Brain Stimulation xxx (2018) 1–8

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

A pilot study of bed nucleus of the stria terminalis deep brain stimulation in treatment-resistant depression

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ARTICLE INFO

Article history:
Received 10 October 2017
Received in revised form
18 April 2018
Accepted 19 April 2018
Available online xxx

Keywords:
Deep brain stimulation
Major depression
Bed nucleus of the stria terminalis
Clinical response
Treatment resistance

ABSTRACT

Background: Studies are increasingly investigating the therapeutic effects of deep brain stimulation (DBS) applied to a variety of brain regions in the treatment of patients with highly treatment refractory depression. Limited research to date has investigated the therapeutic potential of DBS applied to the Bed Nucleus Of Stria Terminalis (BNST).
Objective: The aim of this study was to explore the therapeutic potential of DBS applied to the BNST.
Method: Five patients with highly treatment resistant depression underwent DBS to the BNST in an open label case series design.
Results: BNST DBS resulted in sustained remission of depression in two of the five patients, provided substantial therapeutic improvement two further patients, and had minimal antidepressant effect for the final patient. There were no operative complications and stimulation related side effects were limited and reversible with adjustment of stimulation. However, the time to achieve and complexity of programming required to achieve optimal therapeutic outcomes varied substantially between patients.
Conclusion: DBS applied to the BNST as therapeutic potential in patients with highly refractory depression and warrants exploration in larger clinical studies.

Introduction

Depression is a common disorder with lifetime prevalence of approximately 15% [1]. Despite the use of a range of medications, psychological and externally applied brain stimulation treatments including electroconvulsive therapy (ECT), a significant subset of depressed patients continue to experience highly distressing and disabling symptoms [2,3]. Deep brain stimulation (DBS) is being investigated as an alternative therapy for treatment-resistant depression, as well as a number of other potential clinical indications [4,5]. DBS involves the implantation of stimulation electrodes in specific brain regions with the aim of modifying local and connected brain activity [6]. DBS has been used extensively in neurological disorders such as Parkinson's disease, intractable tremor and dystonia, and less commonly in other disorders such as epilepsy [7,8].

DBS procedures used for the treatment of depression have utilised several anatomical sites [9]. These have included the subgenual area of the anterior cingulate [10,11], the anterior limb of the internal capsule (ALIC)/ventral striatum (VS) and the nucleus accumbens (NA) [12,13] as well as more recently the medal forebrain bundle [14,15]. Most closely related to our approach, a number of studies have investigated the antidepressant properties of DBS applied to either the VS/ALIC or NA. For example, Malone et al. described the effects of DBS to the VS/ALIC in 15 depressed patients [12] implanted with *Medtronic 3391/3387IES* electrodes. On the main outcome measure, 40% of patients had responded at 6 months and over 50% at last follow up. A second study using the *Medtronic 3387* electrodes involved the implantation of 10 patients

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https://doi.org/10.1016/j.brs.2018.04.013
1935-861X/

into the NA itself with a 50% response rate reported [16]. A third study of 25 patients involved electrode implantation in the ventral ALIC (Medtronic 3389 m leads) [17]. Patients were programmed for 12 months in an open label fashion to achieve optimal response and then received blinded active or sham stimulation. Depression outcomes were significantly better during the active compared to sham stimulation phases.

Despite the initial promise of stimulation at this location, a recent industry sponsored trial of VC/VS DBS was ceased early due to a lack of significant effects seen in an early interim analysis [18]. Stimulation parameters for a 16 week blinded treatment phase were chosen after a very rapid survey of the responses to stimulation at multiple single electrode conditions. Although the blinded outcomes for these patients did not show a therapeutic effect, there was a mean 40% reduction in MADRS scores after 2 years and it is noticeable that almost all patients (26 out of 30) chose to continue DBS stimulation after the trial period.

Of note, there has been variability in both the type of DBS systems/electrodes used in clinical studies and in the targeting around the ALIC, the VS and the NA. One report has described how the site for successful DBS stimulation for OCD has shifted more posterior/caudal over time, such that the target location with greatest treatment effects in this disorder appears close to the anterior commissure (AC) rather than substantially more anterior to that location as initially targeted [19]. Systematic analysis of the site of stimulation in the treatment of depression in relation to the site of implantation in this region has not occurred to date making the optimal stimulation target unclear.

One possibility in this regard is that the optimal stimulation site is further posterior than that used in most studies to date. Posterior to the NA is a potential DBS target in its own right, the bed nucleus of stria terminalis (BNST). The BNST is a small but complex structure that extends from the nucleus accumbens to the amygdala. It receives inputs from the amygdala, which are relayed to the hypothalamus and brainstem nuclei. It has multiple subsections with distinct mood relevant connections to the amygdala and the hypothalamus [20]. The juxtacapsular part has a strong inhibitory connection with the main output nuclei of the amygdala (central nucleus) suggesting that modulation of brain activity here is likely to have effects on fear and anxiety related symptoms. It is considered part of an extended amygdala complex and it is thought that it acts as a relay centre integrating autonomic, neuroendocrine and behavioural aspects of mood and anxiety related brain functions [20].

Evidence to date supports a role for the BNST in the regulation of anxiety and mood, and in the pathophysiology of mood disorders. Studies suggest that the BNST is involved in slow onset and long-lasting brain responses to sustained threats [21], rather than short term anxiety responses, a role relevant to the development of long-term affective disorders in relationship to stressful life experiences [22]. In a study that measured local field potentials in the BNST, these were noted to be substantially abnormal in patients with MDD with an excess of oscillatory alpha band activity [23]. In addition, temporary reduction of BNST activity or electrical stimulation has been directly demonstrated in an animal model to produce a significant antidepressant like effects [24] and reductions in anxiety [25]. Despite these promising suggestions, minimal research has explored the therapeutic efficacy of BNST DBS in depression. A recent case report described therapeutic benefits of this type of approach in a patient with depression and anorexia [26] and a recent case series reported some benefit of stimulation at this site in patients with OCD [27].

Aims of the study

Therefore, the purpose of this study was to describe the clinical response to DBS applied at the posterior border of the NA/in the BNST in patients with TRD. We conducted an open-label clinical study in five patients with highly refractory major depression. We used the *Medtronic 3389* electrode as this has closely spaced electrodes (1.5 mm width, 0.5 mm apart) which we hypothesised would allow capacity to differentially stimulate subregions of the posterior NA/BNST.

Materials and methods

Patients

The conduct of the study was approved by the Alfred Hospital and Royal Melbourne Hospital Human Research and Ethics committees and the protocol was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12611000889954). Patients were recruited following referral from their treating psychiatrist.

Five female patients (age range 27–60 years; $M \pm SD = 44.6 \pm 12.3$) participated (Table 1). Each had a diagnosis of major depressive disorder as confirmed via assessment by a minimum of three experienced psychiatrists (including the study psychiatrist (PF)) and the conduct of a Structured Interview for DSM IV (SCID-II). All patients were required to have current depressive symptoms of at least five years duration (current episode duration of at least two years). Detailed lifetime information on psychiatric histories was collated including reports from all relevant treating practitioners. Patients were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) [28] score of more than 25. In addition to psychiatric assessments, all patients were assessed by a clinical psychologist and a clinical neuropsychologist.

Participation of all patients was approved by the Victorian Psychosurgery Review Board, the composition of which included at least one independent psychiatrist, a neurosurgeon, a lawyer and a community member. DBS is considered a psychosurgical procedure by the Board and is available only as a 'treatment of last resort'. Their brief included assessment of the suitability of an individual

Table 1
Patient characteristics.

Patient	Age	Sex	Years of Education	Family History Mood Disorder	Age of Illness Onset	Able to Work	Prior Suicide Attempt/s	Duration Current Episode (yrs)	Number of Prior Episodes	Number of Antidepressants Trialled	Courses of ECT
1	61	F	15	Y	20	N	N	4	4	11	2
2	41	F	17	[b]	17	N	Y	7	2	10	3 and 3 yrs maintenance ECT
3	27	F	15	Y	11	N	Y	>10	[a]	13	1
4	48	F	20	Y	14	N	N	7	[a]	13	2
5	46	F	11	Y	27	N	N	4.5	2	20	6

[a] Episodes too numerous/inter-episode symptom reduction too indistinct to accurately quantify.
[b] Pt was adopted and biological family's psychiatric history is unknown.

Please cite this article in press as: Fitzgerald PB, et al., A pilot study of bed nucleus of the stria terminalis deep brain stimulation in treatment-resistant depression, Brain Stimulation (2018), https://doi.org/10.1016/j.brs.2018.04.013