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EDITORIAL

Deep brain stimulation as a treatment for depressive disorder

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Depression is a frequent, complex, and debilitating condition with a high lifetime prevalence worldwide.[1,2] Gold-standard treatments for depression include psychotherapy and pharmacotherapy. Though most patients respond to these therapies, a subset (approximately 30%) does not benefit, and may be considered as having treatment-resistant depression (TRD).[1] For these patients, options are limited; neuromodulation approaches, such as deep brain stimulation (DBS), have been suggested to reduce suffering and improve quality of life.

DBS is an invasive neuromodulation technique that consists of the implantation of electrodes in deep brain targets, followed by delivery of electrical stimulation to modulate local and neurocircuitry activity.[2] In TRD, promising results have been reported with the use of DBS in distinct targets, which include the subcallosal cingulate gyrus (SCG), ventral capsule/ventral striatum (VC/VS), nucleus accumbens (nAcc), medial forebrain bundle (mFB), inferior thalamic peduncle (iTpn), and habenula (Hb).[2]

The SCG is a portion of the cingulum located ventral to the corpus callosum that includes Brodmann area 25 and parts of areas 24 and 32.[3] Imaging studies have shown distinct SCG metabolic patterns in depressive patients. Specifically, healthy subjects in a sad state or patients with depression exhibit increased cerebral blood flow and glucose metabolism in the SCG, a pattern that is reversed by antidepressant interventions.[2,3]

To date, several studies have been conducted to assess the therapeutic effects of SCG-DBS in TRD. Open-label trials and several case reports have shown long-term clinical benefits, with an overall improvement of 50%. However, randomized clinical trials (RCTs) comparing active vs. sham stimulation failed to confirm these results.[4] Recent work in which diffusion tensor imaging (e.g., patient specific tractography) and volume of tissue activation were used to refine DBS surgical targeting showed pronounced long-term response rates (between 73-82%), indicating that individual variability in fiber tracts may be critical for the antidepressant effects of this technique.[5]

The VC/VS (including the anterior limb of the internal capsule) has been approved by the U.S. Food and Drug Administration (FDA) as a target for DBS in patients with obsessive-compulsive disorder (OCD) that does not respond to standard therapies as a humanitarian device exemption. Interestingly, several studies using VC/VS-DBS for OCD have reported reductions not only in obsessive-compulsive symptoms, but also in anxiety and depression.[2] With this rationale, studies have been performed to investigate the use of VC/VS-DBS for TRD. As with SCG-DBS, the promising results of open-label studies using VC/VS-DBS (an approximate 50% reduction in depressive symptoms) were corroborated in an initial RCT comparing active vs. sham stimulation.[6] In a more recent study, patients were initially treated in an open-label fashion and subdivided into responders and non-responders.[7] Thereafter, they underwent a blinded crossover phase receiving active or sham stimulation. While significant improvement was noticed in responders receiving DBS, non-responders showed no difference in depression scores during active or sham treatment.[7] These results highlight the importance of patient selection for DBS therapy.

The nAcc, mFB, Hb, and iTpn are major structures involved in emotional processing and the neurocircuitry of depression.[8] Open-label trials of nACC-DBS and mFB-DBS have shown long-lasting response rates (nAcc-DBS: 40-50%; mFB-DBS: 75-85%). In particular, results following mFB-DBS have been quite impressive, as antidepressant responses were recorded soon after surgery.[2] A recent trial compared the effects of sham vs. active mFB stimulation for 8 weeks in blinded fashion, followed by a long-term open-label phase. In the long-term, a significant antidepressant effect was observed in all patients. During the blinded phase, both sham and active stimulation groups had significant improvement, with no major differences being recorded across groups.[9] These results are being used to guide the development of future trials.

The findings described above suggest that DBS may exert a beneficial effect on depressive symptoms. Though results from open-label studies have not been corroborated by initial blinded, randomized trials of active vs. sham stimulation, findings from recently published reports are quite encouraging. The use of refined surgical

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targeting techniques (e.g., tractography), the selection of appropriate patients, and a better understanding of the kinetics of DBS have all been shown to increase positive outcome rates. Further studies are necessary to improve this mode of therapy and increase successful outcomes.

Disclosure

The authors report no conflicts of interest.

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