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Review article

The medial forebrain bundle as a deep brain stimulation target for treatment resistant depression: A review of published data

Juan F. Gálvez [a,b,*], Zafer Keser [c], Benson Mwangi [d], Amna A. Ghouse [e], Albert J. Fenoy [e], Paul E. Schulz [e], Marsal Sanches [f], Joao Quevedo [g], Sudhakar Selvaraj [g], Prashant Gajwani [h], Giovana Zunta-Soares [g,*], Khader M. Hasan [i], Jair C. Soares [e]

[a] UT Center of Excellence on Mood Disorders, The University of Texas Health Science Center at Houston, Houston, TX, USA
[b] Department of Psychiatry, Pontificia Universidad Javeriana School of Medicine, Bogotá, Colombia
[c] Department of Physical Medicine and Rehabilitation, TIRR Memorial Hermann Neuro-Recovery Research Center, Houston, TX, USA
[d] UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center, Houston, TX, USA
[e] The University of Texas Health Science Center at Houston, TX, USA
[f] UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, USA
[g] Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, TX, USA
[h] The University of Texas Health Science Center at Houston, TX, USA
[i] Department of Diagnostic and Interventional Imaging, Magnetic Resonance Imaging Research Division, Diffusion Tensor Imaging Lab, University of Texas Health Science Center at Houston, Houston, TX, USA

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ABSTRACT

Introduction: Despite a wide variety of therapeutic interventions for major depressive disorder (MDD), treatment resistant depression (TRD) remains to be prevalent and troublesome in clinical practice. In recent years, deep brain stimulation (DBS) has emerged as an alternative for individuals suffering from TRD not responding to combining antidepressants, multiple adjunctive strategies and electroconvulsive therapy (ECT). Although the best site for TRD-DBS is still unclear, pilot data suggests that the medial forebrain bundle (MFB) might be a key target to accomplish therapeutic efficacy in TRD patients.
Objective: To explore the anatomic, electrophysiologic, neurocognitive and treatment data supporting the MFB as a target for TRD-DBS.
Results: The MFB connects multiple targets involved in motivated behavior, mood regulation and antidepressant response. Specific phenomenology associated with TRD can be linked specifically to the superolateral branch (sl) of the MFB (slMFB). TRD patients who received DBS-slMFB reported high response/remission rates with an improvement in functioning and no significant adverse outcomes in their physical health or neurocognitive performance.
Discussion: The slMFB is an essential component of a network of structural and functional pathways connecting different areas possibly involved in the pathogenesis of mood disorders. Therefore, the slMFB should be considered as an exciting therapeutic target for DBS therapy to achieve a sustained relief in TRD patients.
Conclusion: There is an urgent need for clinical trials exploring DBS-slMFB in TRD. Further efforts should pursue measuring baseline pro-inflammatory cytokines, oxidative stress, and cognition as possible biomarkers of DBS-slMFB response in order to aid clinicians in better patient selection.

Contents

Abbreviations: MDs, mood disorders; TRD, treatment resistant depression; DBS, deep brain stimulation; MFB, medial forebrain bundle; N, neurology; Neuropsychol, neuropsychology; NS, neurosurgery; P, psychiatry.

* Corresponding authors at: UT Center of Excellence on Mood Disorders, Biomedical and Behavioral Sciences Building (BBSB), 1941 East Rd., Suite 3208, Houston, TX 77054, USA.
E-mail addresses: Juan.F.GalvezFlorez@uth.tmc.edu (J.F. Gálvez), Zafer.Keser@uth.tmc.edu (Z. Keser), Benson.Irungu@uth.tmc.edu (B. Mwangi), Amna.a.ghouse@uth.tmc.edu (A.A. Ghouse), Albert.J.Fenoy@uth.tmc.edu (A.J. Fenoy), Paul.E.Schulz@uth.tmc.edu (P.E. Schulz), Marsal.sanches@uth.tmc.edu (M. Sanches), Joao.L.DeQuevedo@uth.tmc.edu (J. Quevedo), Sudhakar.Selvaraj@uth.tmc.edu (S. Selvaraj), prashant.gajwani@uth.tmc.edu (P. Gajwani), Giovana.b.zuntasoares@uth.tmc.edu (G. Zunta-Soares), Khader.M.Hasan@uth.tmc.edu (K.M. Hasan), Jair.C.Soares@uth.tmc.edu (J.C. Soares).

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1. Introduction

Major depressive disorder (MDD) is a chronic and disabling mental illness (Kessler et al., 2005a, 2005b; Murray et al., 2012), associated with increased mortality and shortened lifespan (De Hert et al., 2011; Ferrari et al., 2013; Whiteford et al., 2013). It is characterized by the presence of low depressive mood, anhedonia, and other cognitive and somatic symptoms, as well as suicidal behavior and a significantly increased risk of cardiovascular disorders (Bostwick and Pankrazt, 2000; Charlson et al., 2013; Leung et al., 2012; Zarate et al., 2013). The number of previous episodes, residual symptoms and specific coping styles are predictors of recurrence and chronicity in previously remitted patients (Bulloch et al., 2014; ten Doesschate et al., 2010).

A growing body of evidence highlights that most patients with MDD receiving evidence-based treatments are not achieving sustained remission with first line antidepressants (McIntyre et al., 2014). Treatment resistant depression (TRD) is generally defined as an inadequate clinical response to antidepressants, administered at an effective dose for a sufficient duration (Dodd et al., 2005; Fava, 2003; Hauptman et al., 2008; Rush et al., 2003). Despite the countless advances in the treatment of depression, including newer antidepressants and multiple augmentation strategies such as mood stabilizers, atypical antipsychotics, hormone supplementation, and psychotherapies, treatment resistance remains a significant problem in the clinical management of MDD (Gaynes et al., 2009; Nelson and Papakostas, 2009; Spielmans et al., 2013; Warden et al., 2007; Zarate et al., 2013).

Therapeutic agents acting over the glutamatergic neurotransmission have emerged as an innovative option for some patients with TRD (Liebrenz et al., 2007; Machado-Vieira et al., 2009; Zarate et al., 2006). Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has shown to produce a rapid and efficacious antidepressant response within hours of a 0.5 mg/kg intravenous dose and maintained throughout the following week post-infusion (Carlson et al., 2013; Diazgranados et al., 2010a, 2010b; Zarate et al., 2010). Research efforts have focused on replicating data in both MDD and bipolar depression, alternate routes of drug delivery, identifying methods to prevent relapse following resolution of depressive symptoms, and understanding the neural basis for antidepressant action as well as its effect on neurocognition (Carlson et al., 2013; Ibrahim et al., 2011; Murrough, 2012; Nugent et al., 2014; Salvadore et al., 2010; Zarate et al., 2012).

Electroconvulsive therapy (ECT) has consistently been shown to be the most efficacious treatment for patients with severe MDD (Berlim et al., 2014; George et al., 1995; Heijnen et al., 2010; Nahas et al., 2005; Pagnin et al., 2004; Rush et al., 2005). However, ECT seems to produce more responses than remissions, with greater efficacy in patients with "pseudoresistance" rather than among those suffering from true TRD (Kellner et al., 2006; Rose et al., 2003; Sackeim et al., 1990). Moreover, relapse rates after ECT discontinuation are substantial, even in the presence of continuous post-ECT pharmacological treatment (Prudic et al., 2013; Rabheru, 2012).

Deep brain stimulation (DBS) is a novel technique available for the treatment of a number of specific treatment-resistant neurologic and psychiatric disorders (Williams and Okun, 2013). It involves the stereotactic implantation of electrodes in neuroanatomical targets where stimulation is applied via a stimulator device implanted subcutaneously (Tye et al., 2009). DBS provides a focal electrical network modulation, affecting several brain circuits of interest for neurosurgery, neurology and psychiatry involving movement, neurosensitive, neurobehavioral, cognitive, and psychiatric disorders (Dallapiazza et al., 2014; Miocinovic et al., 2013). When compared to previous ablative neurosurgical procedures such as capsulotomy or cingulotomy, DBS is considered non-destructive, reversible, and adjustable (Greenberg et al., 2008). Evidence points toward a substantial benefit of DBS for patients with severe neurological conditions such as Parkinson's Disease (PD), treatment-resistant essential tremors, and motor symptoms of dystonia and dyskinesia (Andrews, 2010; Creed and Nobrega, 2013; Hariz et al., 2013; Kalia et al., 2013; Kleiner-Fisman et al., 2006; Mentzel et al., 2012; Vidaihelt et al., 2013). Furthermore, the clinical usefulness of DBS therapy in the management of several neuropsychiatric illnesses has recently generated great interest (Hardenacke et al., 2013; Tierney et al., 2013; Tye et al., 2009; Williams and Okun, 2013). While DBS is currently FDA-approved for the treatment of obsessive–compulsive disorder (OCD), limited but promising results have been reported in regard to mood and cognitive disorders (Ashkan et al., 2013; Tye et al., 2009; Williams and Okun, 2013). Therefore, DBS is currently being tested for the treatment of patients who are non-responsive to all evidence-based therapies for TRD (Williams and Okun, 2013). Despite an incomplete understanding of the mechanisms involved in the therapeutic response, DBS seems to produce a significant reduction in symptoms and high rates of remission in TRD (Anderson et al., 2012). Multiple therapeutic DBS targets have been pursued by various research consortiums with initial promising results (Bewernick et al., 2012; Johansen-Berg et al., 2008; Malone et al., 2009; Mayberg et al., 1999; Mayberg et al., 2005; Schlaepfer et al., 2008, 2013). Recently, the medial forebrain bundle (MFB) has emerged as an additional plausible target (Coenen et al., 2011, 2012) and the first pilot study exploring the safety and efficacy of DBS for TRD has been published elsewhere (Schlaepfer et al., 2013).

The main purpose of this comprehensive review is to explore published data on the MFB for TRD-DBS. In order to accomplish our goal, we will briefly review the literature assessing the efficacy and side-effect profile of DBS for TRD. Moreover, we will illustrate extensively the anatomic, electrophysiologic, neurocognitive and treatment data supporting the role of the MFB as a target for TRD-DBS.