Journal of Affective Disorders 203 (2016) 143–151

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Deep brain stimulation of the medial forebrain bundle: Distinctive responses in resistant depression

Albert J. Fenoy [a,*], Paul Schulz [b], Sudhakar Selvaraj [c], Christina Burrows [b], Danielle Spiker [c], Bo Cao [c], Giovanna Zunta-Soares [c], Prashant Gajwani [c], Joao Quevedo [c], Jair Soares [c]

[a] Department of Neurosurgery, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA
[b] Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA
[c] Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, TX, USA

ARTICLE INFO

Article history:
Received 21 March 2016
Received in revised form
26 May 2016
Accepted 27 May 2016
Available online 3 June 2016

Keywords:
Deep brain stimulation
Treatment resistant depression
Medial forebrain bundle
Tractography
Diffusion tensor imaging
Clinical trial

ABSTRACT

Background: Treatment resistant depression (TRD) is a serious, disabling disease. Deep brain stimulation (DBS) to the superolateral branch of the medial forebrain bundle (MFB), as proposed by Schlaepfer et al. (2013), has led to rapid anti-depressant response but has not been replicated.
Methods: In this interim analysis of an ongoing pilot study of ten subjects, we assessed the efficacy of MFB-DBS in a cohort of four TRD patients over a 52-week period using the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary assessment tool. Implanted patients entered a 4-week single-blinded sham stimulation period prior to stimulation initiation. Deterministic fiber tracking analysis was performed to compare modulated fiber tracts between patients.
Results: Intraoperatively, responder patients displayed immediate increased signs of energy and motivation upon stimulation at target. There was no significant mean change in mood during sham stimulation phase. Three of 4 patients had $>50\%$ decrease in MADRS scores at 7 days post-stimulation initiation relative to baseline. One patient withdrew from study participation. At 26 weeks, two of 3 remaining patients continue to have $>80\%$ decrease in MADRS scores. One patient failed to have response; evaluation of modulated fiber tracts revealed reduced frontal connectivity to the target region.
Limitations: This is an interim report, with limited conclusions.
Conclusion: This study of MFB-DBS shows similar rapid anti-depressant effects within the first week of stimulation as initially reported by Schlaepfer et al. (2013). Implementation of anhedonia measurements would greatly augment characterization of the striking motivational effects observed. We urge others to pursue this target to further prove efficacy.
ClinicalTrials.gov (identifier: NCT02046330) https://clinicaltrials.gov/ct2/show/NCT02046330

1. Introduction

Treatment resistance is a serious, disabling condition that affects up to 30% of patients with major depression worldwide (Nemeroff, 2007; Rush et al., 2011), leading to increased utilization of healthcare resources and overall high morbidity and mortality (Berlim and Turecki, 2007). Over the past decade, deep brain stimulation (DBS)[1] has been tested out of the need to help such patients, guided by tractography of older ablative targets and by neuroimaging studies implicating dysfunctional neural circuits. Various DBS trials in treatment resistant depression (TRD) have targeted the subcallosal cingulate gyrus (Cg25) (Mayberg et al., 2005; Lozano et al., 2008; Holtzheimer et al., 2012), ventral capsule/ventral striatum (Malone et al., 2009) and the nucleus accumbens (NAc) (Bewernick et al., 2010). These studies have yielded encouraging results that are mitigated by their variability and

* Correspondence to: Department of Neurosurgery, McGovern Medical School, University of Texas – Houston Health Science Center, 6400 Fannin, Suite 2800, Houston, TX 77030 USA.
E-mail address: albert.j.fenoy@uth.tmc.edu (A.J. Fenoy).

[1] Abbreviations used in this article: DBS, Deep Brain Stimulation; TRD, treatment resistant depression; Cg25, subgenual cingulate; NAc, nucleus accumbens; MFB, medial forebrain bundle; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; GAF, Global Assessment of Functioning; CGI, Clinical Global Impressions; HAMA, Hamilton Anxiety Scale; YMRS, Young Mania Rating Scale; dTi, diffusion tensor imaging; MRI, magnetic resonance imaging; VTA, volume of tissue activated; VTA, ventral tegmental area; PFC, prefrontal cortex; PANAS, Positive and Negative Affective Scales; EC, electrode contacts; FDG, fluoro-deoxyglucose; PET, positron emission tomography; SD, standard deviation; Hz, hertz; us, microseconds; V, volts.

http://dx.doi.org/10.1016/j.jad.2016.05.064
0165-0327/

concerns of placebo effects, which are significant (Holtzheimer et al., 2012). Longer stimulation duration on the order of years led to increased response (Lozano et al., 2008; Holtzheimer et al., 2012). One study, targeting the superolateral branch of the medial forebrain bundle (MFB) in Bonn, Germany reported a rapid antidepressant response in 57% of seven patients within one week and 85% of patients within four weeks of stimulation (Schlaepfer et al., 2013). Such response is unprecedented and has not yet been replicated (Gálvez et al., 2015). Such extreme efficacy is believed to be due to the target chosen, as the MFB lies at the center of the reward pathway connecting dopaminergic inputs from the ventral tegmental area in the midbrain (Nestler and Carlezon, 2006; Russo and Nestler, 2013) with the prefrontal cortex.

The goal of this study is to characterize the effects of MFB DBS on patients with treatment resistant depression and replicate findings from the only other existing study using this approach (Schlaepfer et al., 2013). Here, we have crucially controlled for placebo effects. This preliminary report is important for several reasons. First, as our results support the significant findings of Schlaepfer et al. (2013), it is vital to let others know now about the potential efficacy of the MFB target for treating TRD so that they may test this site sooner than would otherwise occur. Second, the suggestion here of an association between TRD and an anatomic variation in MFB-prefrontal cortical connectivity will allow others to evaluate for such variation in their patients. Third, we now have preliminary data on safety/feasibility of DBS at the MFB target, showing that it does not cause any psychiatric or neurological complications. Lastly, this report is important for suggesting improvements to characterizing the motivational behaviors tested by us and others in treatment trials for TRD. This study is part of an ongoing FDA approved clinical trial.

2. Methods and materials

This study has approval from both the University of Texas Houston Institutional Review Board (IRB) (HSC-MS-13-0004) and FDA Investigational Device Exemption (IDE) (#G130215) for the use of DBS 3389 electrode and Activa system (Medtronic, Minneapolis, MN); it is registered at ClinicalTrials.gov (identifier: NCT02046330).

2.1. Participant patients

Participants were US citizens referred from local area hospitals, clinics, or clinical trials.gov. Screening of candidates was performed using the Structured Clinical Interview for DSM-IV-TR (SCID-I) and all clinical records were assessed to obtain an accurate patient history. Twenty percent of participant patients were screening failures. Ultimately, to date, four patients with treatment-resistant depression have been enrolled in this study out of a target of ten.

Patients were considered eligible for the study if they met the following inclusion criteria, similar to that of published studies on DBS in TRD (Mayberg et al., 2005; Lozano et al., 2008; Malone et al., 2009; Bewernick et al., 2010; Holtzheimer et al., 2012; Schlaepfer et al., 2013): (a) Major depression, severe, unipolar, diagnosed by SCID-I (American Psychiatric Association, 1994), judged to be of disabling severity; (b) Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) score >21 on the first set of items; (c) Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) score >21; (d) Global Assessment of Functioning (GAF) (Jones et al., 1995) score of <45; (e) a recurrent (≥ 4 episodes) or chronic (episode duration ≥ 2 y) course and a minimum of 5 y since the onset of the first depressive episode; (f) age 22–65 y; (g) refractory to >6 weeks of multiple medication regimens; (h) refractory to >20 sessions psychotherapy; (i) refractory to a trial of electroconvulsive therapy (≥ 6 bilateral treatments). Exclusion criteria were the following: (a) current or past bipolar disorder, non-affective psychotic disorder, schizophrenia, or schizoaffective disorder; (b) severe personality disorder (assessed by SCID-II); (c) significant neurological disorder; (d) previous surgery to destroy the target region of the brain; (e) surgical contraindications to DBS.

2.2. Study protocol

Four patients have been enrolled into this study. The planned duration of this study is 52 weeks; one patient has completed 52 weeks. Psychiatric assessments were performed on a weekly basis by a psychiatrist independent of the programmer (see below). These began at one week following implantation. For the initial four weeks following surgery, the patients entered a single-blind sham stimulation phase. Evaluations were performed during this phase. At the conclusion of this period, they were unblinded and stimulation initiated.

At baseline and repeated at 12 months, cognitive functioning was assessed in study patients by a standardized neuropsychological test battery. Measures have also been selected based on specific affected brain areas involved in this DBS trial for depression. Where possible, measures selected have multiple forms used to minimize practice effects on repeated testing. The battery assesses the following domains: learning and memory, executive function, attention, psychomotor function, language, visual-spatial processing, personality, and behavior. Patients were required to maintain their same medication for 6 weeks before and 6 months after surgery.

The primary outcome measure was the anti-depressant response on the MADRS, with 50% reduction of depressive symptom severity interpreted as a positive response. Secondary outcome measures included the Hamilton Anxiety Scale (HAMA) (Hamilton, 1976), the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Clinical Global Impressions (CGI) (Busner and Targum, 2007). Each of the above were collected during the weekly assessment; the 29 point-Hamilton Depression Rating Scale $HDRS_{29}$ (Hamilton, 1967) was completed at baseline and at 6 and 12 month assessments and the GAF was completed at baseline and at 12 month evaluations.

Safety information and adverse events regarding the treatment method were recorded in a standardized document according to FDA regulations. Safety testing included neuropsychological testing to rule out cognitive effects of DBS.

2.3. Imaging and targeting protocol

Pre-operatively, MRI data were acquired on a 3-Tesla Hdxt Release 16.0 Twin speed MR imaging system (GE Healthcare, USA). A T2-weighted 3D isotropic sequence was acquired in sagittal orientation (3000 ms TR, 66.9 ms TE, FOV 24 mm, 288×288 matrix, 190 slices, thickness 1.0×1.0 mm isotropic slices). The resulting data were reconstructed to 1.00 mm^3 isotropic voxels. For diffusion tensor imaging, a spin-echo echo-planar imaging pulse sequence was applied (17,000 ms TR, 86.3 ms TE, FOV 25 mm, 128×128 matrix; 66 slices, 2.0 mm slice thickness, 32 gradient directions, 1,000 s/mm^2 b-value). The sequence resulted in 2 mm^3 isotropic reconstructed voxels, acquired in axial orientation.

The 3D inversion prepared T1-weighted gradient echo sequence (3D-MPRAGE) was acquired in axial orientation after contrast administration (gadolinium DTPA) (TR 7.0 ms, TE 3.8 ms, 8° flip angle, IRP 900, 28 mm FOV, 256×256 matrix, 180 slices, thickness 1.0×1.0 mm isotropic slices). It resulted in 1-mm^3 reconstructed voxels.