

Target Article

# Ethical Focal Points in the International Practice of Deep Brain Stimulation

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Deep brain stimulation (DBS) is a standard therapy for several movement disorders, and the list of further indications that are investigated is growing rapidly. We performed two surveys among DBS experts ( $n_1 = 113$ ) and centers ( $n_2 = 135$ ) to identify ethical focal points in the current global practice of DBS. The data indicate a mismatch between the patients' fears and the frequencies of the suspected side effects, a significant "satisfaction gap," signs of improvements of outcome, habituation effects in terms of involved disciplines, a growing spectrum of novel indications that partly conflicts with the experts' success probability ratings, and differences in the density of supply between countries that might affect the future development of DBS. We formulate ethical recommendations with regard both to patient-related practices (e.g., recruitment, assurance of alternatives) and to institutional development (e.g., measures for quality assurance and for the development of novel DBS indications).

**Keywords:** deep brain stimulation, movement disorders, psychiatric disorders, patient management, center development, biomedical ethics

Deep brain stimulation (DBS) reflects a fundamental shift in the understanding of neurological and psychiatric diseases: namely, as resulting from a dysfunctional activity pattern in a defined neuronal network that can be normalized by targeted stimulation. DBS has been developed since the 1950s (Hariz et al. 2010); its "modern era" began in the 1980s (Benabid et al. 1987; Siegfried 1986). In recent years, the application of DBS has grown remarkably (Müller and Christen 2011) and is increasingly investigated as a therapy option for various intractable neurological and psychiatric disorders (Goodman and Alterman 2012; Holzheimer and Mayberg 2011), primarily for obsessive-compulsive disorder (OCD) (De Koning et al. 2011) and major depressive disorder (Anderson et al. 2012; Schläpfer et al. 2013). The spectrum of indications for which DBS is used in pilot studies is rapidly expanding; it comprises drug addiction (Luigjes et al. 2012), Tourette's syndrome (Müller-Vahl 2013), aggressive and disruptive behavior (Franzini et al. 2012), severe obesity (Halpern et al. 2011; Whiting et al. 2013), anorexia nervosa (Lipsman et al. 2013a), and Alzheimer's disease (Hardenacke et al. 2013;

Laxton and Lozano 2013; Laxton et al. 2010). To date, DBS has been approved (European CE mark) in Parkinson's disease (PD), essential tremor (ET), dystonia, epilepsy, and obsessive-compulsive disorder (OCD).

The beneficial effects of DBS on motor functions are well established (Deuschl et al. 2006; Kleiner-Fisman et al. 2006; Wider et al. 2008). The evaluation of cognitive, affective, and behavioral sequelae of the intervention (Videnovic and Metman 2008; Volkmann, Daniels, and Witt 2010; Witt, Daniels, and Volkmann 2008) is nontrivial, as they may result from surgery, stimulation, or drug reduction, and—in particular in PD—similar effects can result both from disease progression and from medication. Taking these issues into account, the focus of research is shifting to practical issues like decision-making of patients, psychosocial effects of the interventions, and optimal long-term care. Thus, DBS has become an established therapeutic option with new indications on the horizon.

We propose to investigate the practice of DBS along two dimensions: The first dimension relates to all processes that influence the individual intervention (patient-related

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dimension), and the second relates to the development of the infrastructure (infrastructure-related dimension). The first dimension involves information of patients, the referral practice, exclusion criteria, decision-making, the intervention, and the follow-up (Clausen 2010; Kubu and Ford 2012; Lipsman et al. 2012). The infrastructure-related dimension captures aspects of the development of the DBS infrastructure that are decisive for high-quality interventions. This includes issues like the emergence of new DBS indications, involvement of different disciplines, differences in the DBS procedures between centers (e.g., target preferences), center capacities, the financing of DBS research, and the long-term planning of center development given the growing spectrum of DBS indications (Abosch et al. 2013; Bell, Mathieu, and Racine 2009; Fins et al. 2012).

In order to obtain an overview of the global practice of DBS we performed two surveys: a survey of researchers/clinicians and a survey of DBS centers. The surveys addressed the decision-making process of patients, disciplines involved in the DBS procedure, target preferences of centers, exclusion criteria, risk evaluation, outcome analysis, expert opinions about characterization, incidence and causes of “personality changes” following DBS, and a possible “satisfaction gap” (Agid et al. 2006; Kluger et al. 2011). Furthermore, the surveys collected data that allows for assessing the referral practice, trends for novel indications, and the experts’ opinions with respect to controversial DBS issues. Cross-comparison of both surveys allowed for validating the results.

## MATERIALS AND METHODS

### Survey of Experts

The anonymous survey of DBS researchers and clinicians was performed in two waves between mid 2011 and mid 2012, each of them including two follow-ups (by e-mail). The first wave addressed researchers identified by us (Christen et al. 2012) who published about DBS in Parkinson’s disease since the early 1990s. The second wave addressed clinicians whom we identified in a global search of DBS centers. Both search strategies were complemented by bibliometric research to ensure that those 100 authors who published most on DBS are included in the data set. For all persons identified we searched for valid e-mail addresses. In total, 656 persons with valid e-mail addresses have been approached. Since 22 of them did not publish about DBS for more than 10 years, it is unlikely that they are still active in the field, so that the universal set consists of 634 researchers and clinicians.

The survey questionnaire was developed based on previous research (Christen et al. 2012; Christen and Müller 2011; Müller and Christen 2011) and has been cross-checked by a board of researchers (see acknowledgments). It included 31 questions; the mean responding time was 20.5 minutes.

### Survey of Centers

The non-anonymized survey of centers that offer DBS interventions was restricted to 12 countries that ranked highest in the number of DBS research papers published: Australia, Canada, England, France, Germany, Italy, Japan, the Netherlands, Spain, Sweden, Switzerland, and the United States. For these countries we have performed an Internet-based search to find clinics (public and private) that offered DBS according to their website at least sporadically in 2010 or 2011. This was complemented by bibliometric research to identify home institutions of persons that published on DBS. Five hundred and thirteen institutions that claim to offer DBS have been identified. The questionnaire was sent to these institutions by postal mail in June 2012; two follow-ups were performed (via e-mail, until October 2012). In the postal mail, we included the list of all centers of the respective country and asked the responsible person to check the list for completeness and for false entries. We also approached all 12 national neurosurgical associations and the leading DBS supplier Medtronic to check our lists. Based on the feedback, we identified 408 sites in the 12 countries that were confirmed to offer DBS or that are likely to do so at least sporadically. The questionnaire for the survey of centers included only eight questions, to promote a high response rate. It had been pretested in a Delphi study among all Swiss DBS centers (Christen and Müller 2012).

Both the surveys of experts and the survey of centers did not need approval from the responsible ethical review committee (Kantonale Ethikkommission Zürich) given our institutional guidelines, as patients were not addressed by the surveys and no information was collected that could be related to individual patients. Furthermore, we followed the CHERRIES guidelines (The Checklist for Reporting Results of Internet E-Surveys; see <http://www.jmir.org/2004/3/e34>) as far as they were applicable.

### Bibliometric Study and Literature Search

Using the Thomson Reuters Web of Science database, we performed a bibliometric study on January 26, 2012, to check the completeness of our expert database. On December 6, 2012, we identified the funding sources mentioned in DBS papers. The study was accompanied by a study of the DBS literature for identifying controversial issues, and we consulted our review board to make a selection. In addition, we searched for papers for estimating the incidence and prevalence of the major DBS indications. Since we found that the data is rather controversial, we restricted the research to PD, where the data is most reliable. We used Mathematica 9.1 for statistical calculations.

## RESULTS

### Survey of Experts

One hundred and twenty-three persons provided answers in the survey of experts. Ten persons were excluded due to

the low number of answers provided (less than 50%), leaving usable data of 113 persons (response rate: 17.8%; see also Table 1). Ninety-nine experts answered all questions. We note that the search of experts included all (co)authors of DBS papers published since 1991; therefore, most of them were not principal investigators and probably many do not work in the field of DBS anymore. Hence, many of the approached persons may have been reluctant to provide answers, since they are not “true” DBS experts. Thus, the reported response rate is the lower limit of the “true” response rate of experts who are still active in the field of DBS. The DBS core disciplines neurosurgery (46.9%) and neurology (39.8%) are most represented in the expert sample. The median age of the responders was 48 years, and their majority is male (72%). The five most represented countries of origin (17 in total) were the United States (23.9%), Germany (13.3%), France (12.4%), Italy (12.4%), and the United Kingdom (4.4%).

### Survey of Centers

One hundred and thirty-five institutions provided answers to the survey of centers. The overall response rate was 32.8% (see also Table 1); the response rates of the countries varied between 54.5% (Canada) and 23.6% (the United States); the response rate of 100% in Switzerland results from the fact that the pretest of the survey included all Swiss centers. The total number of patients that received a DBS intervention in the responding centers is at least 29,350, that is about one-third of an estimate of 85,000 patients that have received a DBS intervention globally (data as of January 2011; Christen and Müller 2012).

### Validating Expert Experience

On average, the centers in which the experts work (in the following, “expert centers”) had started DBS treatments earlier and had implanted more patients than reported in the survey of centers (data not shown). This indicates that the expert centers tend to be experienced above average. Of the responding experts, 69.9% had treated at least 100 patients; 68.1% are regularly or often involved in research (clinical, basic, validation, technology); 77.0% have expert knowledge in patient selection, 77.9% in patient follow-up, 65.5% in surgery, 64.6% in patient information, 58.4% in device programming; and 36.3% in novel DBS applications. Based on these findings, we conclude that the

sample of the survey of experts consists mainly of experienced DBS researchers and clinicians.

### Patient-Related Dimension of DBS Practice

The first dimension of DBS practice concerns the intervention process in individual patients: that is, the information of patients, the referral practice, exclusion criteria, decision making, the intervention, and the follow-up. The complete results are contained in Figure 1, Table 2, and Table 3.

*Information of patients and referral practice.* With respect to information sources used by the patients and to the referral of patients to DBS centers, the neurologists (in private practice) seem to be the decisive “entry point” to DBS (Table 2).

*Exclusion criteria.* Dementia is the most important reason for excluding a patient from a DBS intervention, followed by general medical risk factors, the psychiatric history, and the age of the patient (Table 3).

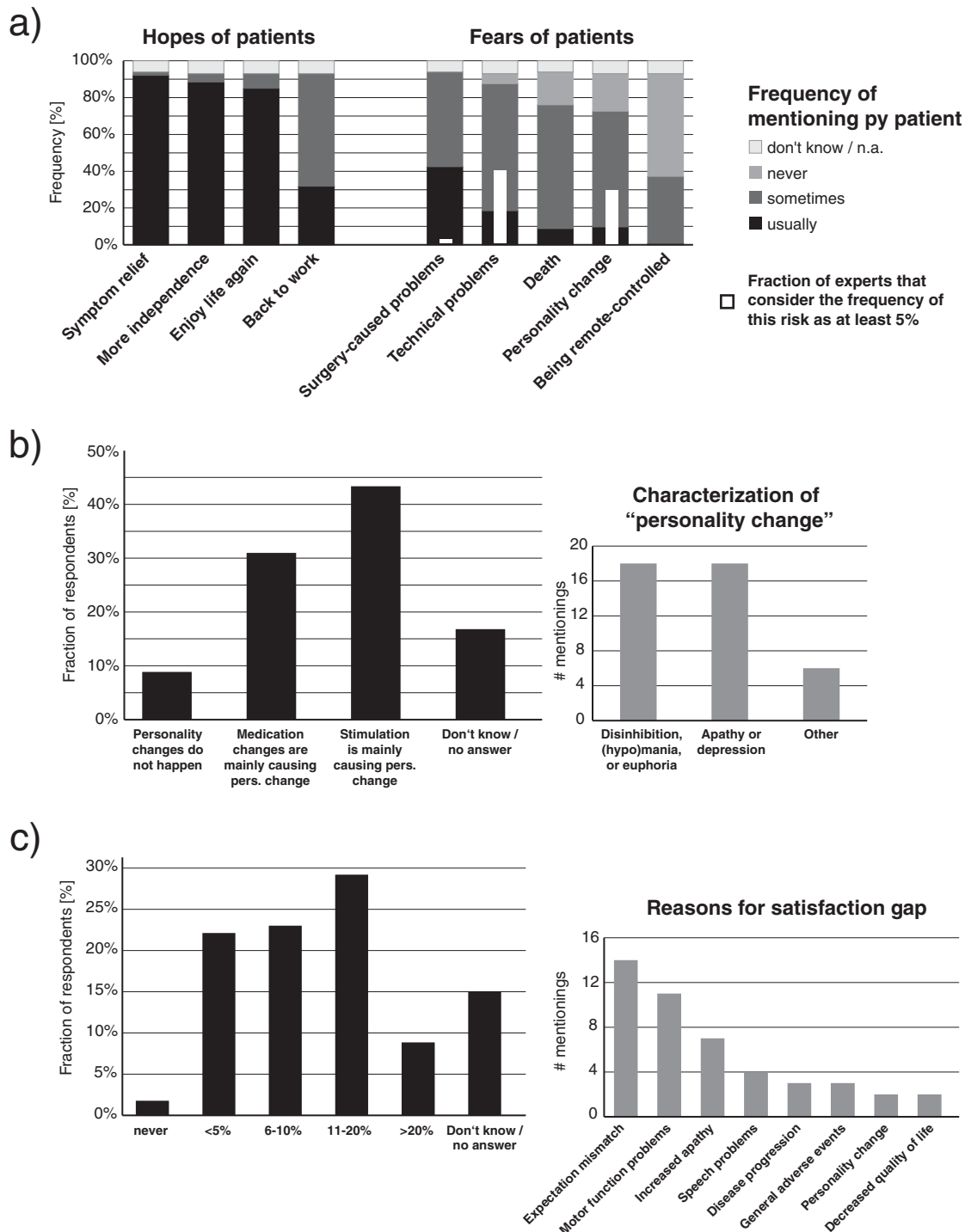
*Decision making.* According to the experts, most patients uttered the hope for symptom relief, followed by more independence, enjoying life again, and going back to work. The patients’ greatest concerns are surgery-caused problems, followed by technical problems, death, personality changes, and being remote-controlled. The frequency of fears uttered by the patients does not always match with the experts’ assessment of risk probability. Particularly, surgical complications are mentioned often by the patients, although they have the lowest probability according to the DBS experts, whereas fears of technical problems and of personality changes are less often mentioned by the patients, although the experts consider these sequelae to be more frequent (Figure 1a).

*Intervention.* In the course of the DBS intervention for movement disorders, a broad spectrum of tests is used: Motor functions, medication dose, cognitive functioning, and mood are always checked before and after the intervention. Emotional functioning, language, quality of life, and social functioning are not always, but still routinely part of the assessment procedure. Other aspects like sleep, autonomous functions, weight change, and sensory systems are often, but not routinely, part of the assessment. The before–after comparison is insufficiently monitored

**Table 1. Response rates of the center and expert surveys**

	Experts	Centers
Initial set of experts/centers that have been approached	656	513
Confirmed or likely set of experts/centers active in DBS	634	408
Valid responses	113 (18%)	135 (33%)
Experts/centers that operated at least 100 patients	79 (70%)	77 (57%)

**Figure 1. Patient-related dimension: (a) Frequency that the patients express specific hopes and fears in the DBS decision-making process. (b) Assessment of personality change by the experts. (c) Assessment of the satisfaction gap by the experts.**



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**Table 2. Factors characterizing the DBS intervention process: information sources of the patient, referral of the patient, and the frequency of exclusion criteria used in patient selection based on the survey of experts**

	Usually/often	Sometimes	Never	Don't know/no answer
<b>Information sources of the patient</b>				
Neurologist in private practice	76.1%	19.5%	0.9%	3.5%
Physician of the DBS institution	53.1%	30.1%	8.8%	8.0%
Internet	53.1%	42.5%	0.0%	4.4%
Support groups	47.8%	40.7%	5.3%	6.2%
Brochure of the DBS institution	42.5%	31.0%	17.7%	8.8%
General media	31.0%	50.4%	8.0%	10.6%
Family and friends	24.8%	67.3%	1.8%	6.2%
Brochure of the device producer	23.9%	46.9%	21.2%	8.0%
General practitioner	11.5%	53.1%	22.1%	13.3%
Scientific literature	12.4%	58.4%	17.7%	11.5%
<b>Referral of the patient by...</b>				
... neurologist in private practice	91.2%	8.0%	0.0%	0.9%
... other medical institutions	47.8%	41.6%	6.2%	4.4%
... departments of the same institution	37.2%	38.9%	12.4%	11.5%
... himself/herself (self-referral)	20.4%	48.7%	20.4%	10.6%
... the general practitioner	15.9%	59.3%	19.5%	5.3%
<b>Frequency of exclusion criteria</b>				
Dementia	71.7%	21.2%	0.9%	6.2%
General medical risk factors	40.7%	50.4%	1.8%	7.1%
Psychiatric history of the patient	38.9%	53.1%	0.9%	7.1%
Age of the patient	37.2%	50.4%	6.2%	6.2%
Insufficient compliance suspected	21.2%	57.5%	12.4%	8.8%
Unrealistic expectations by the patient	22.1%	53.1%	15.9%	8.8%
Alcohol addiction	19.5%	38.9%	32.7%	8.8%
Drug addiction	23.0%	28.3%	39.8%	8.8%
Anxiety of the patient	8.0%	46.9%	37.2%	8.0%

only for weight changes, as eight participants in the survey of experts reported that weight is an issue only before the intervention, but not after.

*Follow-up.* In the bioethical literature on (subthalamic nucleus [STN]) DBS, two issues of follow-up received particular attention, namely, the possibility of “personality changes” and the “satisfaction gap,” i.e., physicians express satisfaction with the result whereas patients are less satisfied. Personality changes as understood in psychology refer to alterations in the “Big Five” personality traits (i.e., extraversion, neuroticism, agreeableness, conscientiousness, openness to experience; see Costa and McCrae 1992), and it is known from the literature that (STN) DBS can influence each of these in some patients (Müller and Christen 2011). We have exemplified the term with examples like hypomania, hypersexuality, aggressivity, and risk-taking behavior. We found that 26.5% of the experts believed that “personality changes” occur in more than 5% of the cases, 38.1% estimate their incidence at 2–5% of all cases, and 23.9% believe that they happen in less than 1% of the cases (11.5%: don't know). Of the experts,

43.4% considered stimulation to be the likely cause of personality changes compared to changes in medication (Figure 1b). The experts described personality changes after DBS mostly as alterations of mood: The patients became either more depressive and apathetic or more hypomanic.

The issue of a satisfaction gap is not uncommon: 38.0% of the experts believed that it occurs in more than 10% of the cases, 23.0% estimate its prevalence at 6–10%, and 23.9% think that it happens in 5% of the cases or less (15.0%: don't know). The experts mention a multitude of reasons, particularly an expectation mismatch, but also motor function problems and increased apathy (Figure 1c).

The experts reported lower incidences of adverse effects for the case of apathy, depression, and language problems than reported in the literature about STN DBS in PD (Table 3). Of the experts, 67.3% document adverse effects (publications, database, or standardized reporting form), although only 12.4% indicated a reporting obligation.

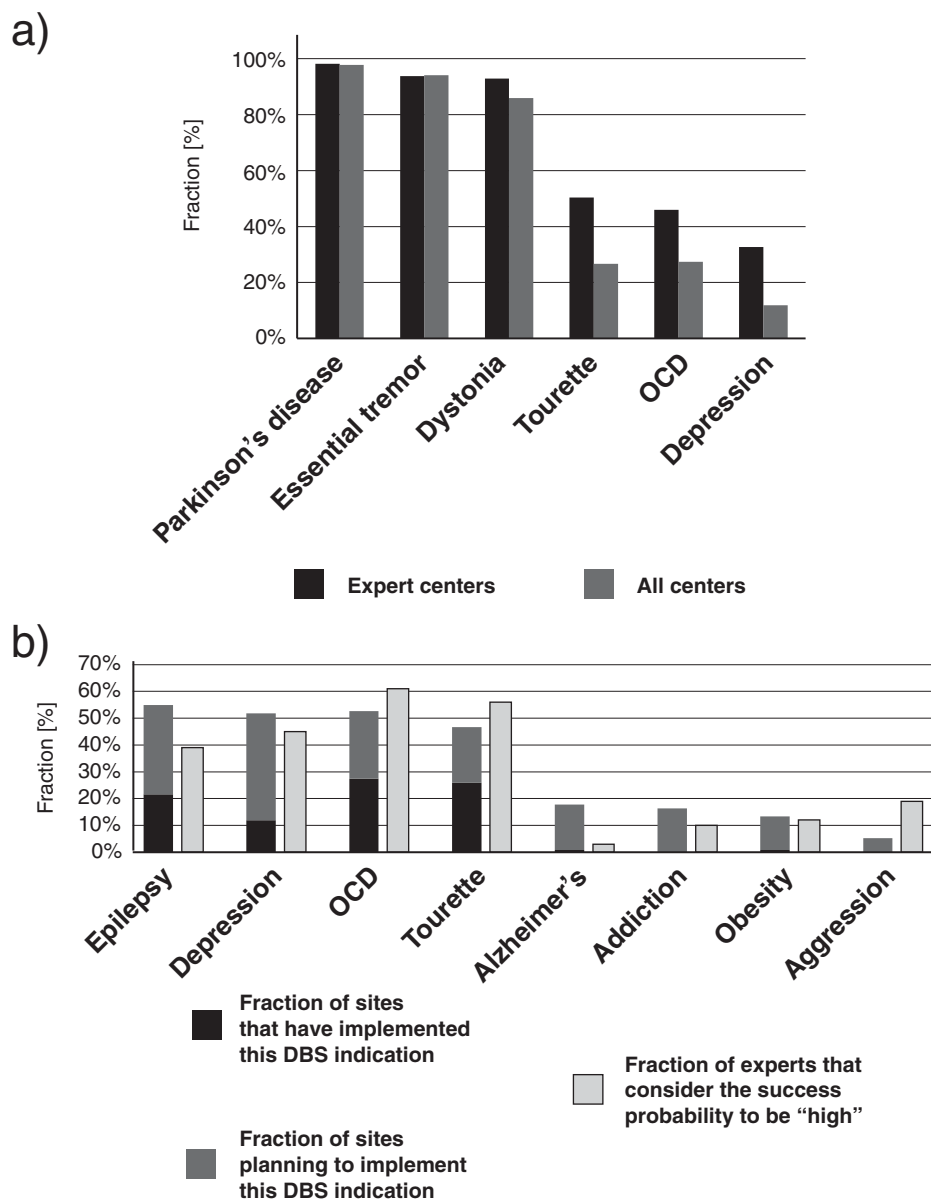
The time span for device programming varied over a remarkably broad spectrum: 10 experts claim to use less than 4 weeks for device programming, 29 use 4–8 weeks,

**Table 3. Comparing the ratings of the experts of the frequency of side effects of STN-DBS in PD patients with data of outcome reviews**

	<1%	1–5%	6–10%	11–20%	>20%	Don't know / no answer	Literature
Apathy	27.4%	26.5%	15.9%	15.0%	2.7%	11.5%	12–25% [a] 3.5% [b]
Language problems (dysarthria)	20.4%	33.6%	22.1%	8.0%	5.3%	10.6%	Up to 24.6% [c] 9.3% [d] 12.8% [b]
Device problems (e: lead fracture; d: electrode or wire replacement; b: malfunctioning, premature loss of battery power, acute failure of the stimulator, etc.)	23.0%	30.1%	29.2%	5.3%	1.8%	10.6%	0–15% [e] 4.4% [d] 4.4% [b]
Personality change (d: manic episodes; f: personality changes, hypersexuality, apathy, anxiety, aggressiveness; g: manic psychosis; a: hypomania; b: hypomania, hypersexuality)	23.9%	38.1%	15.0%	7.1%	4.4%	11.5%	1.9% [d] <0.5% [f] 0.9–1.7% [g] 4–15% [a] 1.2% [b] 6.8% [d] 8% [f]
Depression	16.8%	44.2%	20.4%	4.4%	1.8%	12.4%	1.5–25% [a] 20–25% [g] 4.3% [b] 20–25% [c] 2% [f]
Anxiety	35.4%	30.1%	10.6%	7.1%	1.8%	15.0%	0–10% [e] 3.9% [d] 2.0% [b]
Hemorrhage (f: symptomatic intracranial hemorrhage)	67.3%	19.5%	0.0%	1.8%	0.9%	10.6%	

Note. Sources of data: [a] Voon et al. 2006; [b] Videnovic and Metman 2008; [c] Witt et al. 2012; [d] Kleiner-Fisman et al. 2006; [e] Bronstein et al. 2011; [f] Temel et al. 2006; [g] Volkmann et al. 2010.

**Figure 2. Infrastructure-related dimension: (a) Overview of current main DBS indications offered by centers. (b) Comparison of the frequency of (planned) application of DBS for novel indications with the success evaluation of the experts.**



28 use 9–12 weeks, 16 use 13–24 weeks, and 2 experts use more than 24 weeks (not involved in programming or “don’t know”: 28).

#### Infrastructure-Related Dimension of DBS Practice

The second dimension concerns the institutional development of DBS, particularly the offer of new DBS indications, multidisciplinary teams, differences of the DBS procedures (e.g., different target preferences), center capacities, the financing of DBS research, and the long-term planning of

center development given the growing spectrum of DBS indications. The detailed results are contained in Figure 2 and Tables 4, 5, and 6.

*New DBS indication.* Almost all centers offer DBS for PD, ET, and dystonia, but also Tourette’s syndrome, OCD, and depression are quite common indications (Figure 2a). DBS for Tourette’s syndrome is performed by 25.9% of the centers (and by 50.4% of the expert centers); for OCD by 27.4% (46.0% of the expert centers); and for depression by

**Table 4. Annual numbers of patients that have received a DBS intervention**

	Annual number of patients that received a DBS intervention				
	<10	10–20	21–50	51–100	>100
Survey of experts (excluding 5 that currently do not work in a DBS site)—data of 2010	15.9%	29.0%	33.6%	13.1%	8.4%
Survey of centers: mean numbers for 2009 to 2011 (excluding 4 that did not provide data)	21.4%	37.4%	32.8%	8.4%	0.0%
Survey of centers: current capacity (excluding 1 that did not provide data)	7.5%	27.6%	40.3%	20.9%	3.7%

*Note.* First row: annual numbers reported in the survey of experts (expert centers); second row: annual numbers reported in the survey of centers. The experts reported higher numbers than the centers, reflecting the fact that the experts tend to work at sites that perform more interventions. However, 9 experts reported working at a site that operates on more than 100 patients—a number that is not met by the reporting of the centers. Potential reasons for this mismatch are that some expert centers may not be present in the data of the survey of centers (the survey of experts was anonymous), slight differences in the questions (the experts reported the number of surgeries in 2010, the centers a mean estimate of the last 2–3 years, i.e., 2009 to 2011), or over-/underreporting of the experts or centers.

11.9% (32.7% of the expert centers). For epilepsy, depression, OCD, and Tourette's syndrome, about half of the centers either offer DBS currently or plan to implement it in their programs within the next 5 years (Figure 2b). Further indications that are planned to be offered in the next 5 years by some centers are Alzheimer's disease (17.0% of the centers; one center already does research in this field), addiction (16.3%), obesity (12.6%), and aggression (5.2%). When these numbers are compared to the fraction of experts who expect a high success probability for these indications, two discrepancies have to attract attention: First, 17% of the centers plan to treat Alzheimer's disease with DBS, although only 3.0% of the experts consider the success probability to be high, whereas 68.0% consider it to be low. Second, only 5.2% of the centers plan to treat aggression with DBS, although 19.0% of the experts consider its success probability to be high.

*Multidisciplinary teams.* In routine DBS interventions, 60.7% of the centers involve at least two additional disciplines besides the core disciplines neurology and neurosurgery, for example, (neuro)psychology, care, rehabilitation, or social work. Centers that offer DBS not only for movement disorders but also for further neurological and psychiatric disorders involve significantly more disciplines (3.61 disciplines in the mean) than those centers that restrict DBS to movement disorders (2.89 disciplines) (Mann–Whitney;  $p < .002$ ).

*Differences of the DBS procedures (e.g., different target preferences).* Because of the discussion about the optimal target of DBS in Parkinson's disease, particularly about the STN (stimulation of which can address more symptoms than the other targets, but it has higher risks of psychiatric side effects; Hariz et al. 2008), we investigated the preferences for different stimulation targets for

Parkinson's disease. We found a considerable difference with regard to the preferred stimulation target between U.S. and European centers: By weighting the survey entries of target frequencies (usually = 4, often = 3, sometimes = 2, rarely = 1) we found a relative distribution of STN, globus pallidus pars interna (GPi), and nucleus ventralis intermedius (VIM) target preferences of 74.4%/19.9%/5.6% for European and 60.4%/31.9%/7.7% for U.S. centers. When additionally weighting this data by the number of patients the centers operated, the distribution is 72.7%/20.7%/6.6% for Europe and 54.5%/33.6%/11.9% for the United States. These results show that European PD patients are more likely to be stimulated in the STN than were U.S. patients.

*Center capacity.* Of all DBS centers (survey of centers), 58.8% operated on 20 or fewer patients per year (Table 4). Given the current infrastructure, 64.9% of the centers would have the capacity to operate on more than 20 patients per year. We estimated whether the number of centers available and their capacity match with the expected number of patients that qualify for DBS in PD. The prevalence of PD in industrialized countries is around 0.3% of the entire population; reported standardized incidence rates are 8–18 per 100,000 person-years (De Lau and Breteler 2006). Table 5 gives a rough prediction of the eligibility rate of PD patients, that is, the number of PD patients per year that could qualify for DBS given an estimate of the available capacity and the annual incidence of PD (the number of patients that all centers could operate per year divided by the number of new PD patients per year). The data reveal a large variance of the estimated eligibility rate between the different countries.

*Funding.* The bibliometric study revealed indications of a difference in public funding for DBS between the United



Table 5. Estimating the capacity of DBS centers of 12 countries based on the most important indication (PD)

	AUS	CAN	CHE	DEU	ENG	ESP	FRA	ITA	JPN	NLD	SWE	USA
Number of responding centers	5	6	7	14	5	11	11	16	9	4	2	45
Total capacity of responding centers	237	196	193	562	143	316	336	255	265	140	73	2'655
Total number of centers	10	11	7	44	18	28	25	30	30	8	6	191
Estimated capacity of country per year	470	360	200	1770	510	800	760	480	880	280	220	11'270
Total population of country (in Mio; 2012)	22.5	34.3	8.0	81.9	53.0	47.2	65.4	60.6	126.7	16.7	9.5	314.2
Estimated number of PD patients (in 1,000)	67.5	102.9	24.0	245.7	159	141.6	196.2	181.8	380.1	50.1	28.5	942.6
Number of centers per 1,000 PD patients	6.8	9.4	3.4*	5.7	8.8	5.1	7.8	6.1	12.7	6.3	4.8	4.9
Estimated number of new PD patients per year (in 1,000)	1.8–4.1	2.7–6.2	0.6–1.4	6.6–14.7	4.2–9.5	3.8–8.5	5.2–1.8	4.8–10.9	10.1–22.8	1.3–3.0	0.8–1.7	25.1–56.6
Predicted estimated eligibility rate	11.5–26.1%	5.8–13.1%	13.9–31.3%	12.0–27.0%	5.3–12.1%	9.4–21.0%	6.5–14.5%	4.4–9.9%	3.9–8.7%	9.3–21.0%	12.9–28.9%	19.9–44.8%

Note. The country abbreviations are according to the ISO 3166-1 alpha-3 standard. The numbers of the total population per country are based on [www.wikipedia.de](http://www.wikipedia.de) (November 2012).

\*The number of DBS centers in Switzerland will be reduced to 4 (or 3) (Christen and Müller 2012), i.e., the number of centers per 1,000 PD patients will be 6.0, or respectively 8.0.

**Table 6. Overview of experts' opinions towards claims about DBS**

	Strongly disagree	Disagree	Indifferent	Agree	Strongly agree
Lesion surgery versus deep brain stimulation (DBS) in movement disorders					
Lesions are part of the past, they should not be performed anymore	14.2%	37.7%	18.9%	19.8%	9.4%
It's acceptable to offer lesions to patients who do not have a health assurance that will pay for the following costs of DBS and who cannot pay them on their own.	25.7%	20.0%	19.0%	26.7%	8.6%
Lesioning may be acceptable in some cases only if noninvasive methods (e.g. gamma knife) are used.	12.3%	30.2%	33.0%	22.6%	1.9%
It's acceptable to offer lesions to patients who probably will not comply with postoperative care.	4.8%	21.0%	22.9%	44.8%	6.7%
I expect that soon there won't be experts who master lesion procedures.	1.0%	24.8%	27.6%	39.0%	7.6%
It's acceptable to offer lesions in poorer countries if DBS is too expensive.	4.7%	17.0%	17.0%	46.2%	15.1%
For some patients, lesions may be a valid alternative to DBS.	7.5%	5.7%	9.4%	64.2%	13.2%
Unilateral versus bilateral DBS procedures for movement disorders					
Unilateral procedures should be the standard.	16.5%	51.5%	27.2%	3.9%	1.0%
The question of uni-/bilaterality is of secondary importance.	10.5%	41.9%	21.0%	21.9%	4.8%
Bilateral procedures should be the standard.	2.9%	16.3%	20.2%	35.6%	25.0%
The question of uni-/bilaterality depends on the symptoms or other prerequisites of the patient.	1.0%	7.6%	8.6%	43.8%	39.0%
General opinions with respect to DBS in movement disorders					
DBS surgery has a high risk of complications.	20.8%	51.9%	9.4%	15.1%	2.8%
DBS in movement disorders is still a last-resort treatment.	19.8%	47.2%	17.0%	14.2%	1.9%
DBS is a completely reversible procedure.	2.8%	37.7%	17.0%	38.7%	3.8%
DBS in PD is more cost-effective than medication.	2.8%	17.0%	33.0%	40.6%	6.6%
Patients with movement disorders should be able to obtain DBS even when the disease is still manageable by medication.	0.0%	18.9%	20.8%	49.1%	11.3%
DBS should be offered only in large centers.	1.0%	6.7%	16.2%	57.1%	19.0%
More patients should have the opportunity to obtain DBS.	0.0%	1.9%	15.1%	55.7%	27.4%
DBS in movement disorders allows for a better management of disease symptoms than medication alone.	0.0%	1.9%	6.6%	39.6%	51.9%
General opinions with respect to DBS (all indications)					
I have a bad feeling when I learn about the increasing number of possible DBS applications.	26.5%	45.1%	18.6%	8.8%	1.0%
There is an economic interest to offer DBS as a novel therapeutic approach for other diseases than movement disorders.	4.0%	7.9%	22.8%	55.4%	9.9%
DBS will allow us to understand the neurological basis of psychiatric diseases.	0.0%	3.9%	28.4%	45.1%	22.5%
DBS will be an option for the treatment of severe, otherwise untreatable psychiatric diseases.	0.0%	0.0%	23.5%	56.9%	19.6%
DBS has the potential to substantially improve our therapeutic spectrum for various diseases.	0.0%	0.0%	5.0%	62.4%	32.7%

*Note.* Between 6 and 10% of the respondents did not answer particular questions; they have been excluded in percentage calculations for the respective questions.

States and Europe: Of all U.S. papers, 19.8% mention public funding by governmental institutions, whereas only 5.3% of the European DBS papers do so. In the DBS papers that mentioned a funding source, 53.9% of funding came from companies or private foundations. However, only 1,753 out of 8,016 DBS papers identified (21.9%) contained explicit information on funding that was accessible in Web of Science. This means that this data do not by far reflect all funding sources for DBS. It is likely that many papers do not reveal this information, if the funding source is public. Thus, the result may only indicate differences in funding disclosure between the United States and Europe in the sense that authors from the United States are more likely also to mention public funding.

Finally, we collected the opinions of the experts on various controversial issues raised in the DBS literature. Table 6 provides a summary of the results. In the following, we outline the most important findings.

#### *Lesion surgery versus DBS in movement disorders.*

The majority of the responding DBS experts (51.9%) do not consider lesion procedures as part of the past that should not be performed anymore. A great majority (77.4%) thinks that lesion procedures are a valid alternative to DBS for some patients. Particularly, the majority agrees with offering lesion procedures in poorer countries (61.5%) or to patients who probably will not comply with postoperative care (51.5%). Almost half of the experts expect that soon there won't be experts who master lesion procedures (27.6% are indifferent; 25.8% disagree).

*DBS for movement disorders.* Although a majority thinks that bilateral procedures should be the standard (60.6%), most experts think that the question of uni-/bilateral depends on the symptoms or other prerequisites of the patient (82.8%). Only a minority (17.9) thinks that DBS surgery has a high risk of complications. Interestingly, the majority considers DBS not to be a last-resort treatment (67.0%) and that it should be offered even when the disease is still manageable by drugs (60.4%). The majority supports the claim that DBS should be offered only in large centers (76.1%).

*DBS for novel indications.* The great majority of the experts (76.5%) endorse the expansion of indications for DBS in favor of the enrichment of the therapeutic spectrum for various diseases, and only a minority (9.8%) utters a bad feeling when they learn about the increasing number of DBS indications. Nevertheless, the majority (65.3%) also thinks that there is an economic interest to offer DBS as a novel therapeutic approach for diseases other than movement disorders. Great agreement occurs also in the opinion that DBS will allow us to understand the neurological basis of psychiatric diseases (67.6%).

## DISCUSSION OF ETHICAL FOCAL POINTS

We have investigated the current practice of DBS along two dimensions: (1) the patient-related and (2) the infrastructure-related dimension. We now carve out the ethical focal points in the current practice of DBS.

### Patient-Related Dimension

For the patient-related dimension, we found that neurologists are key players both for information and for referral of patients. This finding highlights the importance of an adequate and up-to-date training of neurologists in private practice about DBS. Correct information is necessary, as a timely elucidation about DBS, as well as responding to the individual concerns by the consulting physician, is essential for the acceptance of the treatment (Südmeyer et al. 2012). Adequate expertise is necessary, as movement disorder specialists are more likely to identify good candidates for DBS (Katz et al. 2011). The development of DBS requires that neurologists are regularly informed about new indications, technological improvements, and newly investigated risks.

Data from the survey of experts show that only a minority of patients utter concerns about technical device problems or stimulation-induced personality changes, whereas the experts consider these risks as relevant. This indicates an information gap between patients and experts. We propose that this information gap may be partly responsible for the relatively high prevalence of the satisfaction gap reported by a considerable number of experts. However, other aspects may contribute to this gap as well: The finding that the experts' ratings of the frequency of the DBS sequelae apathy, depression, and language problems tend to be lower than reported in the literature may indicate a decreased sensibility for the patient's own experience of side effects, although we consider this as less likely (see further discussion). Another potential reason is that even in case of sufficient information the fact that the patient him- or herself experiences side effects may contribute to the satisfaction gap. These hypotheses require further empirical investigation on patients' expectations and how these expectations or other factors determine the evaluation of outcome by patients (e.g., retrospection of the preimplantation health status).

Another relevant finding concerns the mismatch between the experts' ratings of the frequency of the DBS sequelae apathy, depression, and language problems compared to the literature. However, we do not interpret this in the sense that the experts underestimate risks. Rather, the result more likely reflects an improvement in practice not captured by reviews that usually refer to studies some time ago; this, however, needs additional support. More problematic may be that in DBS for movement disorders the number of involved disciplines tends to decrease and that the majority of experts use less device programming time than a recent review on this matter suggests (3–6 months during 4–5 programming sessions; Bronstein et al. 2011). This indicates a habituation effect for established

indications that may be positive with respect to cost-effectiveness, but not adequate to the complexity of DBS in PD.

An interesting finding is that the majority of experts of our survey has a relatively positive attitude regarding lesion procedures in movement disorders. More than two thirds believe that they are a valid alternative to DBS for some patients, but also almost half of the experts expect that soon there won't be experts who master lesion procedures. Also in the literature there is support to keep lesion procedures as an important alternative for appropriately selected patients both for movement disorders (e.g., Parkinson's disease; Bronstein et al. 2011) and psychiatric disorders (Leiphart and Valone 2010) like OCD or anorexia nervosa (Barbier et al. 2011; D'Astous et al. 2013; Greenberg, Rauch, and Haber 2010; Kondziolka, Flickinger, and Hudak 2011). In particular, an international expert panel has recently stated in a consensus paper that "until scientifically proven otherwise, DBS is not superior to ablative surgery for psychiatric disorders" (Nuttin et al. 2014). However, the main disadvantage of lesion surgery is that possible negative effects are not reversible. Adverse effects that have been reported are the development of undesirable personality traits (after subcaudate tractotomy) and transient mania and memory deficits (after cingulotomy) (Feldman, Alterman, and Goodrich 2001). We also remark that there are research initiatives for additional noninvasive lesion procedures like focused ultrasound (Jolesz and McDannold 2014; Lipsman et al. 2013b) such that novel expertise in ablative surgery may emerge.

### Infrastructure Dimension

With respect to the infrastructure-related dimension several aspects require advertence. First, 60% of the centers operate 20 or less patients per year, although 20 patients per year are considered to be the minimum quantity for DBS training centers (Krauss et al. 2009) and although the large majority of experts think that only large centers should offer DBS. This finding indicates that measures might be necessary to ensure quality also in centers with low case numbers.

Second, we found a rapid expansion of new indications for DBS. About half of the centers presently perform or plan to perform DBS for epilepsy, depression, OCD, and Tourette's syndrome. However, research on DBS in particular for psychiatric indications is in an early state, and success rates cannot be estimated correctly, particularly because of the presumed publication bias (Schlöpfer and Fins 2010). DBS is also planned for indications with considerable prevalence, in particular obesity (the prevalence of obesity varies nearly 10-fold among Organization for Economic Cooperation and Development [OECD] countries, from as low as 4% in Japan and Korea, to 30% or more in the United States and Mexico; OECD 2012) and Alzheimer's disease (according to the World Health Organization [WHO 2012], the number of people globally who are living with dementia in 2011 is estimated to be 35.6 million, and studies indicate that this number is expected to

grow at an alarming rate). However, only a small minority of experts considers the success probabilities for these diseases to be high. This indicates that societal need partly triggers the expansion of DBS indications. In the case of Alzheimer's disease, it's worthwhile to mention that dementia is considered to be the most common exclusion criteria for DBS in case of PD. This tension that may have an influence on DBS exclusion criteria is discussed neither in recent reviews (Hardenacke et al. 2013; Heschem et al. 2013; Laxton and Lozano 2013) nor in case studies (Fontaine et al. 2013; Laxton et al. 2010) on DBS in Alzheimer's disease. We identified only one comment that points to potential problems when selecting patients suffering from dementia in clinical DBS trials (Salma, Vasilakis, and Tracy, 2014).

Although more than three-fourths of the experts endorse the expansion of indications for DBS in favor of the enrichment of the therapeutic spectrum for various diseases, two-thirds also think that there is an economic interest to offer DBS as a novel therapeutic approach for diseases other than movement disorders. Evidence on cost-effectiveness of DBS is still limited. A recent study for DBS in the case of PD in the United Kingdom calculated a total of discounted costs in the DBS and best medical treatment groups over 5 years of £68,970 and £48,243, respectively. The quality-adjusted life years (QALYs) were 2.21 and 1.21, giving an incremental cost-effectiveness ratio of £20,678 per QALY gained. Thus the results suggest that DBS may be a cost-effective intervention in patients with advanced PD who are eligible for surgery.

Finally, given these dynamics, the capacity of DBS centers may become an issue in some countries. Unfortunately, there is very little research that estimates the fraction of patients eligible for DBS even for the most important indication, PD. Early estimations range from 1.6% to 4.5% (Morgante, Morgante, and Moro 2007) but have been criticized as underrating the ratio of eligible PD patients (Cacciola 2008). Several factors contribute to this underrating: Referring clinicians may underestimate the number of suitable patients (Oyama et al. 2012), women are underrepresented in those referred (Setiawan et al. 2006), and the amount of suitable candidates could increase if patients were referred earlier to DBS (Charles et al. 2012; Schübach et al. 2013). Therefore, a more reasonable guess is that 10–20% of PD patients may qualify for DBS (Christen and Müller 2012). Given our findings, countries like Canada, England, Italy, and Japan may have insufficient capacities for dealing with the expectable patient load, which may also affect research regarding novel indications.

### CONCLUSIONS AND ETHICAL RECOMMENDATIONS

In summary, our findings indicate a dynamic development of DBS with respect to various issues. To ensure the ethical future of DBS, more emphasis than hitherto should be put on issues that are not directly related to the intervention,

but to issues like the referral practice, the expansion of DBS indications, the financing of DBS research, and the development and quality control of DBS centers. We suggest that the following aspects should become focal points of the ethical discussion about DBS.

### Patient Dimension

- **Entry points:** In movement disorders, the neurologists in private practice are the gatekeepers for patient information and patient selection; that is, they frame significantly whether and how patients will consider DBS as a therapy option. In light of the rapid expansion of DBS indications, we should start to think about who will be the gatekeepers for DBS for patients suffering from addiction, depression, OCD, anorexia nervosa, or severe obesity and what we should expect from them (Christen and Müller 2013).
- **Reducing the satisfaction gap:** A significant number of patients seem to be dissatisfied with the outcome of their DBS treatments. Various reasons may account for this, and it is likely that psychological and social factors play an important role. This phenomenon needs further empirical research, and results of this research should be incorporated as soon as possible in the shared decision-making process with patients.
- **Multidisciplinary teams:** Our study found indications of habituation effects, which regularly occur when a therapy becomes more and more accepted. An important point is the number of experts that are routinely involved, which is lower in centers that treat only movement-disorder patients, although it is known that PD as well as its treatment (DBS and medication) may involve psychiatric effects. Centers should ensure that sufficiently qualified personnel of several disciplines (including psychiatry) can be called in case they are needed.
- **Documenting the outcome:** Clinics should follow each of their patients long enough to evaluate improvements in practice and possible long-term sequelae. This should also include case registries on a national level. Outcome analyses help to prevent the repetition of former failures and to establish a good practice (Lieberman et al. 2008).
- **Ensuring alternatives:** The growing confidence in DBS as a treatment option should not suppress alternative treatments. We support to further investigate lesion procedures (performed by either microsurgery, thermocoagulation, or particularly by Gamma Knife) as an alternative to DBS for particular groups of patients, and to compare their efficiency, risks, and side effects with DBS. There are two important reasons for providing the option of lesion procedures: first, the relative low cost (which is particularly important in poorer countries); and second, certain exclusion criteria or practical limitations of DBS (e.g., patients who could tolerate neither the stress of an operation awake nor an operation under full anesthesia; patients for whom a craniotomy is contraindicated; patients who

would not tolerate implanted devices; or patients who live in remote areas such that compliance with the long-term follow-up after DBS is hard to achieve).

### Institution Dimension

- **Quality standards in smaller DBS centers:** Although in some countries (e.g., Switzerland) there is a discussion to ensure high case numbers per DBS center (Christen and Müller 2012), obviously many centers operate on only a few patients. However, we argue against fixed minimal case numbers for DBS centers, as determining the cutoff is arbitrary and other stereotactic interventions besides DBS (which have not been captured in our surveys) also account for the experience of a center. Nevertheless, it is important to find ways (e.g., binding guidelines) to ensure high quality also in smaller DBS centers, with regard not only to the surgical procedure, but also to patient information, patient selection, device programming, and pre- and postsurgical neurological and psychiatric assessment.
- **Novel DBS indications planning:** It is likely that DBS will become a bearer of hope for many psychiatric disorders—in particular, for depression, OCD, and Tourette's syndrome—for which known therapies have failed (e.g., recent studies estimate that more than 50% of patients suffering from depression may be treatment-resistant; Thomas et al. 2013). However, it will be important that the development of novel DBS indications is theory driven (i.e., based on a good understanding of the network in which one intervenes) and evidence based and not merely demand driven. In particular, the planning should involve the buildup of (optimally international) case registries, which should contain all clinical studies and individual treatment attempts for all novel DBS indications. Case registries are indispensable for preventing a publication-bias and its negative consequences, namely, faulty evaluations of therapies, flawed therapy recommendations, unpromising treatment attempts, and unneeded clinical studies (Müller and Christen 2011; Rabins et al. 2009; Schläpfer and Fins 2010; Woopen, Timmerman, and Kuhn 2012).
- **Evidence-based evaluation of DBS for novel indications:** For novel indications of DBS, an evidence-based evaluation is essential. Whenever possible, each novel indication should be investigated in clinical trials of the appropriate size and statistical power, requiring collaboration of centers. We support the demand of Fins and colleagues (2011) that the U.S. Congress and federal regulators should revisit the Food and Drug Administration (FDA) humanitarian device exemption that allows manufacturers to market a device under certain conditions without subjecting it to a clinical trial, for DBS for treating OCD. They argue convincingly that the humanitarian device exemption is misused for bypassing the rigors of clinical trials, since OCD is not an orphan but a prevalent condition, and that the current market-driven

regulatory strategy is detrimental to patient safety, scientific discovery, and research integrity.

- **Capacity planning:** Due to the rapid expansion of DBS indications, capacity planning in centers—at least for some countries—should become an issue soon. In some countries (e.g., Switzerland; Christen and Müller 2012) not all patients who are suitable for DBS may obtain this therapy. Unfortunately, there are almost no data available even for a disease like PD that allows for such planning (in particular, data that estimate the percentage of patients who suffer from a DBS indication and who are actually good DBS candidates, and data on the optimal case number per center to ensure both sufficient intervention quality—which speaks for higher case numbers per center—and optimal care and follow-up—which sets an upper limit for the number of patients operated per center). Therefore, health service research should put more resources into gaining information needed for DBS center capacity planning.
- **Funding:** A recent market study claims that the brain stimulation market “is expected to grow at a rapid pace and achieve a similar market size to the Global Cardiac Devices market” (Research and Markets 2013). Also according to our data, the experts see economic driving forces in the development of novel indications for DBS. Unfortunately, the current data do not allow assessing reliably the impact of private funding on DBS research. We recommend that papers on DBS (and other fields) should always disclose their funding source, independent of whether this source is private or public.

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Open Peer Commentaries

# Broader Challenges for DBS in the Treatment of Alzheimer's Disease

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The number of indications for deep brain stimulation (DBS) is steadily increasing, with formal approvals for use in Parkinson's disease (PD) and a select group of other indications. Promising symptomatic relief for intractable disorders, the interest in expanding the application of DBS understandably is generating hope where there has been little. Alzheimer's disease (AD), a neurodegenerative disease, stands high on the list of currently most dreaded diseases and, moreover, one for which there is no effective treatment. This coupled with the alarming demographics of Alzheimer's disease points to a need for new treatment approaches. In the United States, an estimated 5 million people currently suffer with dementia and this number is expected to triple by 2050. Worldwide, this number hovers at 18 million (National Institute on Aging [NIA] 2012–2013). With no compelling evidence of an effective treatment on the horizon that would manage this disease, the interest in novel approaches is logical and perhaps even urgent. Thus, as Christen and colleagues (2014) report, 17% of medical centers surveyed plan to offer DBS to treat AD in the next 5 years. Yet in contrast to this experimental embrace of the promise of DBS for AD, only 3% of the experts surveyed were optimistic about the probability of success in treating AD with DBS (Christen et al. 2014). This contrast between the planned pursuit of novel indications and overwhelming skepticism about the likelihood of success merits further consideration, particularly in the context of the ethical focal points raised by Christen and colleagues. This essay points to two aspects of AD that require that the analysis of the ethical focal points be extended beyond those proposed by Christen and colleagues: (1) how do we derive appropriate expectations and (2) the importance of relational aspects of AD.

Alzheimer's disease is rapidly emerging as one of the great challenges of the 21st century, generating an increasing sense of urgency for identifying effective treatment. Despite a growing understanding of associated risk factors, AD progression, and related biomarkers, a cure remains elusive. Sometimes referred to as an impending epidemic, as an age-related disease, the incidence of AD is

escalating in step with the worldwide demographic shift toward older populations. It is against this backdrop of rising incidence and projections of far horizons for success (Bor 2014) that any examination of ethical focal points for the use of DBS to treat AD must take place. Certainly, many issues inherent to the use of DBS transcend disease and disorder applications, for example, capacity to consent, authenticity, and cost-effectiveness. But even a cursory consideration of differences in the nature of the underlying impairment makes it abundantly clear that specific indications require dedicated consideration; for example, capacity to consent to DBS by a person with dementia raises different questions from capacity to consent by a person suffering from obesity, although an aspect of the cost-effectiveness may be similar given increasing characterization as an epidemic.

Christen and colleagues add much to the discussion in their call for quality standards, registries, and capacity planning in the institutional dimension and review of entry points, multidisciplinary teams, and so on in the patient dimension. But these considerations put forth by Christen and colleagues, while meritorious, would permit dismissal of some of the most central concerns regarding appropriate treatment of AD patients.

First, the issue of appropriate expectations must be raised. Christen and colleagues report that only 3% of experts surveyed think that treatment of AD with DBS is likely to be successful, leaving 97% who do not expect success. Yet 17% of centers plan to offer DBS to AD patients. If a community has low expectations for the success for a particular intervention, it is impossible to know what this actually means without more information. What explains this low expectation of success among those arguably in the best position to understand the potential of the technology? Without further data explaining survey responses, it is impossible to know precisely what the basis is for these dismal expectations.

There are critical features about AD that should inform expectations about the likelihood of success of DBS as treatment of AD. First, there is considerable discussion in

the AD research community about what exactly AD is (see Pierce 2014), with theories ranging from the view that it may not be best characterized as a disease, but rather that it is inextricably linked to aging (Lock 2013) and perhaps is more correctly referred to as a syndrome (see, e.g., Swerdlow 2010) and, as such, could suggest that the multiple symptoms indicative of AD should inform expectations. That is, reasonable expectations regarding how DBS may be able to benefit an AD patient may share the same paradigm used to evaluate success in Parkinson's disease, also a syndrome, where the impairment of motor skills is the therapeutic target. If the expectation is that DBS would somehow arrest, halt, or cure AD, then low expectations may well be warranted. But if the expectation is that DBS will ameliorate certain symptoms, like those related to memory or spatial orientation, perhaps there could and, in fact, should be higher expectations. Indeed, early trials have shown that stimulation of the fornix/hypothalamus can result in increased glucose metabolism, yielding the possibility of improvements in the rate of cognitive decline (Laxton and Lozano 2013; Laxton et al. 2010). Calculation of cost versus benefit could illuminate the extent of relief required to justify the use of this intervention. Thus, for AD, where cognitive impairment and improvement may evade neat quantification due to less easily correlated impacts on quality of life, ethical consideration would require that we ask, on what basis do we proclaim that DBS is successful? Is it necessary to demonstrate the dramatic impact of DBS in PD in order to declare success in AD? How much memory must one regain in order to justify the use of the intervention? A threshold or metric could almost certainly be devised, but how should that inform a cutoff? To a spouse or parent who has regained only one memory—the ability to identify their loved one—thresholds that require more substantial and quantifiable demonstrations of success may seem out of touch with the reality of the circumstances of living with and living with someone who has dementia.

This leads to the second point regarding the relational nature of AD. When an individual is diagnosed with AD, probable AD, or even preclinical AD, it is rare that this news is delivered to an individual patient. In most instances, a family member or caregiver is present. The role of family members and caregivers is routinely calculated in the burden of disease, with AD ranking among the highest. In the United States alone, the annual cost of caring for a patient with dementia has been estimated at \$41,000–56,000, totaling \$157–215 billion per year (Hurd et al. 2013). The World Health Organization has estimated the economic burden of disease for AD worldwide at \$604 billion. A primary reason for this staggering sum is that it includes the costs and losses (e.g., lost work days) of caregivers and family members. Indeed, a fundamental truism of AD is that it affects families, not just individuals. As such, any ethical framework for evaluation of the suitability of a particular treatment of an AD patient must also hold in sight the relational aspect of the disease.

Treatment decisions regarding AD patients almost necessarily involve others who stand in relation to the patient. There is a noteworthy exception to this in the phenomenon of the “unbefriended” (Pope and Sellers 2012), people who live in circumstances unsupported by trusted friends or family. Yet even in these circumstances, depending on the extent of disability caused by AD, the relational aspect of AD emerges in the infrastructural caregiving that is found either privately or through state programs.

Thus, questions about the ethical use of DBS as treatment for AD must consider the impact not only on the individual patient, but also on those with whom the patient stands in relationship. Requiring daily check-ins or regular adjustments to equipment are important considerations for the caregiver as well as the individual patient (see, e.g., Bell et al. 2011, on PD). What and how much does the intervention demand of the caregivers and family? If they are not prepared, willingly or unwillingly, to support the patient in the use of this intervention, what impact should this have on access to this treatment? For those who view this from a purely pragmatic standpoint, the response may be clear, but such a view may also result in exacerbating disadvantage if the inability to support the patient is due to socioeconomic factors, thus giving rise to social justice issues in the selection criteria for DBS for AD.

Alzheimer's disease looms as an impending crisis and the need for novel treatment approaches merits support as well as scrutiny. An ethical framework outlining the two dimensions of patient concerns and institutional/ technological issues is a way to enter the discussion, but in the case of AD, this framework alone cannot get us where we need to be in evaluating the ethics of DBS in the treatment of AD. Regard beyond the patient and the technology to include the societal and relational aspects of AD is necessary.

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# Ethical Dilemmas in the Practice of DBS

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Christen and colleagues (2014) identify ethical issues concerning deep brain stimulation (DBS) in the patient dimension (e.g., information, expectations, decision making) and the institution dimension (e.g., quality assurance). They conclude that more attention should be paid to referral practice, expansion of indications, and quality control.

In this contribution, we question this conclusion. We show that it mirrors methodological flaws in the study design, and argue for an approach that does more justice to the experience and dilemmas of professionals involved in the DBS practice. We illustrate the importance of reflection on actual experience with an example of a Moral Case Deliberation meeting with a team involved in DBS practice. From this example, we conclude that DBS implies ethical concerns related to authenticity.

## SOME METHODOLOGICAL COMMENTS

Christen and colleagues (2014) draw their conclusions from two surveys, one among experts and one among centers. The experts were selected based on publications of DBS in Parkinson's disease. The centers were selected from 12 countries that publish most on DBS, through an Internet search aimed to identify centers that offer DBS. The first selection procedure results in a limited perspective on the practice of DBS since other diagnostic categories, such as psychiatric diagnoses, which are limited in patient numbers but more relevant from ethical perspective, are not included. Both selection procedures are based on publication rates, which are not necessarily related to persons or centers with the highest number of patients

treated. Since DBS is a multidisciplinary, complex treatment, often those with the most practical experience (nurses, psychologists) are not the ones who publish.

The questionnaires were based on items selected by the researchers. Thus, the topics reflect the researchers' views of relevant ethical issues. The cross-check procedure by a board of researchers is not clarified, so it is unclear to what degree they could provide input to the choice of topics based on their own experience. The results section seems to follow the items in the surveys. Thus, the surveys give little room for issues to arise other than those raised by the researchers. The answers may shed light on the relative importance of the items, but do not enable a comparison with possible ethical issues not addressed.

## THE IMPORTANCE OF EXPERIENCE IN ETHICAL REFLECTION

We believe that the study design, both the selection procedures and the questionnaires, is not suitable to detect the actual clinical and moral experience of participants in DBS practice. We propose an approach that uses the experience of participants as a source of moral knowledge (Muschenga 2005). In this approach, the aim of empirical research is to elucidate moral considerations of practitioners and investigate their ethical relevance. Elsewhere, we have developed a specific version of this approach, which is called dialogical empirical ethics (Widdershoven, Abma, and Molewijk 2009; Widdershoven, Molewijk, and Abma 2009). This entails inviting practitioners to make explicit their moral knowledge and to reflect on it in a

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dialogue, facilitated by the ethicist(s). The role of the ethicist is to assist participants in expressing their moral experience and in formulating questions, which may help to elucidate the moral concerns of others. Thus, ethical issues are not predefined by the researchers, but emerge in the process of dialogical investigation of the moral experience of participants in practice.

In dialogical empirical ethics, ethical issues are defined and investigated by participants in practice. The ethicist organizes the meeting, structures the deliberation, and helps the group to formulate conclusions. An approach that is perfectly suitable for fostering a dialogical reflection on ethical issues in medical practice is Moral Case Deliberation (Molewijk et al. 2008). A Moral Case Deliberation meeting starts with a real dilemma, experienced in practice (Van der Dam et al. 2012). The professionals involved are guided through a joint process of reflection, facilitated by an ethicist. The outcome of a Moral Case Deliberation meeting is a more profound insight into ethical aspects of a practice and a shared view on how to deal with them.

#### **AN EXAMPLE: A MORAL CASE DELIBERATION MEETING CONCERNING A DBS PATIENT**

Since Moral Case Deliberation meetings are confidential, we have altered some characteristics of the case description given next, to avoid recognition. We have asked for consent from the participants of this meeting.

A medical team of an academic hospital in the Netherlands offers DBS for patients with intractable diseases. The team organizes a Moral Case Deliberation facilitated by an ethicist. The psychiatrist presents a case of a patient who is in care. The patient had suffered of an intractable major depressive disorder for a long period of time. Through DBS, she has regained energy. She has taken up her old work as a musician, and now feels “on top of the world” and “like herself” again. Her family, however, complained to the psychiatrist that she has changed; she is more agitated, and is behaving recklessly. The family asks for the setting of the appliance to be modified. The patient herself wants the treatment to be continued without any change. The psychiatrist experiences a dilemma. He has to choose whether to continue with the current DBS settings, following the patient, or to decrease the voltage (strength of the DBS), following the family. Both sides of the dilemma come with a cost.

After a careful inquiry of the facts of this case and an exploration of the values of various parties involved (the patient, the family, the psychiatrist, the social worker, the nurses), each participant is invited to put him-/herself in the shoes of the psychiatrist, to determine what would be the best choice in this situation, and to make explicit the values that would motivate the choice for him or her. Some participants say they would choose to continue treatment, because of the patient’s autonomy. Others say they would change the stimulation because they consider the patient not able to decide, as she is agitated. Still others

would change the stimulation, as they think that the patient is not really herself in her current state.

Next, the choices are compared, and participants are asked to make their considerations intelligible. Though autonomy appears to be an important value for all professionals, it is conceptualized in different ways. Some participants focus on the patient’s ability to choose (free will), and others on the capacity of the person to be “herself” (authenticity). In the dialogue, the question is scrutinized to what extent the patient’s new behavior fits with her personality. One of the participants says: “In my view, a musician can be a bit eccentric and outspoken; if the patient had been a clerk, I would not think that she should remain functioning as she is now; but for a musician, this does not seem extraordinary.”

The participants conclude that in cases like this, authenticity does play a role. If the patient’s new behavior did not fit in with her identity, one might even need to consider stopping treatment. DBS thus implies issues of authenticity. Decisions about whether to continue treatment or not are not primarily dependent upon informed consent of the patient, but require an assessment of the relation of the patient’s current behavior to her former life plan.

Though this is the report of a single case, it is prototypical for the ethical challenges and reflections that are present with DBS therapy. These ethical issues regarding the identity of a patient and the tension between autonomy and authenticity (sometimes intensified by the social network of the patient) have not been addressed in the study of Christen and colleagues (2014). Such issues might have come up if the study design would have included an empirical ethical approach in which professionals discuss the ethical challenges of DBS based on actual cases from their care practice.

We believe that repetitive meetings with the DBS team according to this Moral Case Deliberation protocol eventually will enhance insight and improve decision making. In the long term, with a larger sample of cases, it should be possible to draw more firm ethical conclusions that may be used as guidelines.

#### **CONCLUSION**

By starting from a real dilemma and fostering reflection on the participants’ moral experience, Moral Case Deliberation may shed light on moral issues and concerns related to DBS practice. This is especially helpful because of the innovative nature and unexpected effects of DBS, which may lead to new challenges for professionals treating an individual patient. In fact, Moral Case Deliberation can be valuable both from a patient dimension perspective and from an institution dimension perspective. The example shows that ethical issues in daily practice are not primarily related to informed choice. Professionals’ concerns include issues related to authenticity, which have also been discussed in the literature (Meynen and Widdershoven 2014;

Kraemer 2013; Wardrope 2014). Rather than studying ethical issues around DBS through questionnaires based on preconceived items, researchers should be open to moral dilemmas experienced by professionals in everyday practice, and foster their reflection on the moral values involved.

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# Just Another Spot? How to Miss the Ethical Target

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Christen and colleagues’ (2014) article offers key insights on today’s international use of deep brain stimulation (DBS). In particular, they report international evidence of significant variation between targeted neuronal sites for treatment of the same neurodegenerative disease, namely Parkinson’s. According to their study, “European PD patients are more likely to be stimulated in the STN than were U.S. patients” (72). Christen and colleagues’ findings are important to help us understand that these variations between targeted areas for treating the same pathology illustrate a lack of consistency and uniformity in today international DBS practices. I think this deficit of uniformity within DBS practices may fail to protect patients during experimental trials, especially psychiatric patients. I use treatment-resistant depression (TRD) to discuss these ethical issues.

## DEPRESSION IN QUEST OF A DBS SPOT

As is often the case for many, if not most, psychiatric disorders, treatment-resistant depression (TRD) needs to be understood within a multidimensional framework with several factors interacting with each other (social, neurobiological, hormonal, etc.). TRD etiology is far from being well understood. TRD is a complex disease; if not properly

treated, some patients can suffer from it and be incapacitated over decades.

There has been a recent surge of interest in using DBS within experimental trials, as a last recourse, to treat patients suffering from TRD (Holtzheimer and Mayberg 2012; Kennedy et al. 2011). In terms of DBS practice, the current challenge is to find the adequate spot to stimulate in the brain. The state of the art is pretty clear: there are three schools of thought that are exploring the potential DBS spot to treat TRD.

The first school believes the ventral striatum, and in particular, the nucleus accumbens, is an appropriate neural area to be stimulated with DBS (Schlaepfer et al 2008). The second one believes the Brodmann area 25, especially the subgenual cingulate, is an adequate neuronal region to be stimulated with deep electrodes (Mayberg et al. 2005). The third school believes the anterior limb of the capsula interna is the appropriate spot to be implanted and stimulated (Malone et al. 2009). From the patients’ points of view, the probabilities to be stimulated within a specific area rather than another one likely depend on which team has enrolled them. In that respect, protecting patients may sometimes become clinically problematic: behind the experimental use of DBS for TRD there are strong competitive medical and financial interests.

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How realistic is it that one day we will learn that three distinct spots in the brain can treat the same psychiatric disease, namely, TRD? How often do we understand that distinct physiological brain regions may be at the origin a single multidimensional psychiatric disease? In some cases, pharmaceutical drugs teach us that different drugs can successfully contribute to alleviated symptoms of patients suffering from the same disease. However, can this model be translated to psychiatry? As a result of the quest for the right DBS spot for TRD by experimentally targeting distinct brain areas, patients may be exposed to unnecessary risk of harms. Should patients be informed that other potential spots are currently explored when consenting to undergo experimental DBS stimulation for a specific spot? How could an informed consent ethically be implemented to guide patients through the exploration of potential DBS spots for TRD and its related risk of harms? The lack of uniformity within international DBS regulation should be addressed quickly.

### LOOKING FOR A TREATMENT RATHER THAN A CAUSE

Incidentally, the quest to find a DBS spot for treatment of TRD takes place in a troubling tendency within contemporary medicine: spending more effort on treatment rather than understanding the cause. Indeed, the current scientific literature addressing TRD origins continues to be unbalanced. Globally, the number of articles that examine TRD etiologies is insufficient compared to the number of articles that focus on how science thinks TRD should be treated (Jenkins and Goldner 2012). Ethical concern is that without clear evidence of TRD etiologies, the scientific validity of using DBS treatment remains strongly experimental. In their 2012 TRD literature review, Jenkins and Goldner indicate that 10% of the TRD literature focused on causal factors leading to treatment resistance, while 80% examined the potential treatments. Among the 345 reviewed articles, 3% directed their attention to psychosocial factors, while 81% focused on biological factors, among which neurostimulation and neurosurgical interventions accounted for 30% ( $n = 104$ ) of the literature. As seen above, in a context where understanding TRD etiology and finding a consistent DBS spot for TRD remain problematic, one can ask, how can the ethical requirements to avoid the risk of severe adverse effects meet the etiological complexity of TRD? The lack of research on the etiology might make it difficult to balance the DBS harms-versus-benefits ratio.

### FROM EPISTEMOLOGY TO ETHICS

This quest to find a DBS therapeutic spot for TRD raises an epistemological question: whether or not a medical team should believe a specific spot can treat TRD. The answer to this question is fundamental and directly engages with ethical discussions. Indeed, ethical prescriptions derive

from what epistemic authorities know and believe. What medical teams believe is known about a specific spot as a potential treatment of TRD implies whether or not they should implant electrodes in this particular brain area. In other words, depending on what is believed by medical teams, a specific spot ought to be prescribed for experimental stimulation.

An underlying problem shared by these three schools of thought described above is how to negotiate a transition from enough experimental evidence that has been shown (or lack of experimental evidence) to a moral conclusion without compromising patients' safety. Is there a connection between what is believed to be enough experimental evidence and the ethical prescriptions medical teams ought to follow?

### CONCLUSION

The lack of consistency in the international use of DBS for TRD is ethically problematic. Without clear regulations on the use of DBS for TRD, it is difficult to standardize and protect patients, especially within experimental trials. Although significant therapeutic outcomes have possibly been shown, DBS remains an experimental quest involving a search for the right spot to stimulate in the brain. Any encouraging results emerging from current research trials are presumably leading the way to make DBS recognized as a therapeutic procedure. Nevertheless, many questions must be answered before DBS can be acknowledged as a safe and effective therapy for TRD. In particular, ethical issues related to severe adverse effects have to be carefully examined (Gilbert 2012, 2013a, 2013b). Importantly, issues associated with variation between targeted neuronal sites for treatment of the same psychiatric disease should be looked at with care in order to avoid harm to patients.

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