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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 3 (March), 2014: pp 283-292
Available online at www.jpain.org and www.sciencedirect.com

Deep Brain Stimulation as a Treatment for Neuropathic Pain: A Longitudinal Study Addressing Neuropsychological Outcomes

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Abstract: Deep brain stimulation (DBS) of the periventricular/periaqueductal gray area and sensory thalamus can reduce pain intensity in patients with neuropathic pain. However, little is known about its impact on quality of life, emotional well-being, and cognition. This study followed up 18 patients who had received DBS for neuropathic pain. Each participant had previously undergone psychometric evaluation of each of the above areas as part of a routine presurgical neuropsychological assessment. Commensurate measures were employed at a follow-up assessment at least 6 months postsurgery. DBS significantly improved mood, anxiety, and aspects of quality of life. Improvements correlated with reduced pain severity. However, the sample continued to show impairments in most areas when compared against normative data published on nonclinical samples. There was little change in general cognitive functioning, aside from deterioration in spatial working memory. However, improvements in pain severity were associated with less improvement (and even deterioration) on measures of executive cognitive functioning. Improvements in emotional well-being also were correlated with changes in cognition. These results suggest that DBS of the periventricular/periaqueductal gray and/or sensory thalamus improves quality of life and emotional well-being in sufferers, although there is some indication of executive dysfunction, particularly among those reporting greatest pain alleviation.

***Perspective:** This article examines the neuropsychological outcomes of DBS surgery as a treatment for neuropathic pain. This intervention was found to improve pain severity, emotional well-being, and quality of life, although such benefits may be accompanied by reduced ability on tasks measuring executive functioning.*

Key words: *Chronic pain, neuropathic pain, deep brain stimulation, cognition, mood.*

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system.[23] It is associated with significant costs to the individual and society.[3,48] Three common forms of neuropathic pain are phantom limb pain, central poststroke pain (CPSP), and cephalalgia. Medical interventions for these conditions have traditionally been pharmacologic. However, their effectiveness has been described as disappointing,[53] and side effects lead many patients to reject their long-term viability.[18] Cognitive-behavioral therapy can reduce pain severity,[31] but effect sizes of such benefits tend to be modest, and a proportion of patients experience little benefit.[55] Such findings necessitate an examination of alternative interventions for those patients who do not respond to more traditional treatments.

Deep brain stimulation (DBS) is a neurosurgical technique involving the stereotactic implantation of

Received January 11, 2013; Revised October 21, 2013; Accepted November 14, 2013.

This research was supported by the NIHR Biomedical Research Centre (Oxford) and the Oxford Institute of Clinical Psychology Training.

None of the authors hold any conflicts of interest.

Research was conducted at the John Radcliffe Hospital, Oxford, England, United Kingdom.

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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.11.003

electrodes that emit electrical stimulation to a targeted neuronal region. Stimulation of the periventricular/periaqueductal gray (PVG/PAG) areas and/or sensory thalamus (ST) has been found to reduce pain severity in CPSP,[34] phantom limb pain,[6] and cephalalgia.[21] The reciprocal relationship between these target sites[40] suggests the presence of a "pain network" in which stimulating either site has an effect on this network. Stimulation is hypothesized to act on both the antinociceptive system in the spinal cord and the central pain network,[44] with evidence indicating involvement of the midanterior orbitofrontal and subgenual cingulate cortices.[27]

Although the beneficial impact of DBS on pain is increasingly recognized,[5] there remains little published research outlining its impact on neuropsychological variables. Yet understanding this relationship can assist neurosurgical teams in selecting the most suitable surgical candidates and can provide patients with an increased awareness of the potential risks of surgery, thus allowing them to make an informed choice regarding their consumption of health care services. This study is therefore concerned with examining the impact of DBS on patients' quality of life, emotional well-being, and cognition.

It is well established that quality of life can be significantly compromised in neuropathic pain sufferers,[24] and the few studies that have examined the impact of DBS in this respect have identified benefits.[6,34] We therefore anticipated finding similar results. However, it was less clear whether postsurgical quality of life would be comparable to that seen in the general population, and this study addressed this question. Despite the well-known association between chronic pain and both major depression[19,20] and heightened anxiety,[1] changes in emotional well-being post-DBS remain unexamined. We predicted a beneficial impact of DBS on emotional well-being, although no prediction was made as to whether it would improve to a level comparable with the general population.

The cognitive outcome of DBS, either iatrogenically or in terms of pain reduction, remains unexamined in this population. Disturbances in attention[16,17] and memory[32] have been reported in chronic pain sufferers, suggesting that alleviation of pain may improve cognition. Yet the neuronal regions targeted by DBS have been linked with cognitive functioning, with neuropathology of the PVG/PAG found in Korsakoff syndrome,[51] a disorder characterized by a severe encoding deficit[26] and executive dysfunction.[50] Impairment of the ST has also been associated with executive dysfunction.[9] Given this complexity, no predictions were made as to the outcome of DBS on cognition.

Finally, we examined the extent to which changes in pain severity were associated with changes in quality of life, emotional well-being, and cognition. It was predicted that reduced pain severity would be associated with improvements in quality of life and emotional well-being. It was also anticipated that reductions in pain would be associated with any improvements in cognitive functioning, although changes in emotional well-being may also be a covariate.

Methods

Participants

Potential participants were identified from a list of all patients who had received DBS of the PVG/PAG and/or ST as a treatment for chronic pain at a National Health Service neurosurgical center (John Radcliffe Hospital, Oxford, England, United Kingdom). All potential participants had previously completed a standardized neuropsychological test battery (administered by a qualified psychologist) as part of their routine assessment for treatment suitability. The list was reviewed and patients were invited to attend a follow-up neuropsychological assessment if 1) they were aged ≥18 years; 2) they had a diagnosis of neuropathic pain as determined by a consultant neurosurgeon; 3) they spoke English as a first language; 4) they had phantom limb pain, poststroke pain, or cephalalgia; and 5) at least 6 months had elapsed between surgery and invitation to participate so as to allow the effects of stimulation to become apparent. Potential participants were excluded if they had visual/auditory deficits likely to impact on neuropsychological test completion, had a history of a significant head injury, or had been diagnosed with a neurologic or neurodegenerative disorder (other than stroke in the group with CPSP). Twenty-eight potential participants met these criteria. Of these, 3 had died, 3 chose not to participate, and 1 was lost to follow-up. Therefore, 21 individuals who attended their postoperative follow-up were asked to participate in the study. However, a further 2 participants were excluded from analysis as they were suffering from dementia. Neither of the dementia patients had shown signs of a neurodegenerative disorder at initial assessment or within the 12 months following surgery. The intervals between their surgery and follow-up assessment were 4 and 6 years, which was slightly longer than the group average (see Table 1). A further patient was excluded after suffering a stroke since surgery. None of the other central poststroke pain patients had suffered any further cerebrovascular impairments since presurgical assessment. The details of the final sample of 18 participants can be found in Table 1.

Design

The study used a longitudinal within-subjects design in which each participant's neuropsychological test scores collected before surgery were compared with their scores obtained following surgery.

Measures

Neuropsychological measures employed to examine cognitive functioning were as follows:

Raven's Standard Progressive Matrices[38]

This is a measure of nonverbal reasoning and problem-solving skills. The participant is provided with a pattern