be placed through burr holes targeting both cortical and deep structures of the brain [55]. Of course, with the added invasive nature comes with risks; SEEG has potential for haemorrhage, neurological deficit, death, and infection rates will be higher than noninvasive approaches, so will require added benefits to justify this pre-DBS.

Going forward with DBS for chronic pain

At present, it may be tempting to categorise types of pain or regions of pain and use this to predict amenability to DBS. However, the distinction of pain in the acute phase and the 'chronification' of pain, the latter involving neuronal plasticity encompassing centrally mediated changes, would suggest

we focus less on pain aetiology in patient selection. Indeed this centrally mediated chronification is suggested by both functional imaging and electrophysiology [56-62]. Consistent with this theory, DBS in spinal cord related patients, including those with failed back surgery syndrome, has shown to be efficacious, suggesting a centrally mediated component to this initially peripheral injury, which is able to respond favourably to thalamic or ACC stimulation [63]. Therefore, until we have established a greater understanding of the use of noninvasive procedures and biomarkers of pain to predict which patients will achieve a successful outcome, it may be prudent to select those whose pain is not complicated by psychogenic factors, proven to be a negative predictor of good outcome [64]. However, in previous reality, DBS has tended to be used for central post-stroke pain, atypical facial pain, brachial plexus injury, and some patients who has failed SCS.

NICE guidelines approve DBS for chronic refractory pain where other methods fail and require a multidisciplinary team to approve the case. Although DBS for chronic pain is not currently funded on the National Health Service in the UK, and used only off-label in the US, the neurosurgical community remain curious. There are continued clinical trials regarding pain and DBS (8 registered on clinicaltrials.gov specifically related to DBS for chronic pain, last accessed 01/06/2021; nil found EudraCT last accessed 01/06/2021).

Future trials (as mentioned above) will aim to optimize target locations and characterize neural substrates of pain to inform algorithms used for closed-loop functionality. Both NeuroPace and Medtronic (Percept) have closed-loop devices available. Understanding these neural substrates/ biomarkers will also aid patient selection, alongside potential use of noninvasive methods to pre-select patients amenable to treatment.

Conclusion

Neuromodulation has been used successfully to help patients with chronic pain, for whom pharmacotherapy has failed. We argue that whilst DBS appears to fall short in the literature, its potential is misrepresented. Whilst DBS does not reduce pain in all patients, and sometimes produces unwanted (mostly manageable) side effects, many patients treated with DBS have been satisfied with their pain reduction. This includes some of those patients who were classified as failed treatment in the literature. Future studies will be able to understand the mechanisms underlying chronic pain, establish key biomarkers, and improve targeting. The improved outcomes will better represent this procedure's capability to reduce chronic pain. Thus, pursuing the use of DBS to provide central neuromodulation has continued validity. This is particularly true for more recent targets, namely ACC. It is important not to lose what could be a vital and improving tool in our armamentarium because of challenges in study design, particularly given ongoing progress in optimizing outcomes.

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