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Review

Deep brain stimulation for chronic pain

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ABSTRACT

Deep brain stimulation (DBS) is a neurosurgical intervention popularised in movement disorders such as Parkinson's disease, and also reported to improve symptoms of epilepsy, Tourette's syndrome, obsessive compulsive disorders and cluster headache. Since the 1950s, DBS has been used as a treatment to relieve intractable pain of several aetiologies including post stroke pain, phantom limb pain, facial pain and brachial plexus avulsion. Several patient series have shown benefits in stimulating various brain areas, including the sensory thalamus (ventral posterior lateral and medial), the periaqueductal and periventricular grey, or, more recently, the anterior cingulate cortex. However, this technique remains "off label" in the USA as it does not have Federal Drug Administration approval. Consequently, only a small number of surgeons report DBS for pain using current technology and techniques and few regions approve it. Randomised, blinded and controlled clinical trials that may use novel trial methodologies are desirable to evaluate the efficacy of DBS in patients who are refractory to other therapies. New imaging techniques, including tractography, may help optimise electrode placement and clinical outcome.

1. Introduction

Pain was redefined in 1994 by the International Association for the Study of Pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. It is an experience with at least three dimensions: sensory (pain intensity), affective (pain unpleasantness) and cognitive. Neuropathic pain is a type of chronic pain in which symptom severity and duration are among the greatest [2]. Jensen and colleagues redefined it as a pain induced by a lesion or disease of the somatosensory system [3]. Chronic pain, with a prevalence of up to 8%, presents a huge burden on society costing at least $150 billion in the USA alone [4].

For patients with chronic pain, neurosurgery offers several types of treatments. In order to relieve intractable pain, several structures involved in the pain processing pathway have been targeted from the peripheral nerve through the dorsal root, spinal cord, midbrain, and thalamus to the cerebral cortex. Historically, these structures have been lesioned, perfused with analgaesics or anaesthetics and, of late, electrically stimulated. This review will focus on deep brain stimulation (DBS) for chronic pain treatment.

2. Pain pathways

Pain comprises several components, therefore, its transmission pathways are complex. It is generally acknowledged that DBS can modulate activity in both lateral and medial pain systems [5]. The lateral one is composed of the spinothalamic tracts connecting the dorsal horn of the spinal cord to the ventral nuclei of the thalamus: the ventral posterior lateral (VPL), ventral posterior medial (VPM) and ventral posterior inferior nuclei. These tracts then project to the somatosensory cortices (primary and secondary). The medial pain system also consists of tracts connecting the spine to the thalamus (medial nuclei), but through the brain stem and connecting the limbic system. This second pathway is slower and is thought to modulate the affective component of pain [6].

3. DBS

DBS is widely used in movement disorders. Its efficacy has also been demonstrated in epilepsy, Tourette's syndrome, obsessive compulsive disorders and cluster headache [7]. The concept of relieving intractable pain with DBS appeared in the 1950s, a decade before the gate control theory.

The first evidence arose from rodent models. In self-stimulation experiments, rats with implanted electrodes robustly sought stimulation of the septal region that resulted in a feeling that Olds et al. interpreted as a form of pleasure [8]. Subsequently, Heath

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hypothesised that, as pain is the opposite of pleasure, stimulation of the septal area could provide pain relief. One of his patients who was suffering from cancer pain reported analgaesia after receiving septal DBS [9]. Later on, other terminal cancer pain patients were also relieved by septal area DBS [10].

At the end of the 1970s, DBS for pain was acknowledged as safe and effective by practitioners in the field [11], and the USA Food and Drug Administration (FDA) asked the three DBS systems manufacturers of the time to conduct studies to demonstrate its benefit. Only one company complied and it provided data that demonstrated only limited efficacy. Consequently, the approved status of DBS for pain was rescinded and it is still "off label", preventing funding approval by insurers [12,13]. Therefore, only a small number of neurosurgeons offer DBS for pain [14]. Moreover, without clear indications, randomised controlled trials and long term follow-up, DBS for chronic pain may not be established. In Europe, DBS for chronic pain has been approved by the European Federation of Neurological Societies and the United Kingdom National Institute for Health and Clinical Excellence [14,15].

Worldwide, an increasing interest in DBS for chronic pain refractory to medical treatment has been observed with the publication of an increasing number of papers over time (Fig. 1).

Among them, several studies, mainly open labelled, have reported its efficacy in various aetiologies including phantom limb pain [16–20], brachial plexus injury [19–22], central post-stroke pain [17–19,21–23], face pain [17,19,24,25], spinal injuries or failed back surgery syndrome [17–19,22] and headaches [25–29] (Table 1).

4. DBS targets

Historically, many brain areas have been targeted, starting with the septal region [9,10], the sensory thalamus (both lateral [VPL] or medial [VPM] nuclei) [16–19,21,24,31,54,61,65,73,74], the periventricular grey (PVG) and periaqueductal grey (PAG) [17–19,23,41,61,65,74], the internal capsule [65,74], the posterior hypothalamus [25–29], the nucleus accumbens [23] and, finally, the anterior cingulate cortex (ACC) [22,75]. The choice of the targeted area depends on the type of pain and its distribution.

4.1. The sensory nuclei of the thalamus (VPL, VPM)

With regards to the VPL and VPM, insights came from ablative surgery [76]. As reported in large case series of DBS for chronic pain, sensory thalamic stimulation has been used with varying effectiveness in several chronic pain syndromes [19,20] with the VPM particularly targeted in facial pain [24]. Thalamic targets are 10–13 mm posterior to the midcommissural point. Depending on the pain site, the best location can be from 5 mm inferior to 2 mm superior to it. The VPM, targeted for face pain only, is found between the wall of the third ventricle and the internal capsule. The VPL is targeted 2–3 mm medial to the internal capsule for the arm pain, and 1–2 mm for the leg area. The stimulation induces a pleasant paraesthesia in the painful area.

4.2. Periventricular grey/periaqueductal grey

Initially, the PVG and PAG were identified as targets for DBS in animal research. Rodent experiments demonstrated PVG and PAG grey regions as DBS targets [77]. These findings were subsequently translated to humans [24,41] and widely used by several functional neurosurgeons. The PVG is surrounded by the medial lemniscus laterally, superior colliculus posteriorly and the red nucleus anteriorly. The electrode is placed 2–3 mm lateral to the third ventricle at the level of the posterior commissure. When these areas are stimulated, the pain is substituted by a sensation of warmth or analgaesia. Stimulation of the PVG also induces some changes of autonomic functions [78–81]. Electrode location in the PAG and the sensory thalamus can be seen in Figure 2.

4.3. Anterior cingulate cortex

While somatosensory homunculi have been demonstrated in the ventral posterior thalamus [82] and later in the PAG/PVG [83], outcomes of DBS of these targets appear less good for whole or hemi-body pain. Hemi-or whole-body post-stroke pain may benefit from targeting of regions involved in the affective dimension of chronic pain such as the ACC [84]. Changes in activity of the ACC have been shown to induce effects on many psychological and motor functions [85,86], and have also been demonstrated to be involved in empathy and pain expectation [87]. Historically, cingulotomy has been used to relieve intractable pain, in particular in terminal cancer. Freehand resective cingulectomy was first performed in Oxford by Cairns [88], and stereotactic cingulotomy later in Massachusetts by Ballantyne [89]. A review of published cingulotomy series showed that the procedure was useful in 32–83% of patients, depending on the study [90]. Interestingly, many positron

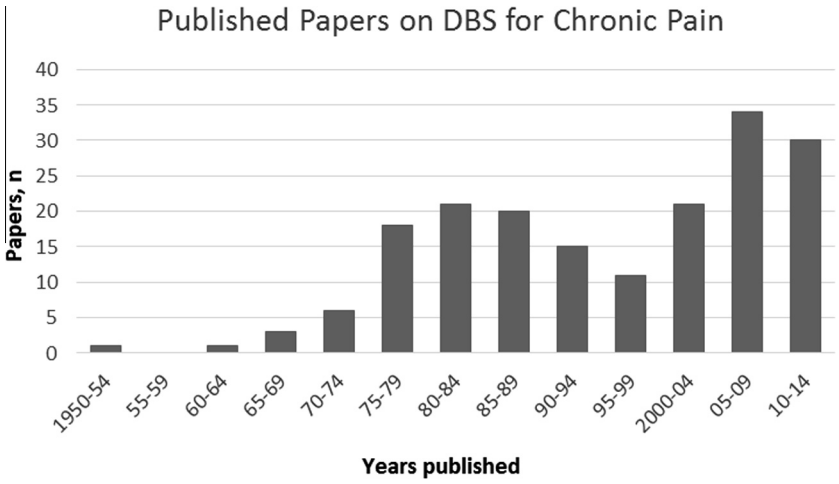

Fig. 1. Graph of the number of papers on deep brain stimulation (DBS) for chronic pain in humans (reviews excluded). The main source of articles for this review was PubMed with the following search terms: "stimulation" + "pain" + "patients"; March 2015. Excluded were studies performed on animals, or those that were not specifically on chronic pain or DBS.