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Current use of deep brain stimulation for treatment-resistant depression in different geographic regions of the world

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Abstract: *Deep brain stimulation (DBS) has emerged as a promising neurosurgical intervention for managing treatment-resistant depression (TRD). In this study, we conducted a literature review to evaluate the geographic distribution of published and ongoing clinical studies of DBS for TRD, along with documenting the anatomical sites used for electric stimulation in studies worldwide. The results showed large variation in the number of studies of DBS for TRD across different geographic regions and countries in the world, with research groups from North America and Europe contributing to 91% (n = 71) of all publications (N = 78) and 97% (n = 837) of all ongoing clinical trials (N = 867). Variation across countries also existed in the anatomical site used for stimulation, although the subcallosal cingulate gyrus was utilized most frequently overall (in 45 out of the 78 published studies), followed by the medial forebrain bundle and ventral capsule/ventral striatum including the nucleus accumbens. We conclude that DBS is increasingly being recognized worldwide as a promising intervention for TRD. To date, however, relatively few studies of DBS for TRD have been conducted by research groups from countries in Asia and Australasia. Clinical studies of DBS for TRD have come so far mainly from research groups located in North America and Europe, which poses a threat to the external validity of many reported study results, as well as representing a major challenge for future research.*

Keywords: *Deep Brain Stimulation, Treatment-Resistant Depression, Therapy*

1. Introduction

Major depressive disorder (MDD) is a common and clinically challenging psychiatric disorder associated with a lower quality of life, impaired daily functioning, and even a shortened life expectancy. While many patients with MDD clinically respond to evidence-based pharmacological or psychological therapies, about 20% of patients do not respond or display an insufficient response to these conventional treatments, including the combination of antidepressant medication and cognitive behavioral therapy. As a result, there is a need for alternative therapeutic approaches that can help to manage the symptoms of these patients who suffer from so-called treatment-resistant depression (TRD) [1,2]. One promising approach to symptom management of TRD involves deep brain stimulation, which has been applied successfully to manage symptoms of certain neurological disorders, most notably Parkinson's disease. DBS is a neurosurgical procedure aimed at relieving symptoms by delivering electric stimulation to specific brain regions and networks implicated in the pathophysiology of the disease. In recent years, DBS has also been used for symptom management of severe and treatment-resistant psychiatric disorders. So far, DBS has been approved by the U.S. Food and Drug Administration (FDA) as a last-resort treatment of select cases of obsessive-compulsive disorder, but clinical efficacy of DBS for TRD has not yet been well-established.

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The first studies evaluating the potential clinical usefulness of DBS treatment for TRD were reported by research groups from Canada [3-5] and Germany [6]. Lozano et al. examined 20 patients with TRD before and after treatment with DBS of the subcallosal cingulate gyrus (SCG). They reported significant improvements in depressive symptoms following SCG-DBS, which were largely maintained at 12-month follow-up (FU). McNeely et al. examined the neuropsychological status of 6 patients with TRD before and after SCG-DBS [5]. Treatment with SCG-DBS was found to have no significant adverse side effects on patients' neuropsychological functioning, except for some effects on motor function at 1- and 6-month FU, which were no longer evident at 12-month FU. Instead, McNeely et al. observed that patients' cognitive functioning improved over the SCG-DBS treatment course, which was accompanied by, but not correlated with, mood improvement. Finally, Schlaepfer et al. observed improvements in depressive symptoms in 3 patients with TRD following DBS of the nucleus accumbens (Nac) [6].

After these initial reports, a total of 17 studies originating from Canada were published, all focusing on the SCG as the DBS target of interest for TRD treatment [4,7-18]. Moreover, DBS studies emerged from other countries, including the USA and China, which utilized other DBS targets for TRD treatment, including the inferior thalamic peduncle (ITP), ventral capsule/ventral striatum (VS/VC), medial forebrain bundle (MFB), habenula (HB), and bed nucleus of the stria terminalis (BNST) [19-25]. While employing different DBS targets, most of these studies were focused on limbic areas and networks implicated in the pathophysiology of TRD and known to mediate motivation, memory, and emotional behavior.

In the present study, we evaluated the geographic distribution of the research studies that have been published so far on DBS treatment for TRD. This distribution does not seem to be balanced, with research groups from North America and Western Europe being the main contributors to the field. Our study is descriptive in nature and does not consider the complex economic, cultural, and social factors that are involved in the availability, access, acceptability, and actual use of DBS for TRD in different countries and geographic regions of the world. In addition, we evaluated the various DBS targets used for TRD treatment as a function of country and geographic region. Finally, by examining the number of ongoing clinical trials, we assessed whether research groups from Asia, Australasia, and other geographic regions of the world are catching up behind their colleagues from North America and Europe.

2. Method

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA [26]). We conducted a literature search by entering the terms 'DBS' and 'treatment-resistant depression' into the Title/Abstract field of the PubMed database and the terms 'TRD' into the Condition or Disease field and 'DBS' in the Other Term field of the database of Clinical Trials to identify published clinical studies and ongoing clinical trials of DBS for TRD worldwide. We excluded reviews, animal research, papers not written in English, and clinical trials that were suspended or withdrawn. The publications included were double-checked manually to ensure that no other studies were missed. Subsequently, we categorized the included study publications and ongoing clinical trials according to the country indicated in the institutional affiliation of the corresponding author.

3. Results

3.1. Publications and ongoing clinical trials of DBS for TRD by geographic region and country

During the systematic searching based on the searching strategies, 312 references from the electronic databases and 36 additional records from other resources were identified and the last searching was performed on April, 3, 2022. After screening stage where the titles and abstracts of the retrieved records were reviewed, 50 records were excluded due to duplication or non-relevant content (Figure 1). Of the remaining references, 78 studies were retrieved and included in this study.

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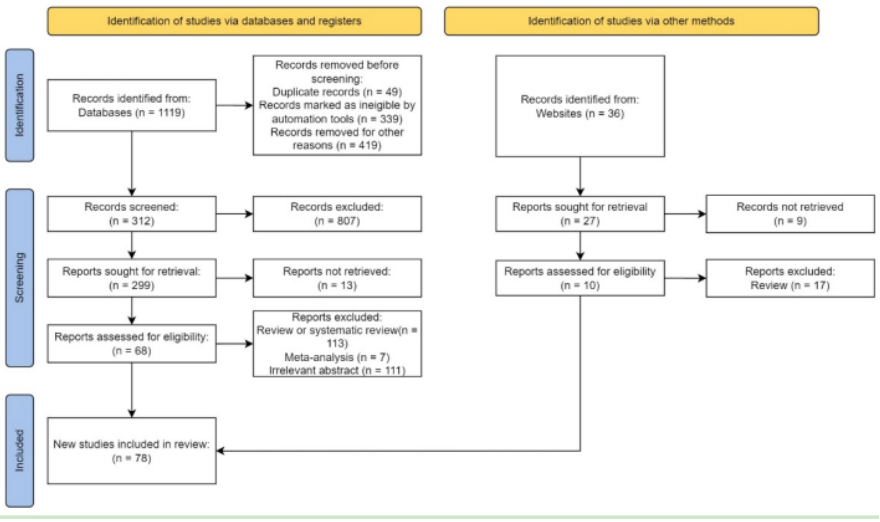

Figure 1: PRISMA flowchart. This flowchart represents the literature selection and elimination process taken to obtain the final 78 studies that were included in this review

In the total 78 published reports of DBS for TRD (Blue histograms in Figure 2), as expected, publications by research groups from North America (USA: n = 24, 31% of all papers; Canada: n = 18, 23%) and Europe (n = 29, 37%) contributed most to the published literature, amounting to 91% (71 out of 78) of all papers on DBS for TRD. Among the countries in Europe, research groups from Germany produced the most papers (n = 15, 19% of all papers), followed by Spain (n = 7, 9%). The remaining publications (9% of all papers) were produced by research groups from Asia (China: n = 3, 4%), Australasia (Australia: n = 2, 3%), Middle East (Israel: n = 1, 1%), and Central and South America (Mexico: n = 1, 1%; Argentina: n = 1, 1%) (Figure 2).

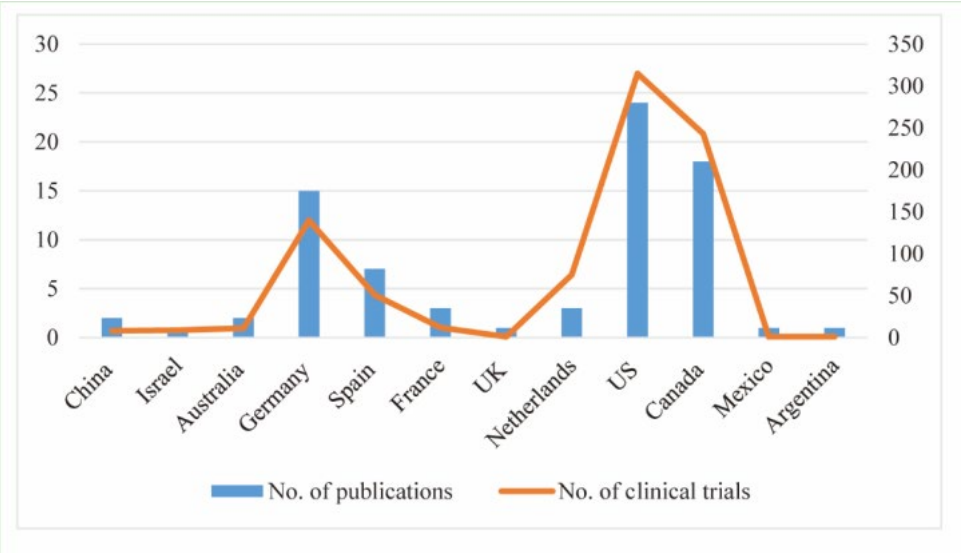

Figure 2: The number of published papers and ongoing clinical trials of deep brain stimulation for treatment-resistant depression by country

A similar picture emerged after we classified a total of 867 ongoing clinical trials of DBS for TRD by geographic region (Orange line in Figure 2). Again, most ongoing clinical trials originated from research groups located in North America (USA: n = 315, 36% of all ongoing trials; Canada: n = 243, 28%) and Western and Southern Europe (primarily in Germany: n = 140, 16%; Netherlands: n = 75, 9%; and Spain: n = 51, 6%), amounting to 97% (837 out of 867) of all ongoing trials worldwide (Figure 1). The remaining ongoing trials (3% of all trials) emerged mainly from research groups in Australia (n = 11, 1.3%), Israel (n = 9, 1.0%), and China (n = 8, 0.9%) (Figure 2).

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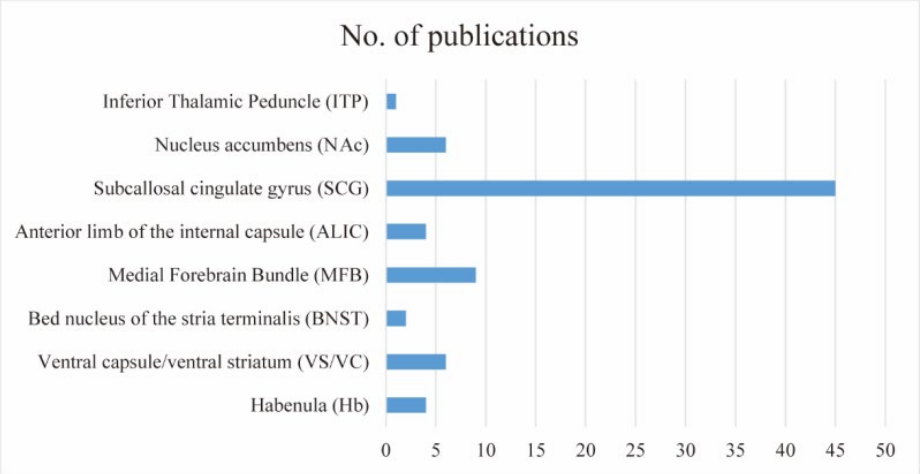

Figure 3: Anatomical targets used in published clinical studies of deep brain stimulation for treatment-resistant depression

3.2. Anatomical targets used in published clinical studies of DBS for TRD

The SCG has mostly been used (in 45 out of the 78 published studies) as the DBS target for TRD worldwide, followed by the MFB and VC/VS including the nucleus accumbens (NAc) (Figure 3). The SCG has not been utilized as the DBS target of interest in all countries, though. The SCG has been the most common target for TRD among research groups from Canada, USA, Spain, UK, Israel, and Argentina, as well as being a frequently used DBS target in Germany and France (Figure 3). By contrast, the SCG has not received attention as a DBS target for TRD by research groups from China, Australia, the Netherlands, and Mexico, which focused on the HB, BNST, anterior limb of the internal capsule (ALIC), and inferior thalamic peduncle (ITP), respectively. So far, the MFB has been used only by research groups from Germany and the USA (Figure 4).

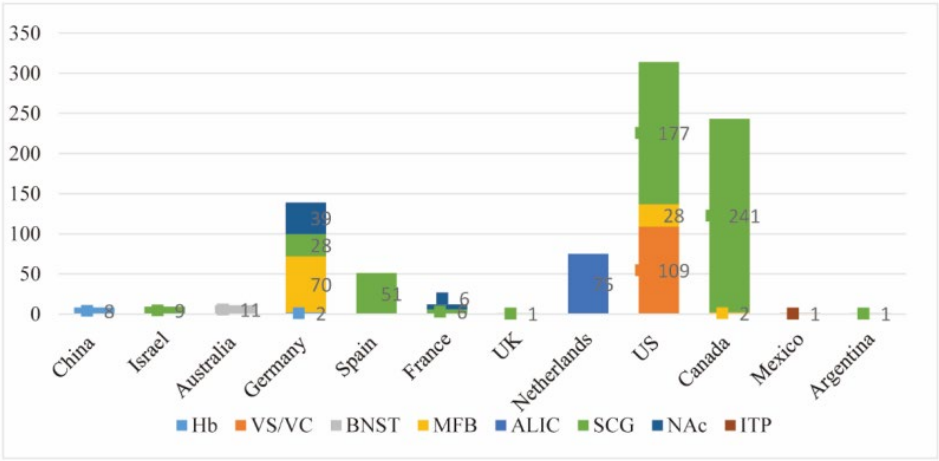

Figure 4: Anatomical targets used in published clinical studies of deep brain stimulation for treatmentresistant depression by country. Hb, Habenula; VS/VC, Ventral Capsule/Ventral Striatum; BNST, Bed Nucleus of the Stria Terminalis; MFB, Medial Forebrain Bundle; ALIC, Anterior Limb of the Internal Capsule; SCG, Subcallosal Cingulate Gyrus; NAc, Nucleus Accumbens; ITP, Inferior Thalamic Peduncle

3.3. Studies of DBS for TRD in Asia and Australasia

Relatively few studies of DBS for TRD have been conducted so far by research groups from countries in Asia (China: n = 2) and Australasia (Australia: n = 2). Although the number of clinical trials initiated has grown in these geographic regions (China: n = 8 ongoing trials; Australia: n = 11), this will probably amount to only a small fraction of the total research volume produced by research groups from North

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America and Europe. This situation, however, may change in the near future. The past three years have seen a sharp rise in the number of DBS centers in China, with more than hundred centers devoted to patients with TRD. Although used only for select cases, the large number of patients treated with DBS for TRD in China will likely offer unique research opportunities and outcome data relevant to clinical efficacy, outcome prediction, and patient stratification, basic clinical issues that remain to be resolved.

4. Discussion and Conclusions

This study evaluated the geographic distribution of published and ongoing clinical studies of DBS for TRD. Two main findings emerged. First, the distribution of research into DBS for TRD varies significantly across different geographic regions and countries, with research groups from North America and Europe contributing most to the field. This state of affairs forms a major challenge for the future because results obtained from patient groups in North America and Europe cannot automatically be generalized to patients living in other geographic regions and cultures of the world. Second, we identified a large number of clinical trials ongoing worldwide (N = 867) relative to the number of published clinical studies (N = 78), indicating that DBS is increasingly being recognized around the world as a potentially effective intervention for TRD. Indeed, we expect that DBS along with noninvasive brain stimulation techniques, such as transmagnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), will provide a valuable complementary or alternative approach for managing psychiatric disorders, including TRD. The challenge for the future lies in making the clinical benefits from neuromodulation available to psychiatric patients living in all geographic regions of the world.

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