Received: January 18, 2012 Accepted: January 31, 2012

(onlinelibrary.wiley.com) DOI: 10.1111/j.1525-1403.2012.00439.x

Deep Brain Stimulation in China: Present and Future

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Objective: We reviewed the clinical applications, academic communications, and specialized training required for deep brain stimulation (DBS) in China. Current problems and possible solutions also were discussed.

Materials and Methods: We reviewed all literature on DBS by Chinese authors. The WANFANG and PUBMED (2000–2009) data bases were searched to collect publications on DBS by Chinese authors. To compare the Chinese academic publications on DBS with those by American authors, data from publications by American authors also were collected. Information on the DBS population as categorized by year, by province, and by indication was collected from the Medtronic Neuromodulation data base.

Results: From 2000 to 2009, there were 187 publications on DBS in Chinese journals and 23 in English journals by Chinese authors. American peers contributed 569 articles during the same period. In total, 2082 patients received DBS treatment in China by the end of 2009.

Conclusions: DBS has evolved significantly during the past decade in China. There are still several problems. The advent of Chinese homemade DBS hardware, multidisciplinary cooperation, and the establishment of guidelines and regulations for DBS will improve the application of this surgical treatment in China.

Keywords: Deep brain stimulation, dystonia, neurostimulation, Parkinson's disease, review article

Conflict of Interest: Dr. Jian-Guo Zhang is a consultant for Medtronic. The other authors reported no conflicts of interest. The planning, conduct, and conclusions of this study are those of the authors and not of the company.

INTRODUCTION

China is the largest developing country with a population of 1.3 billion, which accounts for 20% of the total global population. Health conditions in China have improved tremendously over the past three decades. However, due to inadequate insurance coverage, high out-of-pocket payments, escalation of costs, inefficient use of scarce resources, and other problems (1), the performance of China's health system cannot meet the people's demands. A survey in 2003 showed that the urban and rural health-system coverage only included 88% and 64% of the population, respectively (2).

Deep brain stimulation (DBS) was initially applied in psychotic patients in 1952 (3) and then in intractable pain patients in the 1960s. It began to flourish in the 1990s as a vital treatment for movement disorders and psychiatric diseases, including Parkinson's disease (PD), essential tremor (ET), dystonia, and obsessive-compulsive disorder (OCD). In the 1990s, China lagged behind western countries in the development of DBS. The first Chinese article introducing DBS was published in 1995 (4), and the first DBS surgery was performed in a PD patient in 1998 (5). In the 2000s, although DBS has boomed in China and become well accepted as a treatment modality for patients with certain movement disorders, due to the high cost of implantable hardware, it is still unaffordable for the majority of patients. We believe that with the economic development in China and the advent of DBS hardware made in China, more and more Chinese patients will be able to afford treatment with this medical technology. In the present article, we reviewed the development of DBS in China over the past decade, discussed the remaining problems, and focused on possible solutions for the future.

MATERIALS AND METHODS

A computerized search of the WANFANG data base from 2000 to 2009 was conducted for publications in Chinese using the keywords *deep brain stimulation*, *pallidal stimulation*, *thalamic stimulation*, and *subthalamic stimulation*. The PUBMED data base also was searched for publications in English using the query *(deep brain stimulation[MeSH] OR pallidal stimulation OR subthalamic stimulation OR thalamic stimulation) AND China[AFFL]*. We also searched the PUBMED data base using the query *(deep brain stimulation[MeSH] OR pallidal*

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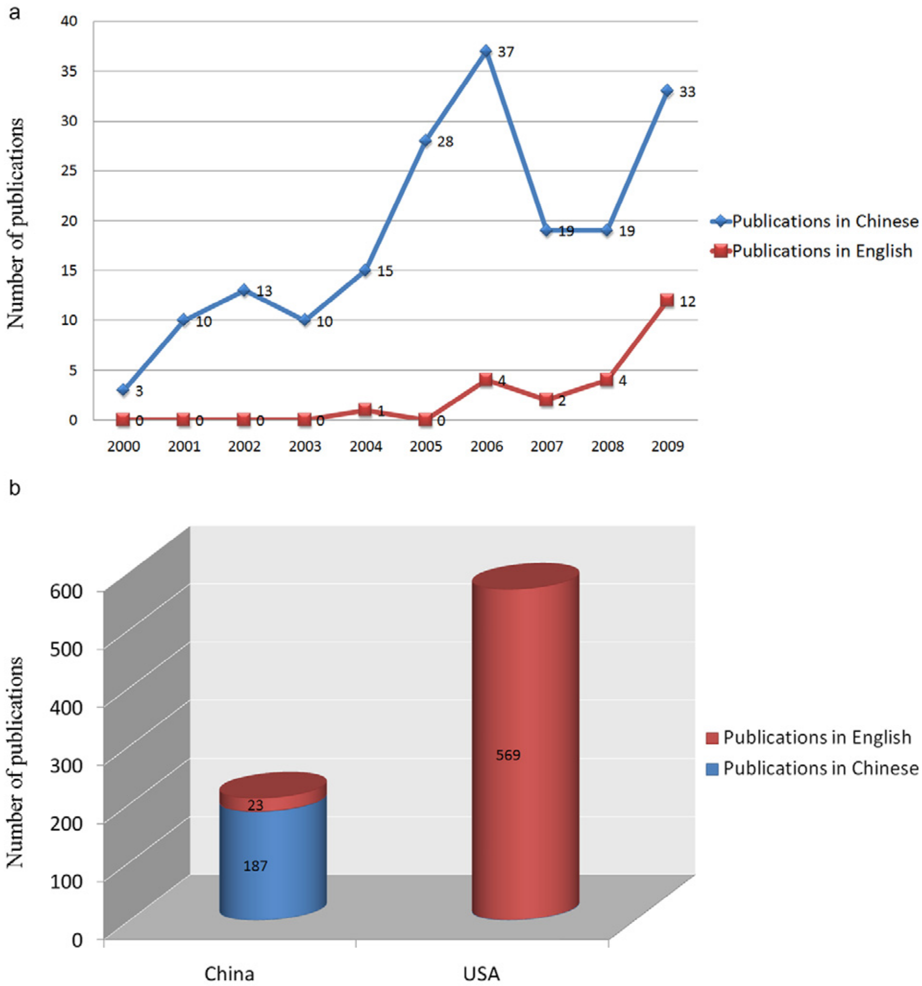

Figure 1. a. Annual number of publications by Chinese authors over the past decade; b. comparison of the number of publications on DBS between China and USA over the past decade. DBS, deep brain stimulation.

stimulation OR subthalamic stimulation OR thalamic stimulation) AND USA[AFFL] to compare the Chinese academic publications on DBS with those by American authors. The title, abstract, and address of the corresponding author were reviewed; only those articles on DBS with Chinese or American corresponding authors were included in our study. A data extraction table was created to code the articles by Chinese authors. This table included authors, title, year of publication, corresponding author's institution, indications for DBS, and article type. Because only Medtronic implantable hardware is approved for DBS in China, information on the DBS population by year, by province, and by indication was collected from the Medtronic Neuromodulation data base. The data from Medtronic were approved for academic communication by the Academic Board of Beijing Tiantan Hospital.

RESULTS

From 2000 to 2009, there were 187 publications on DBS in Chinese and 23 in English journals by Chinese authors (Fig. 1a). According to the indications for DBS, there were 131 (62.38%) articles focusing on PD, 17 (8.10%) focusing on dystonia, 13 (6.19%) focusing on epilepsy, 7 (3.33%) focusing on psychiatric diseases, 7 (3.33%) focusing on drug addiction, 15 (7.15%) focusing on other neurologic diseases, such as ET and Huntington's disease (HD), and 20 (9.52%) focusing on multiple diseases (Fig. 2a). With respect to article type, 105 (50.00%) were clinical studies, 54 (25.72%) were reviews, 36 (17.14%) were animal studies, and 15 (7.14%) were case reports (Fig. 2b). According to the institutions of the corresponding authors, Beijing Tiantan Hospital, Changhai Hospital, Xuanwu Hospital, Ruijin Hospital, Tangdu Hospital, Anhui Provincial Hospital, and Zhujiang Hospital contributed 29 (13.81%), 28 (13.33%), 22 (10.48%), 16 (7.62%), 15 (7.14%), 7 (3.33%), and 3 (1.43%) articles, respectively (Fig. 2c). There were 569 articles on DBS by American authors during the same period (Fig. 1b). Data from Medtronic Neuromodulation showed that 2082 patients had received DBS treatment in China by the end of 2009, including 1684 (80.89%) PD patients, 156 (7.49%) dystonia patients, 31 (1.49%) ET patients, 94 (4.51%) patients with other diseases, such as OCD, Tourette's syndrome (TS), and anorexia nervosa, and 117 (5.62%) patients with unclassified diseases (Fig. 3b).

DISCUSSION

Clinical Applications of DBS in China

The application of DBS in China has developed rapidly (Fig. 3a): 312 patients underwent DBS treatment from 1998 to 2003, while the

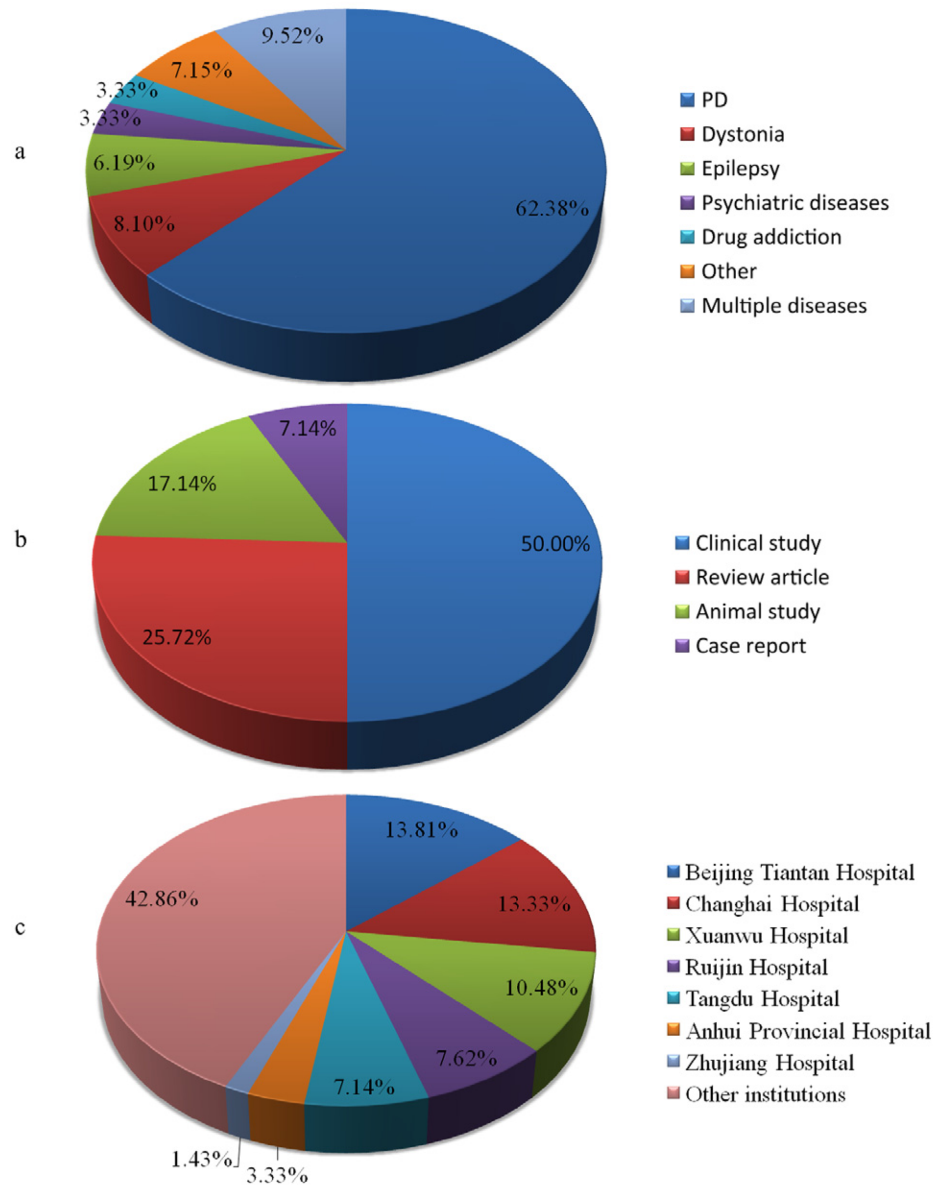

Figure 2. Distribution map of Chinese publications on DBS based on a. indication, b. article type, and c. institution of the corresponding author. DBS, deep brain stimulation; PD, Parkinson's disease.

number reached 1770 from 2004 to 2009. We postulate that the gradually increasing acceptance of the concept of DBS by neurologists and the increase in the number of DBS centers might account for this development. Similar to the situation in other countries, PD patients account for the largest DBS population, followed by dystonia (6–8) and ET (9) patients (Fig. 3b).

The use of surgical procedures reported by those Chinese authors was similar. The entire DBS procedure consists of two stages: the electrode implantation stage and the implantable pulse generator (IPG) implantation stage. At the beginning of the surgery, the head frame was first secured to the cranium of the patient and was followed by a magnetic resonance imaging (MRI) scan. MRI data were transferred to the surgical planning system to calculate the coordinates of the target nuclei. Frame stereotactic systems were widely applied for DBS in China. Although frameless stereotactic systems were introduced to China, there was no literature on the use of a frameless stereotactic system for DBS. The electrode implantation procedure was performed under local anesthesia whenever possible to evaluate the improvement of symptoms and side-effects. Microelectrode recordings also were widely used to confirm the precise location of the targets. The C-arm x-ray system was used in some centers to avoid electrode dislocation after fixation (10–12). In some centers, IPG was implanted in all patients immediately after the first stage without postoperative trial stimulation (13,14). In other centers, trial stimulation was used in patients with dystonia and some other diseases to confirm that the surgery was effective. Only patients with satisfactory outcomes were able to receive IPG implantation during the second stage (7,15–17). Postoperative care including programming and medication adjustment was provided by neurosurgeons and neurologists at outpatient clinics. Table 1 shows the most commonly used DBS instruments in China (12,18–21). Although the introduction of DBS in China was later, a lot of our work

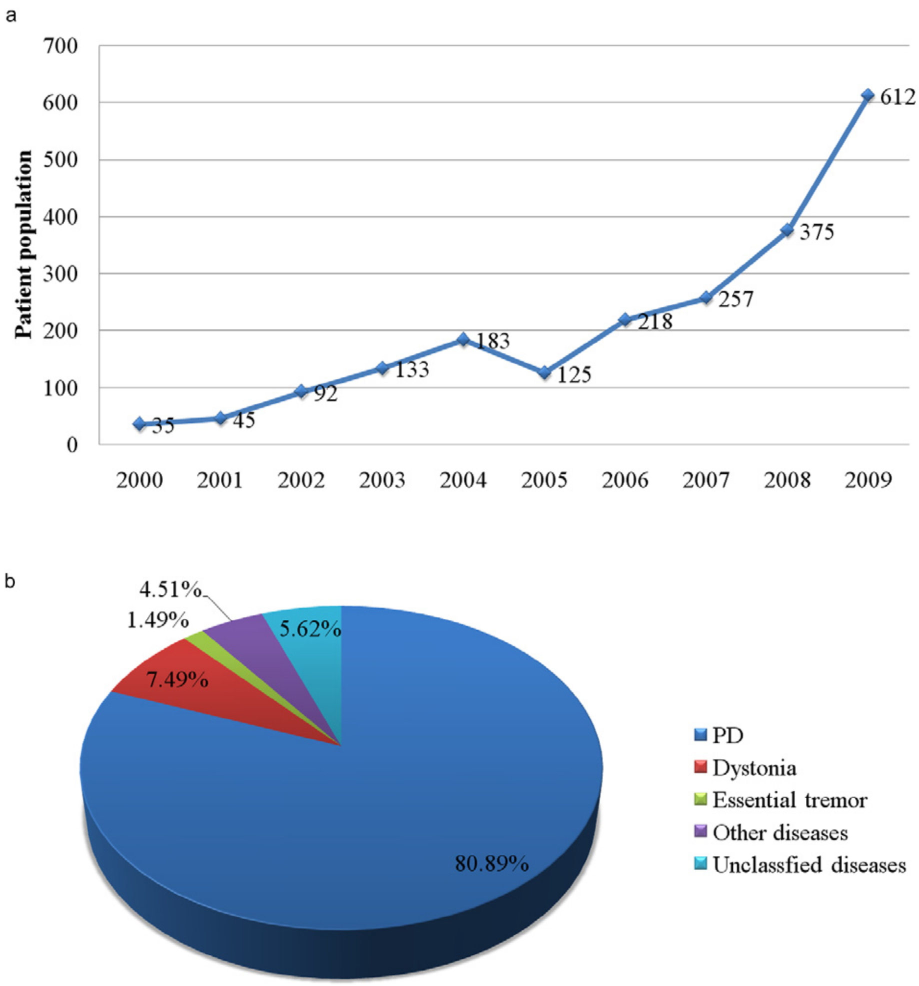

Figure 3. a. Annual number of DBS patients in China during the past decade; b. distribution map of cases with different indications treated with DBS in China by the end of 2009. DBS, deep brain stimulation; PD, Parkinson's disease.

Table 1. Instruments Commonly Used in Chinese DBS Centers.

DBS center	Stereotactic system	MER system	Stimulation electrode	IPG
Beijing Tiantan Hospital	Leksell	Medtronic Leadpoint	Medtronic quadripolar electrode	Medtronic Kinetra 7428 or Soletra 7426
Xuanwu Hospital	Cosman-Roberts-Wells	Alpha Omega Engineering		
Ruijin Hospital	Leksell	Medtronic Leadpoint		
Changhai Hospital	Cosman-Roberts-Wells	FHC		
Tangdu Hospital	Cosman-Roberts-Wells	FHC		
Anhui Provincial Hospital	Leksell	FHC		
Zhujiang Hospital	Cosman-Roberts-Wells	FHC		

DBS, deep brain stimulation; IPG, implantable pulse generator; MER, microelectrode recording.

achieved satisfactory outcomes. For example, for the subthalamic nucleus (STN) DBS in the treatment of PD (22–26), the 6- to 19.3-month follow-up results suggested that patients significantly improved their Unified Parkinson's Disease Rating Scale Motor Score (38.2–62.3%) (Table 2). Our data were similar to those reported by a meta-analysis that demonstrated that the mean improvement was 54.3% (27). However, there were also sporadic reports of unsatisfactory outcomes, side-effects, and complications after DBS treatment (28–30) (Table 3). The complications were similar to those reported by the American peers, while the complication rates were lower in Chinese publications (14.9% and 16.3% reported by Hu et al. and Li et al., respectively, vs. 21%, 27.7%, and 25.9% reported by Beric et al., Bhatia et al., and Lyons et al., respectively) (31–33).

Because the expense of DBS implantable hardware has not been covered by medical insurance in China, the out-of-pocket cost for each patient reaches approximately $30,000 (bilateral DBS). Compared with the per capita national income in China, which was $2770 in 2008 (data from the National Bureau of Statistics of China),

Table 2. Surgical Effects of Bilateral STN DBS in Chinese Studies.

Authors and year	No. of patients	Mean patient age (years)	Duration of follow-up (months)	Baseline UPDRS motor score*	Postoperative UPDRS motor score†	% improvement
Wang et al., 2005	41	59.8 ± 6.1	12	47.9 ± 14.5	29.6 ± 11.4	38.2
Hu et al., 2005	33	67	7.3	N/A	N/A	62.3
Zhang et al., 2006	46	63.8 ± 7.8	19.3 ± 8.4	49.2 ± 19.3	29.7 ± 13.7	39.6
Liang et al., 2006	15	64.3 ± 7.9	12	42.1 ± 3.3	24.6 ± 1.8	41.6
Guo et al., 2008	15	61.1 ± 7.8	6	49.8 ± 9.7	26.6 ± 7.1	46.6

*Medication off.
†Medication off and stimulation on.
DBS, deep brain stimulation; N/A, not available; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 3. Complications of DBS in PD, as Reported by Chinese Studies.

Authors and year	Operation method related	DBS equipment related	Stimulation related	Complication rate
Sun et al., 2003	Intracranial hemorrhage, electrode misplacement, pocket seepage	Electrode migration, electrode fracture, device malfunction	Dyskinesia, diplopia, dystonia, headache, dysarthria, paresthesia	N/A
Li et al., 2007	Intracranial hemorrhage, multiple brain infarction	Canker, electrode dislocation	Imperative side-effects	16.3%
Hu et al., 2008	Electrode misplacement, infection, skin erosion, pocket seepage	N/A	Dyskinesia, hypomnesia, emotional changes, hoarseness, dysphagia	14.9%

DBS, deep brain stimulation; N/A, not available; PD, Parkinson's disease.

the medical expense is a heavy burden for the DBS candidates. Due to the high expense of implantable hardware, some DBS candidates have to receive ablation surgery.

Although there are 31 provinces in mainland China, only a limited number of DBS centers from a few large cities can provide this treatment. These cities, including Beijing (Beijing Tiantan Hospital, Capital Medical University and Xuanwu Hospital, Capital Medical University), Shanghai (Ruijin Hospital, Shanghai Jiaotong University and Changhai Hospital, Second Military Medical University), Guangzhou (Zhujiang Hospital, Southern Medical University), Hefei (Anhui Provincial Hospital, Anhui Medical University), and Xi'an (Tangdu Hospital, Fourth Military Medical University), are national central cities in mainland China. Some DBS centers in Beijing and Shanghai present the highest level of DBS in China. However, this treatment has not been applied in a lot of other medium-sized cities, even in some provincial capitals. Most patients from those cities have to go to the above-mentioned national central cities for DBS treatment. For example, the following data are from our institution: 82 patients received DBS treatment at our institution in 2009. Among them, 67 patients came from other cities, accounting for 81.71%. Figure 4 shows the distribution of DBS centers and the DBS population in different Chinese provinces in 2009. This figure indicates that the number of DBS surgeries differs greatly among various regions due to the imbalance in economic development. The southeast coastal provinces with developed economies have larger DBS populations than the west-middle provinces.

Academic Communications on DBS in China

From 2000 to 2009, there were 210 publications on DBS in China. Most studies were published in Chinese journals and domestic symposiums. During this period, the early literature focused on the clinical application of DBS in PD patients, including issues related to target selection (34), electrode localization (11,20), stimulation parameter programming (5), and the analysis of the side-effects and complications of DBS (28). The application for ET (35–38), which Chinese authors rarely mentioned, as well as the application for PD (39–41), garnered ample attention in early DBS articles by American authors. Because the concept of DBS was not generally accepted at that time, some authors compared the effects and complications between DBS and ablation surgery. It was concluded that bilateral DBS was the optimal surgical treatment for advanced PD patients and that ablation could only be applied with careful consideration due to the frequent occurrence of complications (10). The disease spectrum of DBS has become much wider over the past decade. New indications, including dystonia (6,8,17), TS (14), anorexia nervosa (42), and drug psychological dependence (43), have been investigated by Chinese authors. A case report showed that a patient with Meige's syndrome received bilateral STN DBS and that a short-term follow-up of three months showed an 89% improvement on the Burke-Fahn-Marsden Dystonia Movement Scale (44). Sun and his colleagues have treated more than 50 patients with anorexia nervosa by nucleus accumbens DBS and anterior internal capsule capsulotomy since 2006. Sixty-nine percent of patients restored their body mass index to within the normal range (more than 17.5 kg/m^2), and significant improvements in obsessive-compulsive and anxiety symptoms were observed in many patients (42). In Xu et al.'s study, a patient with a greater than five-year history of opiate drug taking, who had undergone five ineffective detoxifications, was admitted for treatment. The patient met the Chinese Classification of Mental Disorders Version 3 criteria for an opiate-induced psychiatric disorder and the *Diagnostic and Statistical Manual of Mental Disorders* Version 4 criteria for substance dependence and abuse. The patient ceased drug use shortly after bilateral nucleus accumbens DBS. No relapse occurred during the three-month follow-up period. Psychological assessment indicated that

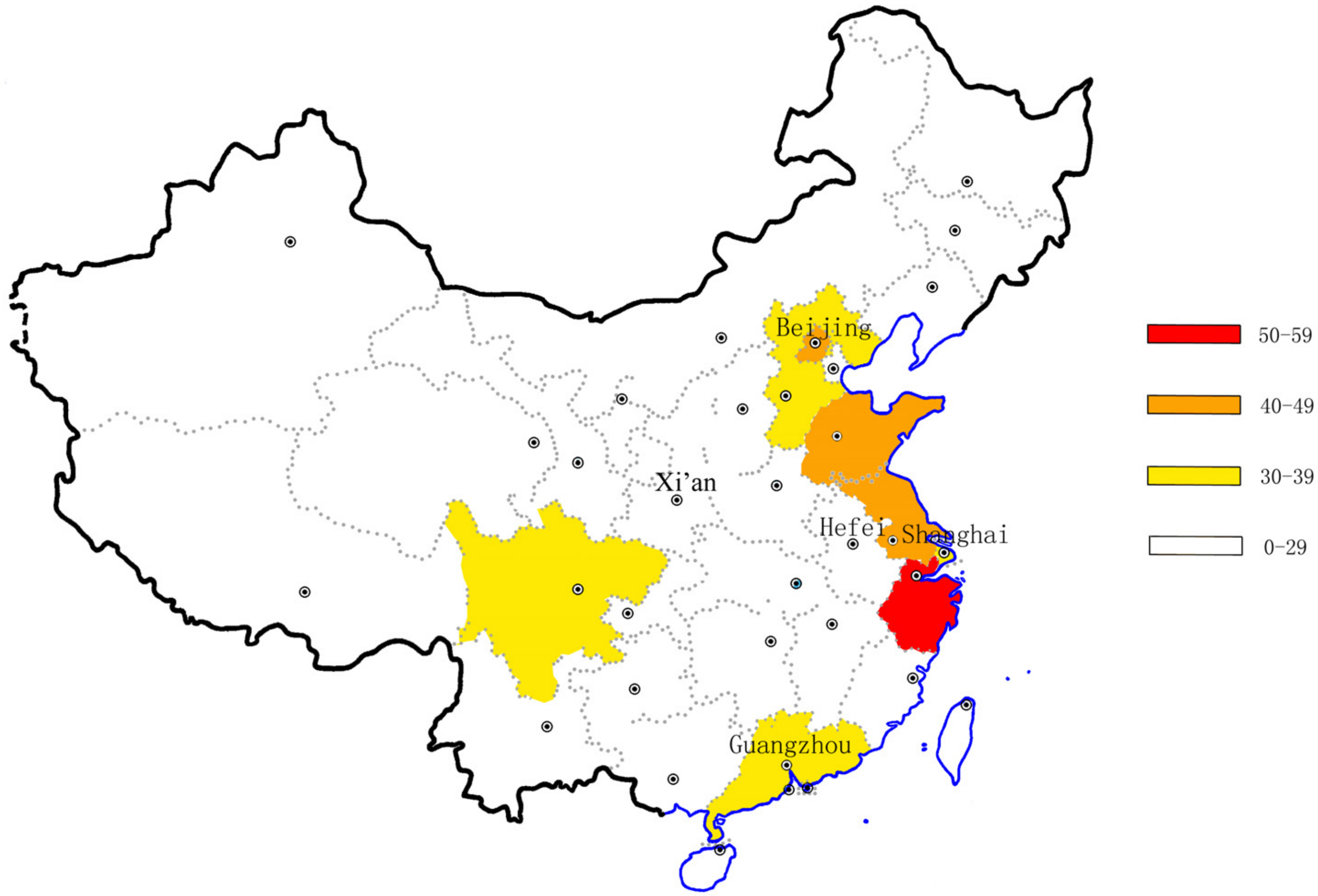

Figure 4. Distribution map of DBS centers in Mainland China and the population of patients who received DBS treatment in different provinces during 2009. The color intensity represents the number of DBS cases; the blue line represents the coastline. DBS, deep brain stimulation.

there were no obvious changes in psychohygiene, personality, or intelligence (43). To our knowledge, this is the first report on DBS in the treatment of psychological drug dependence. Animal experiments also have been performed to investigate various theories of DBS in the treatment of PD (45,46), drug addiction (47–50), epilepsy (51–53), and HD (54). However, there were huge academic gaps between China and other developed countries. In addition to the lag in terms of publishing-related studies, Chinese authors also published fewer reports than their American peers (Fig. 1b). Furthermore, the spectrum of diseases that have been treated with DBS was narrower (5,9,14,17,35,37,39,43,47,55–72) (Table 4).

There are three academic committees for DBS specialists in China. The Chinese Neurosurgical Society and the Chinese Congress of Neurosurgical Surgeons, which were established in 1986 and 2004, respectively, both hold annual national academic conferences, which include stereotactic and functional forums. The Chinese Neuromodulation Society, which was founded in 2010, is the Chinese chapter of the International Neuromodulation Society. This is a committee dedicated to neuromodulation, including DBS, in China.

Specialized Training in DBS

Chinese neurosurgeons who are interested in DBS can obtain specialized training through medical educational programs, including postgraduate clinical training and visiting scholar programs. As previously mentioned, there are several DBS centers in China, but only institutions, such as Beijing Tiantan Hospital, Xuanwu Hospital, and Ruijin Hospital, can provide specialized surgical training in DBS.

Current Problems and Possible Solutions

With an aging society, China is facing a large population of PD patients; an epidemiologic survey indicated that there were 1.7 million people aged 55 years or older suffering from PD in mainland China (73). Many will become drug resistant after five to seven years of intense levodopa usage and require surgical intervention. As previously mentioned, from 1998 to 2009, only 2082 patients received DBS treatment. The high out-of-pocket expense of implantable hardware, we believe, might be the chief obstacle in DBS implantation. A similar but much cheaper (approximately $15,000 for bilateral stimulation) homemade device (Fig. 5) that was developed by researchers from Tsinghua University is under clinical trial. Thirty-eight PD patients have been implanted with homemade hardware since November 26, 2009 (personal communication with Professor Lu-Ming Li of Tsinghua University). With the decrease in the cost of hardware, more Chinese patients will be able to afford this treatment in the future.

Although DBS is well accepted by neurologists as a treatment modality for movement disorders, its effects on psychiatric diseases including refractory depression and OCD have not been recognized

Table 4. The Spectrum of Diseases Treated With DBS in the Chinese and American Original Literature (Clinical Study, Case Report, or Animal Study)*.

		PD	Dystonia	ET	Epilepsy	TS	OCD	TRD	Drug addiction
China	Clinical study	Guan et al., 2001	Sun et al., 2006	Li et al., 2005	N/A	Zhang et al., 2009	Chen et al., 2008	N/A	N/A
	Case report	N/A	Zhang et al., 2004	N/A	N/A	N/A	N/A	N/A	Xu et al., 2005
	Animal study	Cao et al., 2005	N/A	N/A	Zhu-Ge et al., 2007	N/A	N/A	N/A	Liu et al., 2008
USA	Clinical study	Ondo et al., 1998	Halbig et al., 2005	Hubble et al., 1996	Kerrigan et al., 2004	Maciunas et al., 2007	Abelson et al., 2005	Malone et al., 2009	N/A
	Case report	Iacono et al., 1995	Umemura et al., 2004	Lucas et al., 2000	Handforth et al., 2006	Flaherty et al., 2005	Anderson and Ahmed, 2003	N/A	N/A
	Animal study	Chang et al., 2003	N/A	N/A	Velisek et al., 2002	N/A	McCracken and Grace, 2007	N/A	Vassoler et al., 2008

*All of the records were the first reports on the different applications of DBS by Chinese or American authors.
N/A, not available; ET, essential tremor; TS, Tourette's syndrome; OCD, obsessive-compulsive disorder; TRD, treatment-resistant depression; DBS, deep brain stimulation; PD, Parkinson's disease.

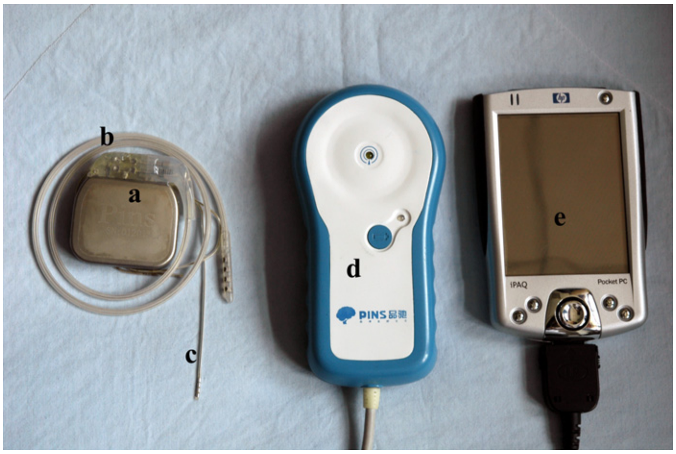

Figure 5. The DBS hardware made in China, also called a Programmable Implantable Neuro-Stimulator, is now in clinical trials. This system was developed by researchers from Tsinghua University and made by Beijing Pingchi Medical Treatment Equipment, Ltd. The implantable parts of the stimulator include the following: a. the pulse generator, b. the extension wire, and c. the electrode; the telemetry/programming parts include the following: d. the controller and e. the personal digital assistant. The IPG is 47 mm × 52 mm × 11 mm in size and 35 g in weight. The expected lifespan is two to six years depending on usage and stimulation parameters. This homemade device shares the same basic principles and user interface with Medtronic products, and it has unique designs in terms of circuitry, structure, and software. The estimated price of this system is about $15,000, which is half the price of the Medtronic system (personal communication with Professor Lu-Ming Li of Tsinghua University). DBS, deep brain stimulation; IPG, implantable pulse generator.

by psychiatrists in China. As a result, there are only sporadic Chinese reports presenting a few cases of DBS in the treatment of psychiatric diseases (14,58). Multidisciplinary cooperation is necessary for the application of DBS in this field. More communication and collaboration should be conducted between neurosurgeons and psychiatrists in the future.

Compared with routine neurosurgical techniques, DBS is a complex procedure that is relatively new. To our knowledge, standardized guidelines for DBS are still absent in China. Guidelines could include criteria for patient selection and evaluation, target selection, stimulation electrode localization, and postoperative programming. Specialists from major DBS centers should convene and establish guidelines to standardize this surgical therapy. There were no government regulations regarding the application of medical technologies, including DBS, until the Ministry of Health of China promulgated the Management Practices on Clinical Application of Medical Technology in 2009. Nonetheless, this is a general set of regulations. Detailed approval standards, including specialized training and basic equipment, also are lacking in DBS centers in China. Medical research ethics has been a growing issue in China over the past two decades. Requirements, including ethical review, were issued by the State Food and Drug Administration for Good Clinical Practice in 1999 (revised in 2003). The Ministry of Health issued regulations on the ethical review of biomedical research involving human subjects in 2007. Data from the websites of the above-mentioned DBS centers indicated that all of these institutions require that any treatment has been approved by the Institutional Review Board (IRB). However, the declaration of IRB approval was absent in some clinical trials on DBS in Chinese journals (14,43,44), which suggested that the establishment of the IRB was rather inadequate. It must be emphasized that the concept of ethical review should be deeply rooted in clinicians' minds.

CONCLUSION

In conclusion, DBS has evolved significantly over the past decade in China and plays an increasingly important role in the successful treatment of PD. However, there are still some problems to be solved. The advent of Chinese homemade DBS hardware, multidisciplinary cooperation, and the establishment of guidelines and regulations for DBS will facilitate the further development of this surgical treatment in China.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (30872661 and 81070901). This work also was supported by a basic-clinical combination grant from Capital Medical University (09JL42).

Authorship Statements

The study was designed by Jian-Guo Zhang, and the manuscript was prepared by Wen-Han Hu. Data collection and analysis were executed by Wen-Han Hu and Kai Zhang, with much appreciated help from Fan-Gang Meng and Yu Ma. All authors approved the final manuscript.

How to Cite this Article:

Hu W.-H., Zhang K., Meng F.-G., Ma Y., Zhang J.-G. 2012. Deep Brain Stimulation in China: Present and Future. Neuromodulation 2012; 15: 251–259

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COMMENTS

This extensive review of the use of deep brain stimulation in China is of considerable interest, not only because of the number of patients represented, but also because of the report of which diseases are treated. Many questions require review of large populations in order to recognize trends or evaluate outcomes, and our Chinese colleagues are in a position to provide such information.

It is interesting to see how financial concerns impact treatment choices in health care systems that are so different. Stating the average income, however, does not take into account a bimodal distribution of income and the absolute numbers of patients who can afford an option such as DBS. Patients who may opt for a less expensive lesioning procedure must also be recognized.

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This is a timely manuscript describing the advent of DBS in China. Its value lies in the fact that it demystifies what is going on China, and that the Western world can learn from what has been published in the Chinese literature, otherwise unaccessable to non-Chinese speaking clinical neuroscientists. This is important as to prevent what happened before with regards to important Russian neuroscientific literature that was published before the end of the USSR, and only became known in the Western world many years after it was initially published in Russian.

It further demonstrates that analogous to what has been described in Hermann Hesse's novel Siddhartha, the development of DBS in China is going through the same stages as those of the initial development of DBS in the USA, albeit at a later date. Considering the rapid technological evolution described in the manuscript, the improving complication registration and developing ethical conscience, manuscripts such as these might also pave the way to international collaborations between Western and Chinese DBS centers, collaborations that will benefit both neuroscience as well as patient outcomes.

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Comments not included in the Early View version of this paper.

