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Ethical Focal Points in the International Practice of Deep Brain Stimulation

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Abstract (143 words)

Deep brain stimulation (DBS) is a standard therapy for several movement disorders, and the list of further indications that are investigated grows 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 both with regard 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).

Key words: 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 (Siegfried 1986; Benabid et al. 1987). 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 (Holzheimer & Mayberg 2011; Goodman & Alterman 2012), primarily for OCD (De Koning et al. 2011) and major depressive disorder (Anderson et al. 2012). 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 (Whiting et al. 2013; Halpern et al. 2011), anorexia nervosa (Lipsman et al. 2013), and Alzheimer's disease (Laxton et al. 2010; Laxton and Lozano 2013; Hardenacke et al. 2013). Up 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 et al. 2008; Volkmann et al. 2010; Witt et al. 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 dimension), 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 et al. 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 that published most on DBS are included in the dataset. 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 acknowledgements). 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. 513 institutions that claim to offer DBS have been identified. The questionnaire has been sent to these institutions by postal mail in June 2012; two follow-ups were performed (per 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 confirmed to offer DBS or that are likely to do so at least sporadically. The questionnaire for the survey of centers included only 8 questions to promote a high response rate. It had been pre-tested 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 Reuter Web of Science® database, we performed a bibliometric study on January 26th 2012 to check the completeness of our expert database. On December 6th 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: 123 persons provided answers in the survey of experts. 10 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). 99 experts answered *all* questions. We remind 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 no "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 USA (23.9%), Germany (13.3%), France (12.4%), Italy (12.4%), and the UK (4.4%).

Survey of centers: 135 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% (USA); 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 1/3 of an estimate of 85'000 patients that have received a DBS intervention globally (data as of January 2011; Christen and Müller 2012).

INCLUDE TABLE 1

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. 69.9% of the responding experts 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; i.e., 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).

INCLUDE 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 1.a).

INCLUDE FIGURE 1

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 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.

INCLUDE TABLE 3

Follow-up: In the bioethical literature on (STN-) DBS, two issues of follow-up received particular attention, namely the possibility of "personality changes" and the "satisfaction-gap", i.e., that 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 them 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 with 2-5% of all cases, 23.9% believe that they happen in less than 1% of the cases (11.5%: don't know). 43.4% of the experts considered stimulation to be the likely cause of personality changes compared to changes in medication (Fig. 1.b). 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 their prevalence with 6-10%, and 23.9% think that they happen 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 (Fig. 1.c).

The experts reported smaller 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). 67.3% of the experts document adverse effects (publications, database or standardized reporting form), although only 12.4% indicated a reporting obligation.

The time span for device programming varied within a remarkably broad spectrum: 10 experts claim to use less than 4 weeks for device programming, 29 use 4-8 weeks, 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, Tables 4, 5 and 6.

New DBS indications: Almost all centers offer DBS for PD, ET and dystonia, but also Tourette's syndrome, OCD and depression are quite common indications (Fig. 2.a). 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 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 (Fig. 2.b). 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.

INCLUDE FIGURE 2

Multidisciplinary teams: In routine DBS interventions, 60.7% of the centers involve at least two additional disciplines besides the core disciplines neurology and neurosurgery, e.g., (neuro-) psychology, care, rehabilitation or social work. Centers that offer DBS not only for movement disorders, but 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; $p<0.002$).

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 (whose stimulation can address more symptoms than the other targets, but 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 US 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, GPi and VIM target preferences of 74.4%/19.9%/5.6% for European and 60.4%/31.9%/7.7% for US 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 USA. These results show that European PD patients are more likely to be stimulated in the STN than US patients.

Center capacity: 58.8% of all DBS centers (survey of centers) operated 20 or less patients per year (Table 4). Given the current infrastructure, 64.9% of the centers would have the capacity to operate more than 20 patients per year. We estimated whether the number of centers available and their capacity matches 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, i.e., 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 reveals a large variance of the estimated eligibility rate between the different countries.

INCLUDE TABLE 4

INCLUDE TABLE 5

Funding: The bibliometric study revealed indications of a difference in public funding for DBS between USA and Europe: 19.8% of all US papers 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 does by far not 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 US and Europe in the sense that authors from the USA 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 which should not be performed anymore. A great majority (77.4%) think 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-/bilaterality 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 other diseases than

movement disorders. Great agreement consists also in the opinion that DBS will allow us to understand the neurological basis of psychiatric diseases (67.6%).

INCLUDE TABLE 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 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, as well as 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 below). Another potential reason is that even in case of sufficient information the fact that the patient himself 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 pre-implantation 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 have a relatively positive attitude regarding lesion procedures in movement disorders. More than three 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 et al. 2010; Kondziolka et al. 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 subcaudatetractotomy) and transient mania and memory deficits (after cingulotomy) (Feldman et al. 2001). We also remark that there are research initiatives for additional non-invasive lesion procedures like focused ultrasound (Lipsman et al., 2013b; Jolesz and McDannold 2014) 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 a early state, and success rates cannot be estimated correctly, particularly because of the presumed publication bias (Schläpfer and Fins 2010). DBS is also planned for indications with considerable prevalence, in particular obesity (the prevalence of obesity varies nearly tenfold among 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 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; Hescham 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 et al. 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 other diseases 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 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 this 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 et al. 2007), but have been criticized to underrate 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 under-represented in those referred (Setiawan et al. 2006), and the amount of suitable candidates could increase, if patients would be referred earlier to DBS (Charles et al. 2012; Schüpbach 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 gate keepers for patient information and patient selection; i.e., 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 here. This phenomenon needs further empirical research, whose results 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 it is 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 analyzes 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 its 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 a wake-operation 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 only a few patients. However, we argue against fixed minimal case numbers for DBS centers, as determining the cut-off is arbitrary and other stereotactic interventions beside 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, not only with regard to the surgical procedure, but also to patient information, patient selection, device programming, and pre- and post-surgical 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 built-up 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 et al. 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 et al (2011) that the US Congress and federal regulators should revisit the FDA's 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 that are suitable for DBS may obtain this therapy. Unfortunately, there is almost no data available even for a disease like PD that allows for such planning (in particular data that estimates the percentage of patients that suffer from a DBS indication and that 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 in 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 does 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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CAPTIONS OF FIGURES AND TABLES

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.

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.

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

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.

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. Sources of data: [a]: Voon et al. 2006; [b]: Videnovic et al. 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.

Table 4: Annual numbers of patients that have received a DBS intervention. 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 which perform more interventions. However, 9 experts reported to work at a site that operates 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-/under-reporting of the experts or centers.

Table 5: Estimating the capacity of the DBS centers of the 12 countries based on the most important indication (PD). 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 (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, respectively 8.0.

Table 6: Overview of the experts' opinions towards claims about DBS (between 6 and 10% of the respondents did not answer particular questions; they have been excluded in percentage calculations for the respective questions).