THE CLINICAL AND ETHICAL PRACTICE OF NEUROMODULATION – DEEP BRAIN STIMULATION AND BEYOND

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PUBLISHED IN: Frontiers in Integrative Neuroscience

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88945-373-3
DOI 10.3389/978-2-88945-373-3

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THE CLINICAL AND ETHICAL PRACTICE OF NEUROMODULATION – DEEP BRAIN STIMULATION AND BEYOND

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Neuromodulation - how will it change our brain and mind?

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Neuromodulation is among the fastest-growing areas of medicine, involving many diverse specialties and affecting hundreds of thousands of patients with numerous disorders worldwide. It can briefly be described as the science of how electrical, chemical, and mechanical interventions can modulate the nervous system function. A prominent example of neuromodulation is deep brain stimulation (DBS), an intervention that 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. The application of DBS has grown remarkably and more than 130,000 patients worldwide have obtained a DBS intervention in the past 30 years—most of them for treating movement disorders. This Frontiers Research Topics provides an overview on the current discussion beyond basic research in DBS and other brain stimulation technologies. Researchers from various disciplines, who are working on broader clinical, ethical and social issues related to DBS and related neuromodulation technologies, have contributed to this research topic.

Citation: Christen, M., Müller, S., eds. (2017). The Clinical and Ethical Practice of Neuromodulation – Deep Brain Stimulation and Beyond. Lausanne: Frontiers Media.
doi: 10.3389/978-2-88945-373-3

Table of Contents

frontiers in Integrative Neuroscience

EDITORIAL
published: 09 November 2017
doi: 10.3389/fnint.2017.00032

Editorial: The Clinical and Ethical Practice of Neuromodulation – Deep Brain Stimulation and Beyond

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Keywords: deep brain stimulation, ethics, medical, neuromodulation, social issues, neurology, psychiatry

Editorial on the Research Topic

The Clinical and Ethical Practice of Neuromodulation – Deep Brain Stimulation and Beyond

Neuromodulation is among the fastest-growing areas of medicine, involving many diverse specialties and affecting hundreds of thousands of patients with numerous disorders worldwide. It can briefly be described as the science of how electrical, chemical, and mechanical interventions can modulate the nervous system function. A prominent example of neuromodulation is deep brain stimulation (DBS), an intervention that 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. The application of DBS has grown remarkably and more than 130,000 patients worldwide have obtained a DBS intervention in the past 30 years—most of them for treating movement disorders. These numbers will grow further for several reasons. First, DBS is investigated for various novel neurological and psychiatric indications. Second, current research suggests that stimulation may be more beneficial if it is applied earlier in the course of the disease, especially for Parkinsonian patients. Third, the number of countries, centers, and companies that get involved in this field is steadily increasing.

This Frontiers Research Topics provides an overview on the current discussion beyond basic research in DBS and other brain stimulation technologies. Researchers from clinical disciplines (e.g., neurology, neurosurgery, and psychiatry), neuroethics, social science, law, and economics who are working on broader clinical and social issues related to DBS and related neuromodulation technologies have contributed to this research topic. In the following, we provide a brief overview on the content of the e-book on "The clinical and ethical practice of neuromodulation – deep brain stimulation and beyond."

The paper from Ineichen and Christen exemplifies the impressive publication activity in the field. They analyzed more than 7,000 papers published between 1991 and 2014 on DBS using quantitative methods. The study confirms known trends within the field such as the emergence of psychiatric indications with a particular focus on depression and the increasing discussion of complex side-effects such as personality changes. Other findings are more surprising, e.g., that hardware-related issues are far more robustly connected to ethical issues compared to impulsivity, concrete side-effects or death/suicide. This indicates that the bioethical discussion on DBS may underestimate ethical problems due to DBS hardware.

The issue of complex side-effects are in the center of the opinion article of Cyron. He argues that psychiatric side effects are an integral part of DBS for Parkinson's disease. Particularly, hypomania, reckless behavior, suicidality, changes in personality, and moral competence are issues with a confounding ethical impact. He pleads for a sober and unprejudiced discussion about neuropsychiatric effects of DBS for Parkinson's disease.

OPEN ACCESS

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Received: *09 August 2017*
Accepted: *30 October 2017*
Published: *09 November 2017*

Citation:
Christen M and Müller S (2017) Editorial: The Clinical and Ethical Practice of Neuromodulation – Deep Brain Stimulation and Beyond. Front. Integr. Neurosci. 11:32. doi: 10.3389/fnint.2017.00032

Kocabicak et al. address the vividly discussed question whether there is still need for microelectrode recording, given that the subthalamic nucleus can be well-visualized with MR imaging. Based on the literature and their own experience, they argue that intra-operative electrophysiology is not necessary to find the STN. However, they have decided not to abandon it, particularly because with multiple-electrode recordings, an alternative trajectory is immediately available, if necessary.

Müller et al. broaden the view on psychiatric neurosurgery in their contribution. They compare the rivaling paradigms DBS and modern ablative procedures with microsurgery or radiosurgery, and argue that none of the procedures is absolutely superior. Rather, they have different profiles with respect to advantages and disadvantages. They conclude, that the patients' social situation, individual preferences, and individual attitudes are crucial when deciding, which of the methods are preferable.

Crowell et al. describe their observations of the response of patients with treatment-resistant depression to DBS. They find that the typical time course consists of different phases, beginning with changes in mood reactivity, followed by a transient worsening prior to stabilization of response. The authors hypothesize that this characteristic recovery curve reflects the timeline of neuroplasticity in response to DBS.

Beeker et al. discuss the ethical concern that DBS for patients with major depression might threaten their ability to make autonomous decisions. The authors argue that DBS in these patients might increase the patients' autonomy by reducing anhedonia and increasing energy, so that it can rather restore than threaten autonomy.

A summary of the current state of the discussion on the many facets of DBS is provided by the "Proceedings of the Fourth Annual Deep Brain Stimulation Think Tank" from Deeb et al. that took place in 2016 and gathered leading researchers such as James Giordano, Helen Mayberg, Jens Volkmann, and Michael Okun. The spectrum of addressed topics is very large and includes research and clinical practice, policy issues such as the formation of registries and novel technological innovations such as closed-loop DBS. Readers gain an up-to-date overview when consulting this contribution.

The contribution of Glannon provides a more philosophical focus on the issue of neuromodulation. He pleads for a non-reductive materialist model of the mind and brain relation. He argues that the fact that DBS can modulate dysfunctional brain circuits to make them amenable to cognitive-behavioral therapy underscores the complimentary of brain-based and mind-based techniques in controlling the symptoms of psychiatric disorders.

Finally, Cabrera and Reiner have investigated the public's understanding of the proposed use of a non-invasive neuromodulation technique: transcranial direct current stimulation (tDCS). They investigated the use of tDCS for enhancement by analyzing and comparing online comments in key popular press articles from two different periods: pre-commercialization and post-commercialization. They found that the public's attitude has shifted from misunderstanding to cautionary realism—probably a common pattern when analyzing the public reception of new neurotechnologies.

Overall, the contributions that form this eBook on clinical and ethical practice of neuromodulation demonstrate the many facets of a fascinating new research field that poses important and challenging ethical and social questions. It is encouraging to see that researchers from many different disciplines have begun to tackle them.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

We thank Oguzkan Sürücü for his support in managing this Research Topic.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer ARB and handling Editor declared their shared affiliation.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 26 October 2015
doi: 10.3389/fnint.2015.00052

Analyzing 7000 texts on deep brain stimulation: what do they tell us?

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The enormous increase in numbers of scientific publications in the last decades requires quantitative methods for obtaining a better understanding of topics and developments in various fields. In this exploratory study, we investigate the emergence, trends, and connections of topics within the whole text corpus of the deep brain stimulation (DBS) literature based on more than 7000 papers (title and abstracts) published between 1991 to 2014 using a network approach. Taking the co-occurrence of basic terms that represent important topics within DBS as starting point, we outline the statistics of interconnections between DBS indications, anatomical targets, positive, and negative effects, as well as methodological, technological, and economic issues. This quantitative approach confirms known trends within the literature (e.g., regarding the emergence of psychiatric indications). The data also reflect an increased discussion about complex issues such as personality connected tightly to the ethical context, as well as an apparent focus on depression as important DBS indication, where the co-occurrence of terms related to negative effects is low both for the indication as well as the related anatomical targets. We also discuss consequences of the analysis from a bioethical perspective, i.e., how such a quantitative analysis could uncover hidden subject matters that have ethical relevance. For example, we find that hardware-related issues in DBS are far more robustly connected to an ethical context compared to impulsivity, concrete side-effects or death/suicide. Our contribution also outlines the methodology of quantitative text analysis that combines statistical approaches with expert knowledge. It thus serves as an example how innovative quantitative tools can be made useful for gaining a better understanding in the field of DBS.

Keywords: deep brain stimulation, text analysis, network analysis, co-occurrence of terms, bibliometrics, bioethics

OPEN ACCESS

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Received: *09 July 2015*
Accepted: *27 September 2015*
Published: *26 October 2015*

Citation:
Ineichen C and Christen M (2015) Analyzing 7000 texts on deep brain stimulation: what do they tell us? Front. Integr. Neurosci. 9:52. doi: 10.3389/fnint.2015.00052

INTRODUCTION

A characteristic of modern knowledge production is the enormous increase of the number of scientific publications (original papers, reviews, conference abstracts, editorial material, etc.) that is made accessible through digital technology. In neuroscience alone, it is estimated that more than 100,000 papers a year are added to a text corpus that contains many millions of publications (Grillner, 2014). This information overload poses a substantial challenge for researchers to keep pace with the developments in their own fields; and it is well-known that the biomedical sciences are especially vulnerable in this regard, since they are strongly oriented toward text-based knowledge sources (Hölzer et al., 2006). This problem certainly also holds within the field of Deep Brain Stimulation (DBS) (Hariz et al., 2013), that has experienced a substantial growth of publications since the late 1990s (Müller and Christen, 2011). In this paper we propose a way to handle this challenge by using quantitative text analysis that combines statistical approaches with expert knowledge.

Quantitative approaches using bibliometrics, scientometrics, and text mining have gained popularity, as they may serve as navigational prospects and orientation aids. They enable researchers to identify relevant topics, trends, and publications in a fast-growing text corpus. Among other methods, network approaches, and data visualization techniques that aim to identify connections between topics within a given text corpus are being used (Popping, 2000, 2003; Ryan, 2007) and have shown to be useful to grasp important concepts within a text of any length. While being applied in a wide field, such approaches have a long tradition in enabling researchers exploring possible configurations of the unknown, shared visual representations which may open new ways for channeling collective attention, envisaging innovative interpretations and help us to make sense of data at different scales (Okada et al., 2014). The ultimate advantage of network analyses and their visual representation in general is recognized from a wide and diverse field. Ideally, the results of such a methodological approach will verify conjectured trends within the field, enrich the discourse, and support unconventional ideas or interpretations of the ongoing scientific development. In the following, we will explore the techniques of sized graphs in combination with sophisticated text preprocessing in order to find features in the network structure of the DBS text corpus which otherwise would be difficult to detect.

In general, a graph visualizes relations of a given set of data and is composed of nodes and edges. Nodes typically represent items or concepts whereas edges connect nodes according to some association rules. Graphs are widely used for e.g., analyzing social networks where people represent the nodes and edges represent relationships between people. To convert information (e.g., of text) into a visual representation can facilitate the handling and perception of hidden structures from large data sets. By following paths and detecting clusters of closely related nodes, one may detect unique features of a given data set. However, if the data set exceeds a certain level of magnitude, the task of exploring, and navigating becomes increasingly difficult. More specifically, there is extensive work on representing textual data as graphs and the subsequent application of network text analysis (e.g., Losiewicz et al., 2000; Grbic et al., 2013; James et al., 2013; Guan et al., 2014) for gaining an increased understanding of influential concepts, text's meanings, and structure. Network analysis is therefore also suitable for linguistic comparative analyses which focus on semantic relations between words, often framed through the co-occurrence of terms (i.e., relevant terms that more often appear in the same text are more likely to share some semantic connection). By making use of the large number of published DBS papers as well as a statistics driven quantitative approach, a potential subjective bias may be diminished.

In the following, we will use graph analysis and visualization techniques for investigating (1) most influential topics, (2) their mutual connections as well as (3) the temporal development of topics by retrieving the titles and abstracts of all published publications from 1991 to 2014 in the field of DBS (see Material and Methods for more specific information). We expect to be able to reproduce known phenomena (e.g., an increase in discussing psychiatric disorders in the DBS literature, well-described anatomical targets for the treatment of various disorders, or known treatment methods for various disorders) which might become obvious in different ways (e.g., direct connections or by reference to how e.g., anatomical targets are being discussed). Additively, we are interested in detecting how specific topics (e.g., lesioning-methods, personality, and bioethics) develop over time and/or how they interrelate with other topics. The original text corpus was composed of more than 10,000 DBS publications, based on which 7154 texts (titles and abstracts) containing more than 400,000 potentially relevant words have been selected for analysis. Using the co-occurrence of key terms as association rule, we conducted graph visualization techniques, community analyses and quantitative metrics to get insight into how DBS has been discussed during the last 23 years.

The results of this analysis are then reflected by referring to issues that dominated the DBS literature. Beside others, we are interested in how some topics that have been identified as ethical focal points in the international practice of DBS (Christen et al., 2014) are represented in this quantitative approach. In this way we explore the potential of such quantitative approaches for identifying subject matters that are of relevance from a bioethical perspective. The study will conclude by a discussion of limitations of quantitative approaches as heuristics to deal with information overload.

MATERIAL AND METHODS

Textual data is complex due to syntactic (verb forms, declination, etc.), semantic (homonymy, synonymy, etc.) and pragmatic (context-dependency etc.) variation. Therefore, any quantitative analysis based on textual data has to ensure appropriate preprocessing of text data such that it can be correctly used for statistical processing. In the following, we first describe text preprocessing to generate the final word set that was then used for trend and co-occurrence analysis, before we outline the network analysis and visualization methodology. The aim of the study was to obtain a comprehensive set of DBS publications as a set for quantitative analysis. We restricted ourselves to papers published since 1991, as earlier papers on DBS are rather sparse and do not yet contain in all cases the string "deep brain stimulation" as a simple identifier for a text that can be attributed to the DBS text corpus.

Abbreviations: ALIC, Anterior limb of internal capsule; BC, Betweenness Centrality; DBS, Deep Brain Stimulation; ECT, Electro-convulsive therapy; ET, Essential tremor; GP, Globus pallidus; GPi, Globus pallidus internal segment; MDD, Major depressive disorder; STN, Nucleus subthalamicus; Nacc, Nucleus accumbens; OCD, Obsessive-compulsive disorder; PD, Parkinson's disease; PPN, Pedunculo-pontine nucleus; QoL, Quality of life; SCS, Spinal cord stimulation; SG, Subgenual cingulate; TS, Tourette syndrome; tDCS, Transcranial direct current stimulation; VNS, Vagus nerve stimulation; Vim, Ventral intermediate nucleus; Zi, Zona incerta.

Text Preprocessing

Text preprocessing contained three steps as outlined in **Figure 1**. The starting point was a search in the Web of Science Core Collection database (the search was performed on December 5th 2014)[1]. We used the search string "deep brain stimulation" in the "topics"-field, restricted to the time range 1991 to 2015. We excluded the "Proceedings Citation Index," because entries in this database only contain the title of contributions without abstract. This resulted in a set of more than 10,000 contributions and a text corpus of almost 1.2 million words. In a first preprocessing step, we deleted special characters (e.g., "(" or "?" including number signs) as well as the search string itself (because it is unspecific), we transformed all letters into lower case and we merged frequent word pairs (e.g., "informed consent" to "informedconsent"). This last step was based on a word-pair statistics over the whole text set to identify very frequent pairing of words (a cutoff value of about 80% was chosen). We identified frequent word pairs by selectively looking through potential word-pairs and decided whether they should be merged based on our experience with the DBS vocabulary (in total, 130 word pairs were merged).

In a second preprocessing step, we deleted standard stop words[2] like "the," "is" etc., and we performed a lemmatization, i.e., we transformed all nouns, verbs, and adjectives into their ground form using standard lookup tables[3]; for example the plural "brains" is replaced by "brain" or the past tense "came" is replaced by "come"—the latter step served for removing the amount of variability. We refrained from stemming (another standard procedure in text processing), because a stemmer operates on a single word without knowledge of the context, and therefore cannot discriminate between words which have different meanings depending on the text. Finally, we computed the text length distribution and we deleted all short texts[4]. The remaining text corpus consisted of 7154 texts and 597,474 words, 22,034 of which were distinct words.

Finally, a third preprocessing step was necessary due to area-specific stop-words and terms that were not contained in standard lemmatizing lists. We first deleted all words that were present in less than 0.1% of the texts (i.e., that are contained in maximal seven texts), because these rare words are not suitable for statistical text analysis. Then, two raters (the authors) independently assessed which words are considered to be unspecific. If both raters independently rated the same words as unspecific, they were deleted (1308 in total). In a similar way, we identified 1380 replacement-pairs for area-specific lemmatization[5]. In this way, we generated a set of 7154 texts that

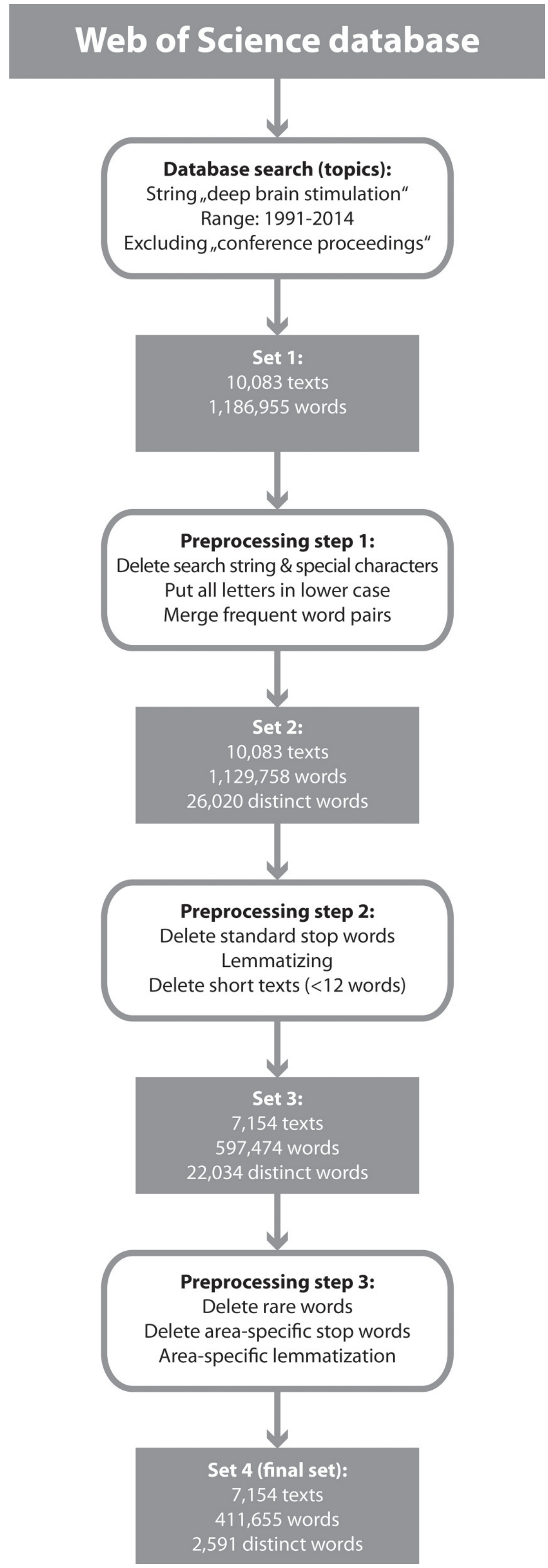

FIGURE 1 | Scheme outlining the generation of the final text set for network analysis.

[1] WoS, Thomson Reuters, access through https://webofknowledge.com/

[2] Available at: https://code.google.com/p/stop-words/

[3] Available at: http://www.lexiconista.com/datasets/lemmatization/

[4] The text length distribution displayed a peak for very short texts (e.g., editorial material that is only present in the WoS database with its title). In the mean, there were 36 texts per bin, the standard deviation was 57. Thus, the distribution was cut where there were more than $36 + 57 = 93$ texts per bin, which was the case for texts that contained 11 or less words).

[5] In some cases, we also replaced verbs or adjectives with nouns; e.g., "painful" was replaced with "pain," because the number of words of one category was considerably lower compared to the number of words of the other category.

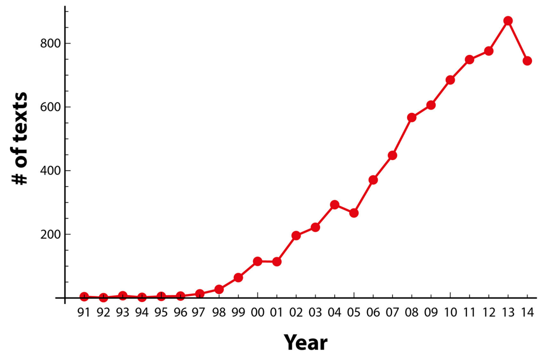

FIGURE 2 | Distribution of publication years of all texts of the final set (7154 texts), indicating a steep growth in the number of DBS texts since the late 1990s.

consisted of 411,655 words, consisting of 2591 distinct words. This set was used for the quantitative analysis.

Figure 2 provides an overview of the text corpus in terms of publication years which shows the quantitative basis for our analysis and reflects the substantial growth of publication within the field of DBS. Text size distribution and term frequency are shown in Supplementary Figure 1.

Text Analysis

The text analysis consisted of an expert evaluation part and a statistical part. The expert evaluation (performed by the authors) aimed to identify terms that are characteristic for issues and topics that are widely discussed in the field of DBS. For issue identification, we also referred to earlier publications from us, i.e., we included issues and topics which were identified as relevant based on an analysis of DBS conference contributions (Christen and Müller, 2011) and a large review covering the literature on DBS in the Nucleus subthalamicus (Christen et al., 2012). "Issues" refer to overarching themes (such as anatomical localization), "topics" refer to defined subject matters within an issue (such as specified anatomical localizations), and "terms" refer to the actual words that appear in the text. As outlined in **Table 1**, seven issues containing 73 topics were chosen for further analysis, based on the authors estimation of relevance (some topics could be in more than one issue; e.g., pain as indication or side-effect). Topics sometimes are composed of different terms (e.g., "accumbens" and "nucleusaccumbens"). In that case, the terms describe the same topic.

In addition, we analyzed ethical issues as a single topic characterized by the terms "ethic," "moral" and "social" because we were interested in investigating on how ethical aspects are being discussed in the literature. In total, we had 74 topics and 162 terms. For these topics, we performed a trend analysis, i.e., we counted the appearance of terms belonging to different topics in all texts of a single year starting from 2000 (due to the low number of texts in the 1990s that contained topic terms). We always normalized the trend data with the total number of publications per year for detecting trends within the whole DBS publication body.

Furthermore, we calculated the pairwise *co-occurrence* $C(X, Y)$ of two topics X and Y as:

$$C(X,Y) = \frac{\left|T(X,Y)\right|}{\min(\{|X|\,,|Y|\})}$$

Where $\left|T(X, Y)\right|$ denotes, how often the terms characteristic for topic X and Y appear in the same text and $|X|$ respectively $|Y|$ denotes, in how many texts these terms appear in the whole set. $C(X, Y)$ is between 0 (the terms of two topics never occur in a same text) and 1 (the terms always occur in same texts). The co-occurrence is used as similarity metrics for the network analysis.

For visualizing the co-occurrence matrix, we used Gephi, an open source software for analyzing graphs and networks[6]. In the resulting graph, the thickness of the edges reflects the co-occurrence, i.e., a higher probability that two terms appear in the same text is reflected by a thicker and more saturated connection.

The sizes of the nodes (= topics) reflect their betweenness centrality (BC), which is equal to the number of shortest paths from all vertices to all others that pass through that node. The betweenness centrality $BC(X)$ of topic X is defined as:

$$BC(X) = \sum_{X \neq Y \neq Z} \frac{\sigma_{Y,Z}(X)}{\sigma_{Y,Z}}$$

Where $\sigma_{Y,Z}$ is the number of shortest paths between topics Y and Z, and $\sigma_{Y,Z}(X)$ is the number of shortest path between those two topics that pass through X. For example, if there are three different shortest paths between two nodes and a third node is part of two of them, then the BC of this third node and for this specific configuration is 2/3. As a result, nodes with higher BC are more influential, because they functions as junctions for "communication" within the network (Freeman, 1977; Brandes, 2001). Terms with high BC are therefore hypothesized to play the most important role in establishing the meaning for the text and its interpretation.

We visualized the whole network of all topics as well as the networks that only contained topics of two issue classes (we performed six specific visualizations in total: anatomical targets-indication, indication-side effects, anatomical targets-side effects, technological issues-indication, economic issues-indications, positive-effects-anatomical targets. In the following, we display the three of them that yielded the most interesting results.

In some cases, we also looked at Page rank values of each node in order to make a statement about the importance of the term. Page rank is an algorithm that was originally developed to measure the relative importance of web pages. It formed the basis for ranking results when using the Google search engine and was named after Larry Page (Brin and Page, 1988; Page et al., 1999). Today, Page rank is a common tool in network analysis aiming at assessing linked documents based on their

[6] Available at http://gephi.github.io/

TABLE 1 | Issues and associated topics, characterized by terms that were contained in the final set.

Issue	Topics associated with issue (in brackets: terms that characterize the topic)
Anatomical localization	15 topics: {accumbens, nucleusaccumbens}, {alic, limb}, {amygdala}, {caudatenucleus}, {centromedian, centromedianparafascicularcomplex}, {cingulatecortex}, {cingulum}, {globuspallidus, globuspallidusexternus, globuspallidusinternus, pallidus}, {hippocampus}, {pallidum}, {pedunculopontine, pedunculopontinenucleus}, {stn, subthalamicus}, {subgenual, subgenualcingulate, subgenualcingulatecortex}, {vim}, {zonaincerta}
DBS indication	20 topics: {addiction, alcoholism, smoke}, {alzheimer}, {anorexianervosa, eatingdisorders, obesity}, {anxiety}, {ataxia}, {bradykinesia}, {chorea, huntington}, {clusterheadache, headache}, {depression}, {dyskinesia}, {dystonia}, {epilepsy}, {essentialtremor, tremor}, {hypomania, mania}, {memory}, {obsessivecompulsive, ocd}, {parkinson}, {schizophrenia}, {sclerosis}, {tourette}
Positive effects	3 topics: {qualityoflife, wellbeing}, {alleviation, relief, remission}, {enhancement}
Negative effects	18 topics: {safety}, {aberrant, adverse, adverseevents, complication, decline, deterioration, distress, impairment, perseverative, sequela, sideeffect}, {apathy}, {ataxia}, {character, personality}, {death, die, suicide}, {dysarthria}, {dyskinesia}, {fluency, language, speech}, {hemorrhage, hemorrhage}, {hypersexuality}, {hypomania, mania}, {impulsecontrol, impulsivity}, {infection, inflammation}, {memory}, {pain}, {psychosis}, {psychosocial}
Methodological issues	15 topics: {ablation}, {radiosurgery, ultrasound, gammaknife}, {capsulotomy}, {cingulotomy}, {pallidotomy}, {subthalamotomy}, {thalamotomy}, {psychosurgery, lobotomy, leucotomy}, {computertomography, diffusiontensorimaging, eegfmri, electrocorticography, electroencephalography, fmri, magnetoencephalography, mri, tomography, transcranialsonography, ventriculography, pet, spect}, {spinalcordstimulation}, {transcranialdirectcurrentstimulation}, {transcranialmagneticstimulation}, {vagusnervestimulation}, {electroconvulsivetherapy}, {dopamine, dopaminereplacementtherapy, duodopa, ldopa}
Economic issues	3 topics: {commercial, cost, costeffectiveness, economic, expensive, financial, inexpensive, market, socioeconomic, expenditure}, {industry, manufacture, manufacturer, medtronic, kinetra}, {effectiveness}
Technological issues	3 topics: {battery, cable, device, electrode, hardware, implantablepulsegenerator, lead, pacemaker, recharge, rechargeable, stimulator, wireless}, {closedloop, responsiveneurostimulatorsystem}, {program}

Remind that Lemmatizing in step 3 has mapped most of the different manifestations of topics (e.g., abbreviations) on a single term (e.g., the abbreviation "PD" on "parkinson"). The topics ataxia, dyskinesia, (hypo)mania, and memory are present in two issue classes.

connectivity structure. The principle of this measure can be explained as follows: the more links (in our case connections) refer to a site (in our case to a node/topic), the more weight a given site receives. As a consequence, the more weight a given site/node acquires, the bigger its importance. If one interprets co-occurrence of topics as a measure of "linking" two topics, then the page rank value would determine the order of "search results" in the network determined by the topics chosen by us. Since we are only rarely referring to page rank, we refrain from describing the mathematical basis of this algorithm in detail and refer to the original work by Brin and Page, to a brief description by Chen et al. (2007 p. 9) and to an in-depth review by Langville and Meyer (Brin and Page, 1988; Langville and Meyer, 2004; Chen et al., 2007).

Graphs were represented by use of a Force Atlas 2 algorithm (Jacomy et al., 2014). This algorithm is used to spatialize the network: nodes repulse each other similar to charged particles whereas edges attract their nodes like springs. The specific spatial distribution of each node therefore depends on the nodes' connections to other nodes. As a result, the specific coordinate of one single node cannot be interpreted on its own but has to be analyzed in combination with other nodes (Jacomy et al., 2014). Since edges are weighted, we added the "Edge Weight Influence" δ ($\delta = 3.0$, a pre-programmed selection option) to the visualization in order to prevent edge weights to be ignored.

RESULTS

Trend Analysis over Time

The trend analysis of potential anatomical DBS targets over time suggests a crosscurrent tendency: while the discussion of psychiatric DBS indications such as addiction, major depressive disorder (MDD), schizophrenia, Tourette syndrome (TS), and obsessive-compulsive disorder (OCD) (among others) are increasingly being discussed, the discussion of conventional, motor-related indications such as Parkinson's disease (PD) and essential tremor (ET) recedes (see **Figure 3A**). Dystonia, on the other hand, shows a surprisingly stable pattern over time. In confirmation of the above, the trends for anatomical DBS targets mainly match the ones depicted in the DBS indication analysis: while traditional anatomical targets used in movement disorder therapy decline over time—globus pallidus (GP), ventral intermediate nucleus (Vim), subthalamic nucleus (STN) –, a marked increase of "psychiatric" targets—e.g., nucleus accumbens (Nacc) or subgenual cingulate (SG)—is visible (see **Figure 3B**). Interestingly, the increase of psychiatric targets is less pronounced than the one for psychiatric indications, suggesting that psychiatric indications have become *per se* an emerging topic within the DBS literature. The above described pattern is again partly backed when including the trend analysis for lesion methods (including radiosurgery, capsulotomy, gammaknife, pallidotomy, to name a few) specifically: the discussion of such alternative techniques in the context of motor disorders decreases substantially. Interestingly, there is no trend in the case of psychiatric indications (see **Figure 3C**).

In line with these results is the fact that overall, the trend analysis for negative effects shows an increased emphasis in discussing "psychiatric" phenomena (including anhedonia, hypomania, personality, and impulsivity among others) whereas phenomena associated with traditional, motor related indications (apraxia, ataxia, dysarthria, among others) are consistently less often discussed. Surgery related issues (such as hemorrhage, infection, and ischemia, to name a few) are quite stable. The data also confirm earlier findings (Müller and Christen, 2011) that general terms which indicate side-effects non-specifically such as "aberrant," "adverse," "complication," "distress," "impairment," "sequel," "sideffect" (among others), are also less often mentioned.

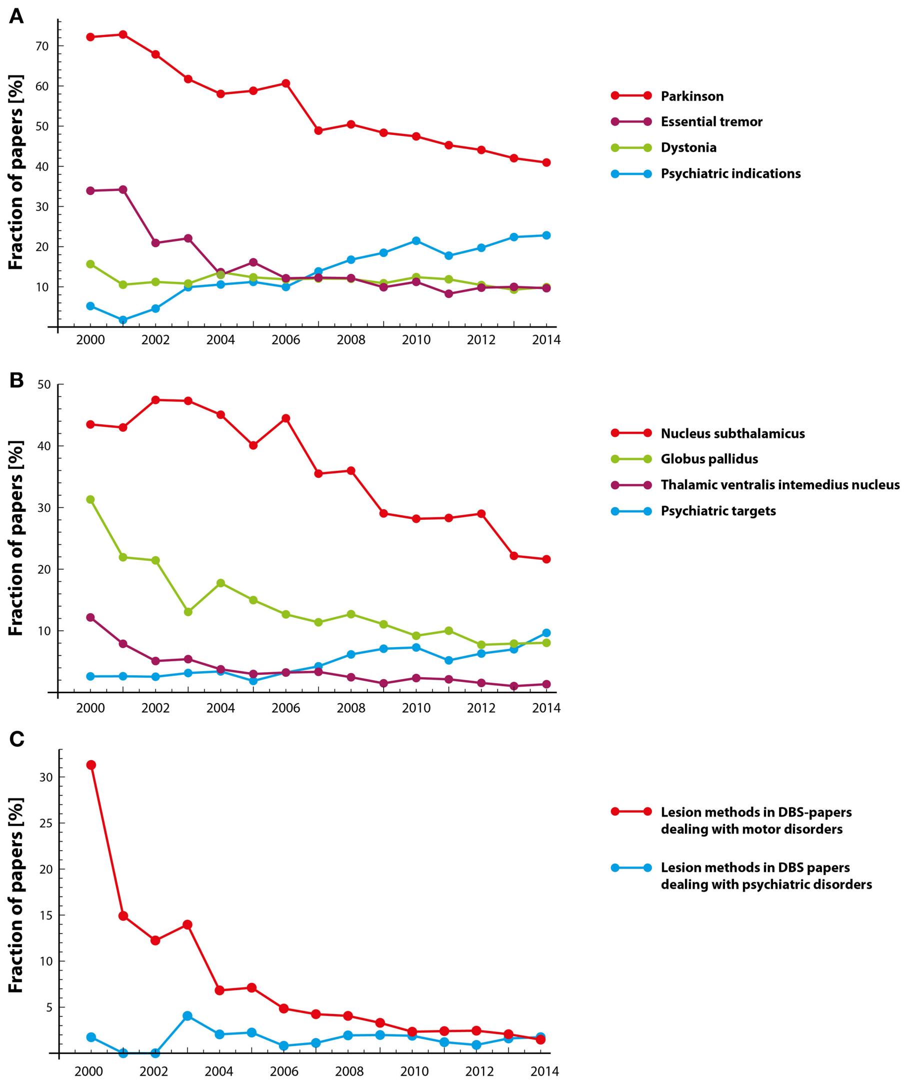

FIGURE 3 | Trend analysis for selected topics. (A) Movement disorders vs. psychiatric indications; **(B)** DBS targets for movement disorders vs. targets for psychiatric indications; **(C)** mentioning of lesion methods in papers also mentioning movement disorders vs. psychiatric indications.

Finally, technological terms associated with new stimulator systems such as "closed loop," "responsive neurostimulator system," "rechargeable," and "wireless" have partly displaced the discussion about conventional technological and hardware-related terms which themselves are less often discussed (e.g., "battery," "cable," "electrode," "implantable pulse generator," "lead," "pacemaker," and "stimulator"; data not shown).

Analysis of Whole Data Set

General Structure of the Graph

Overall, the aggregated graph (except the issue ethic which was analyzed separately) consists of 73 nodes and 1908 edges (**Figure 4**). We observe the average shortest path length to be pretty small (1.3) (Jackson, 2008) (i.e., we can move from one point in the network to another point quite easily, the graph is therefore well-interconnected). The graph furthermore shows a high number of influential nodes besides a high value of average degree (i.e., a quite diverse text corpus). In general, degree is a measurement of connectedness in graph theory which means that a specific node in a given network with high degree consequently has many neighbors in that network. A high average degree therefore means that the graph is highly interconnected. Because of this high average degree, no contextual clusters have been identified using the community detection algorithm of Blondel et al. (2008).

Thematic Structure of DBS Publications

The betweenness centrality (BC) analysis reveals that apparently five main topics dominated the DBS field in terms that they occupied an exceedingly central space within the whole text corpus. Those are effectiveness, safety, side-effects, and hardware related issues apart from PD, the main indication for DBS

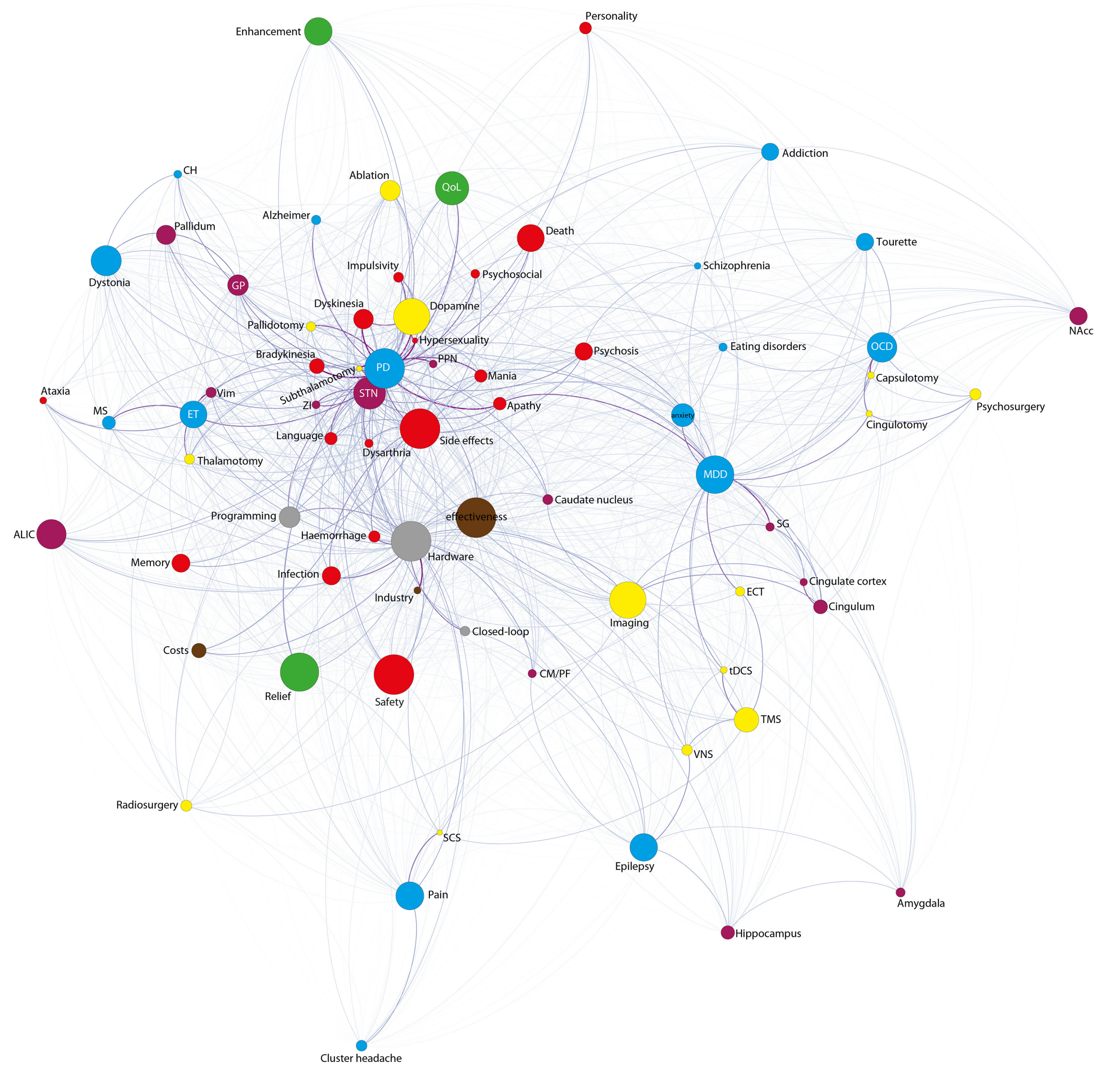

FIGURE 4 | Network of all 73 topics (except ethic). Color-code: Blue: indications; purple: anatomical targets; yellow: methods; green: positive effects; red: negative effects; brown: economic issues; gray: technological issues.

(equal BC values; see **Figure 4** and Table 1 in Supplementary Materials). Moreover, those topics are adjacent to most of the words in the network and therefore function both as local hubs (i.e., a node with many connections) and as important junctions within the whole text corpus.

Apart from the five main topics, the topics including positive effects (alleviation, relief, remission), MDD, imaging methods, dopamine, quality of life (QoL), STN, dystonia, OCD, anterior limb of the internal capsule (ALIC), pain, enhance(ment), epilepsy, death, ET, and imaging methods (with decreasing values across sequence) also show high betweenness centrality. Concrete side-effects appear at place 25 and 27 (dyskinesia and infection). The topics personality (place 41), psychosocial (place 56)—both inherently difficult variables –, subthalamotomy, alternative therapies [such as electro-convulsive therapy (ECT), vagus nerve stimulation (VNS), spinal cord stimulation (SCS), or transcranial direct current stimulation (tDCS)] and hypersexuality [which itself occurs quite rarely (in 19 abstracts only)] (place 72) receive especially low BC.

A Google's page rank analysis revealed the following sequence of importance: PD, hardware related terms, side-effect, STN, MDD, effectiveness, dopamine, ET, imaging-methods, GP, OCD, safety, dystonia, and positive effects (alleviation, relief, remission). The BC values of neuroanatomical targets indicates a higher BC value for ALIC than for GP and a higher one for Nacc than for Vim. However, this sequence changes when conducting Page-rank analysis: highest values are accredited to the STN, GP, ALIC, Vim, and Nacc. Also, the lesional approaches (pallidotomy, subthalamotomy, and thalamotomy) receive dramatically more weight (in the middle field) when performing Page-rank (among lowest if conducting BC).

Analysis of Specific Topics

Next we performed a co-occurrence analysis incorporating the five terms (effectiveness, safety, side-effect, PD, and hardware) with highest BC (see Table 2 in Supplementary Materials for detailed information on all co-occurrence-values). Firstly, the topic effectiveness is most often mentioned in combination with the topics PD and hardware. Likewise, the second topic safety is most often discussed in the context of PD and hardware. Third, we were interested in the topic side-effect, which shows to be, apart from PD, the topic with most above-threshold co-occurrences (co-occurrences > 0.3, determined by the authors based on distribution of the data; see Table 2 in Supplementary Materials). It is most often mentioned with hardware- and motor-related side-effects but also includes side effects of the psychiatric/psychological domain: infection, hemorrhage, dysarthria, apathy, speech, psychosis, memory, mania, dyskinesia, psychosocial, anxiety, hypersexuality, subthalamotomy, STN (among others, with decreasing values across sequence). Fourth, the main indication PD, is discussed to a greater extent with hypersexuality (or more accurately; whenever there is a text including the term "hypersexuality," "parkinson" is most often also present), bradykinesia, subthalamotomy, and apathy. Please note that the term "hypersexuality" appears quite rarely (in 19 abstracts only). The results therefore have to be complemented and analyzed in combination with how often a term actually occurs within the texts (for frequency distributions see Supplementary Figure 1B). The last and fifth key-topic with highest BC includes hardware-related issues which is discussed most often with industry, hemorrhage, new systems (terms: "closed loop," "responsive neurostimulation system"), program, infection, PD, and general economic-topics (terms "cost," "commercial," "economic," "financial" among others).

Analysis of Interactions between Different Issues

In order to investigate on potential interactions of different issues, we conducted a co-occurrence analysis. First we outline the co-occurrence of topics related to the issues indications, anatomical targets, and side-effects.

Interaction between Indications and Side-effects

As for the combination of indications and side-effects (**Figure 5**), the strongest co-occurrence connections yielded the following results. The topic PD is most commonly discussed with hypersexuality (as already stated above). Moreover, PD is often discussed with apathy, dyskinesia, mania, impulsivity, speech (and dysarthria), psychosocial, death/suicide, and psychosis. ET, on the other hand, is most often discussed with dysarthria. Of note is the fact that neither MDD nor dystonia is strongly connected to any concrete side-effect. Additionally, and as a side note, an intracategorial analysis shows most often co-occurring side effects to be impulsivity and hypersexuality.

Interaction between Indications and Anatomical Targets

The combination of indications and targets (**Figure 6**) showed strongest co-occurrence connections between PD and the STN, followed by the pedunculo-pontine nucleus (PPN), the zona incerta (ZI) and lastly with the GP. ET, on the other hand, is clearly connected with the Vim. MDD is most often linked to the SG, the cingulate cortex, and Nacc, while the indications bradykinesia and dyskinesia show most frequent connections to the STN. Finally, OCD is most often discussed with the Nacc and schizophrenia with the hippocampus.

Interaction between Side-effects and Anatomical Targets

Finally, the strongest co-occurrence connections between the issues side-effects and anatomical targets (**Figure 7**) yielded the following results: The STN is most often discussed with apathy, mania, speech, dysarthria, impulsivity, death, and hypersexuality. We found no robust co-occurrence between neuroanatomical targets relevant for the treatment of psychiatric disorders and concrete side-effects (such as infection and the like). Also no marked co-occurrence of side-effects and anatomical targets other than the STN were observed.

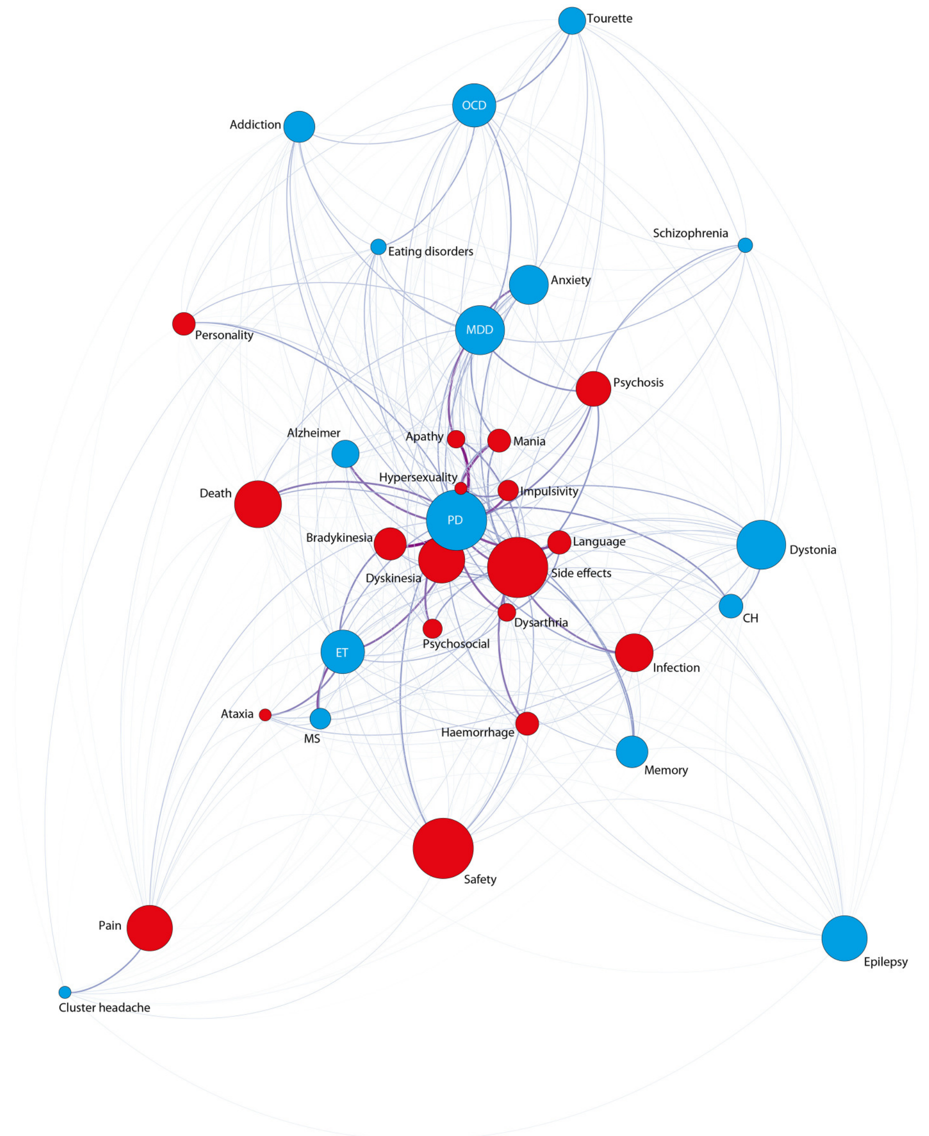

FIGURE 5 | Network-Analysis for the issues indications (blue nodes) and side-effects (red nodes).

Additive Relationships

Additively, we were interested in potential connections between topics from economic issues, technological issues, and positive effects.

The topic industry is most often discussed with PD, imaging methods, safety, and ET. Interestingly, terms like "costs," "economic," "commercial" and the like are markedly linked to the indication PD solely. The issue positive effects including the topics alleviation, relief, and remission are most often associated with PD, pain, and dopamine. The terms "quality of life" and "wellbeing" on the other hand are most often connected to PD, side-effect-related terms, psychosocial, and apathy while most prominent connections with regard to the topic enhance(ment) are PD, hardware, and STN. In particular, the strong connection between QoL and psychosocial is important because it may highlight an increased interest in psychosocial issues in the context of QoL. Finally the topic program is most often discussed with PD and STN whereas the topic of new-devices (terms: "closed loop" and "responsive neurostimulation system") is most often connected to PD and epilepsy.

When integrating how methods other than DBS are discussed within the DBS-literature, one finds the following outcomes:

Concerning indications, PD is most often connected to subthalamotomy, dopamine, and pallidotomy. OCD on the other hand is robustly connected to capsulotomy and to a minor degree to cingulotomy whereas ET is mentioned most often in combination with thalamotomy. Finally, MDD is most often discussed with ECT, cingulotomy and still quite often with tDCS whereas epilepsy is most often discussed with VNS.

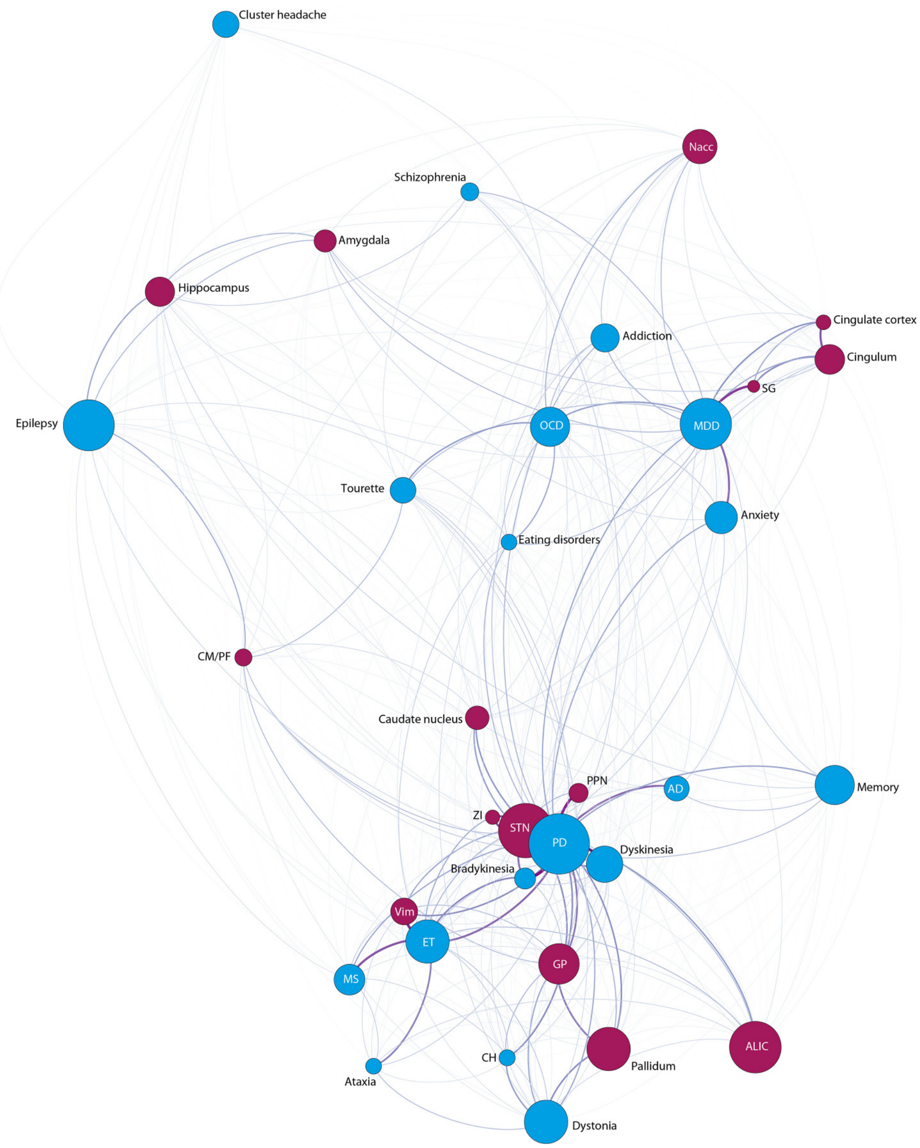

FIGURE 6 | Network-Analysis for the issues indications (blue nodes) and anatomical targets (purple nodes).

Regarding side-effects, dopamine is apparently most often discussed in combination with hypersexuality, impulsivity, psychosis, apathy, and dysarthria. Psychosurgery on the other hand, is mostly discussed in the context of cingulotomy whereas pain (here probably meant as indication) most often with SCS.

Associations with the Topic "Ethic"

There is a rich discussion which deals with ethical aspects in the context of DBS. Ranging from personality changes and side-effects (Christen et al., 2012) to topics taking up the debate of human enhancement (Synofzik and Schlaepfer, 2008; Schermer, 2013) and research ethics (Fins et al., 2011), the discussion is clearly multifaceted. Hence, ethical questions are a constant topic of debate. Therefore, we were interested in how ethics-terms interrelate with other terms of the text corpus. We therefore investigated the co-occurrence of the topic ethics with all other topics (see **Figure 8**). Apart from the rare topic psychosurgery (present in only 52 texts) and the very frequent topic PD (present in 3544 texts) which yielded the strongest co-occurrences, the ethics-topic is most often linked to personality, psychosocial, side effect, hardware, MDD, and hypersexuality. Of note is the very rare connection between ethical issues to the GP (in only 3% of the total possible co-occurrences) compared to the STN (in 14% of the total possible co-occurrences).

DISCUSSION AND CONCLUSION

We will first outline some of the findings which underpin the validity of our approach directly followed by discussing

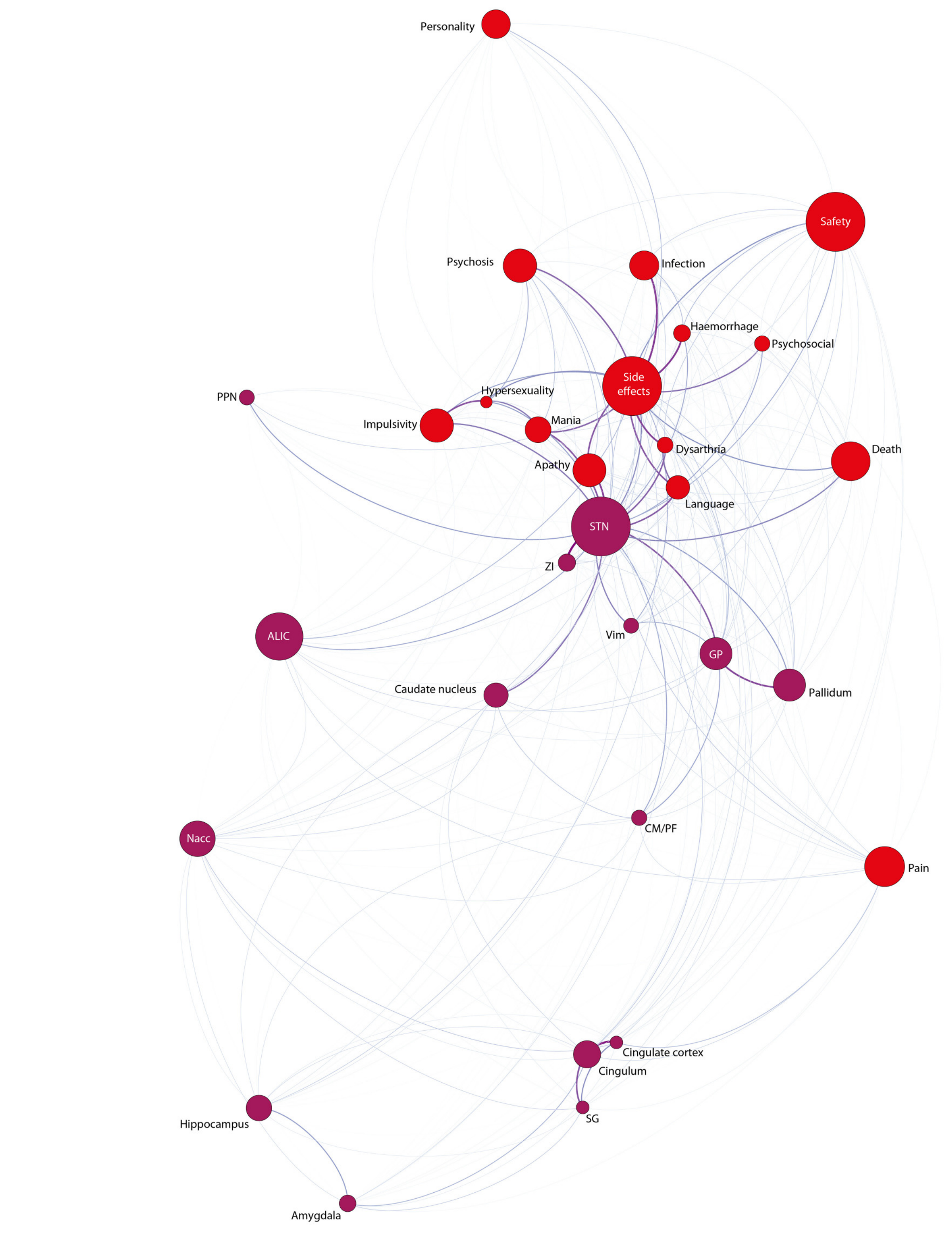

FIGURE 7 | Network-Analysis for the issues negative effects (red nodes) and anatomical targets (purple nodes).

findings acquired from the trend analysis over time and then guide the discussion toward the graph analysis based on BC and co-occurrence. Finally, we will outline pertinent ethical questions.

Findings Corroborating the Validity of Our Approach

We detected a multitude of findings which underpin the validity of our approach, some of which we highlight in the following.

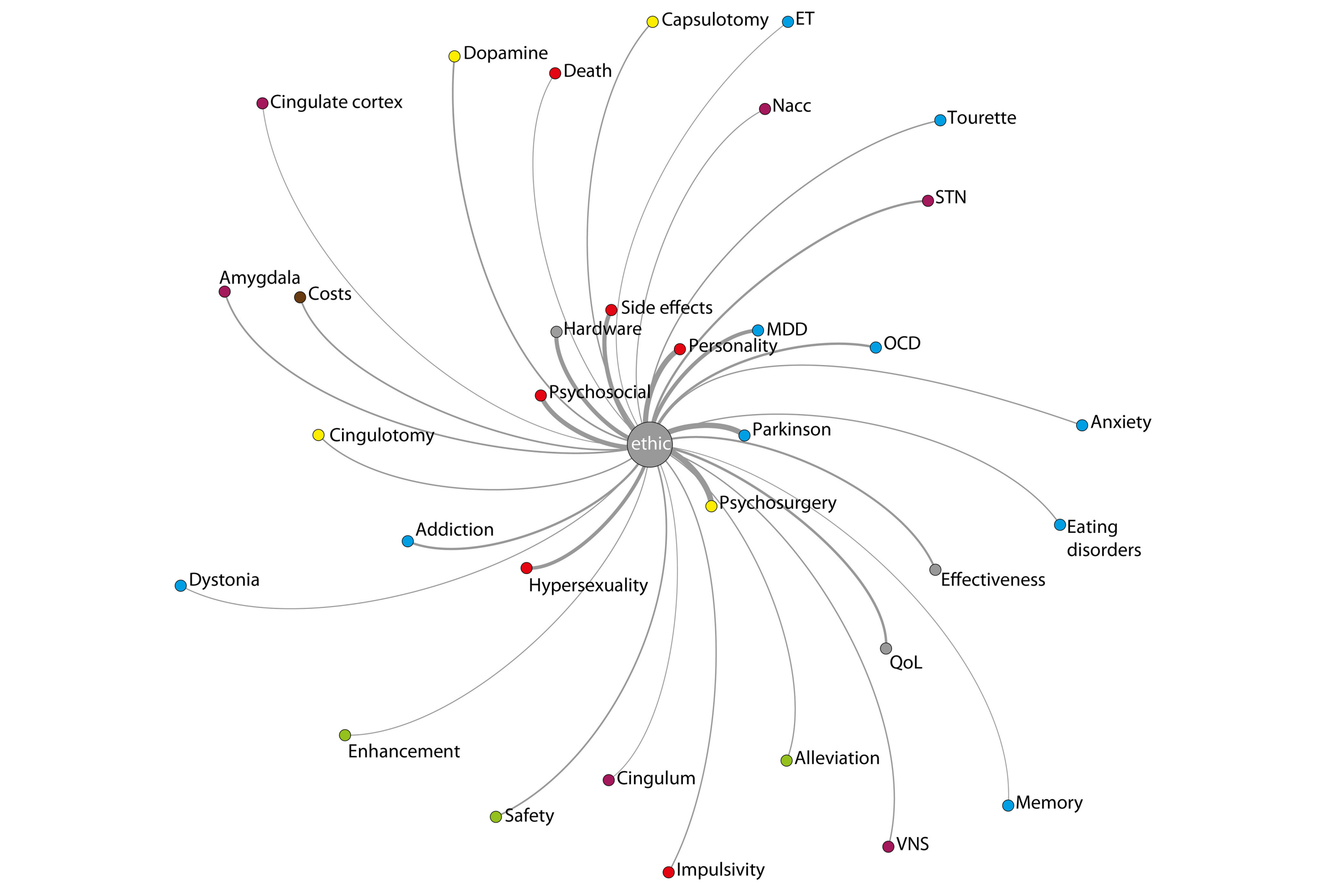

FIGURE 8 | Interrelation of the topic ethics to all other topics with at least 5% co-occurrence (for color code see caption of Figure 4).

Chronic pain for example, is a well-described indication suitable for spinal cord stimulation (Wolter, 2014). The findings including indications and lesion methods also confirm known connections as evidenced in the case of ECT, a well-known therapeutic option for the treatment of MDD, besides others. The relationship of epilepsy and closed-loop systems might also underpin the robustness of our methodological approach by bearing in mind that epilepsy characterizes a promising indication for the application of closed loop devices (Armstrong et al., 2013; Krook-Magnuson et al., 2013; Paz et al., 2013; Nagaraj et al., 2015). Regarding anatomical targets and side-effects, we highlight a distinct connectivity between the STN and impulsivity which has been described elsewhere (Zavala et al., 2015). Regarding the detected intracategorial connection between impulsivity and hypersexuality, a recent publication confirms a tight connection between the two topics (Kor et al., 2013). Hence, a multitude of identified co-occurrences incorporating the different issues such as indications and corresponding lesion methods, or indications and anatomical targets among others, serve as validation of our method.

Trend Analysis

When analyzing the data set including DBS-indications and relevant anatomical targets, one can identify a clear shift away from motor-related neuroanatomical targets (GP, Vim, STN) (even though numerically still predominant) toward an emphasis on anatomical targets which are especially relevant in psychiatric indications (Nacc, amygdala, hippocampus, SC) (see **Figures 3A,B**). Such a tendency is indicative for the broadening of the therapeutic spectrum of DBS. A multitude of scientific publications highlighted this circumstance already (e.g., Hariz, 2012; Hariz et al., 2013; Christen et al., 2014, to name a few). Even though we cannot make a qualitative statement about how such topics are being discussed (i.e., the discussion may be framed in a supportive, critical, or neutral way), the identified increase may represent the seen utility in DBS for the treatment of psychiatric indications. Questions about suitability of such complex disorders for the therapeutic application of DBS and the difficult search of anatomical loci for the treatment of such indications (e.g., for MDD (among others): Nacc, ALIC, and SG) may also be indicative for such an increase. Additionally, the data highlights no standard locus for the treatment of MDD (e.g., Hariz et al., 2013 for the unspecific use of neurostimulation targets in the context of MDD, TS, and OCD; or Da Cunha et al., 2015; Kocabicak et al., 2015). Finally, the trend analysis incorporating negative effects (data not shown) completes the picture; while motor side effects are less frequently discussed, complex issues such as personality are increasingly the topic of the current debate. In the context of psychiatric disorders, such phenomena seem to be prevalent to a greater extent.

The trend analysis involving lesion based therapy approaches revealed that lesion approaches recede in the context of motor-related disorders and are quite stable in the case of psychiatric disorders. This might demonstrate—and under the assumption that medication based therapy is still the most frequently used therapeutic approach—that (1) lesions are still considered to be an effective and reliable means for patients refractory to drug-therapy and (2) that DBS was not (yet) able to replace lesion-based therapy approaches in psychiatry. When talking about an observed decline of the discussion of topics related to lesion approaches, one has to emphatically point out that this reflects how lesions are being discussed within the DBS-literature only. This means that we are limited in our interpretation of observations related to lesion methods and look with a narrow "DBS-perspective" on relationships which are discussed in these articles. Moreover, lesion approaches are still considered therapeutic competitors and as such might receive little attention. We have outlined elsewhere (Christen et al., 2014, but see also Müller et al., 2015) the importance of ensuring alternative therapeutic approaches which of course would not quantitatively carry much weight when extracting abstracts from numerous DBS-publications.

Network Analysis

Thematic Structure of DBS Publications

Our results suggest that the topics PD, side-effect, hardware, safety, and effectiveness play a conducive role within the DBS literature and this to a greater degree than other terms because the relation of their influence to the total number of connections was calculated to be highest (reflected in BC). One could say that the backbone of any publication in the context of DBS is composed of issues about safety, side-effects, effectiveness, hardware, and PD. These junctions act as mediators within the discursive field of the textual graph. The broader backbone of a publication in the field of DBS can be inferred to be generated through the mentioning of the remaining major topics: relief, MDD, imaging methods, dopamine, QoL, STN, dystonia, OCD, ALIC, pain, enhance(ment), epilepsy, death, ET, and TMS. This furthermore means that by analyzing the top 20 terms and by allocating those to the major topics, it is evident that indications are most numerously represented ($n = 7$), followed by negative effects ($n = 4$), methods ($n = 3$), and anatomical targets ($n = 2$). As the discussion in the DBS literature is shifting toward new and more specific questions, specific anatomical targets tend to be less often associated with more general topics. The strong representation of indications again reflects the trend of broadening the therapeutic spectrum in the context of DBS.

Personality and Psychosocial Issues in DBS Publications

The growing discussion about personality (trend analysis) is not yet reflected in BC because the topic personality shows one of the lowest BC-values. This can be explained by referring to the low frequency of the topic itself within the whole text corpus and may likely change as such issues have to be addressed in the context of measuring pre-post-effects in the case of psychiatric neurostimulation. The circumstance of personality and psychosocial issues receiving low BC may indicate that their associated concepts represent genuinely vague and difficult variables and consequently are not utterly useful for clinical research. As validated instruments to objectively and qualitatively measure changes in the personality and the psychosocial dimension are often missing or criticized for not accurately measuring the topic under investigation, such much needed concepts cannot easily enter clinical research (Dimitrov and Rumrill, 2003). The fact that psychiatric indications are increasingly being addressed by means of brain-stimulation, the need for the accurate and thorough observation and measure of psychosocial and personality-related issues (and also in the context of movement and other disorders, Pham et al., 2015) is obviously most important. Therefore, with more accurate insights into the neuronal circuitries exerting maladaptive effects on many disorders despite high complexity and limited means of investigation (Rossi et al., 2015) and the eagerness to evaluate results beyond short-term quality of life (Ooms et al., 2014), indications for DBS should get more individually tailored (Galati and Stefani, 2015). Additively, the accurate and longitudinal measure of psychosocial issues has already been proposed also in the context of movement disorders (Schüpbach and Agid, 2008). Combined with the fact that the topic QoL is robustly connected to the topic psychosocial, as well as the fact that a limited number of scales for the measurement of personality- and psychosocial-related issues do exist, the introduction of such instruments combined with the eagerness to improve such instruments, is greatly needed.

Economic Issues

The restriction of the discussion incorporating economic issues to PD only, also poses questions. Given the increase of psychiatric indications, economic considerations should be in place and extended toward other indications in order to adequately address socio-economic issues. The often observed co-occurrence between the topic economic and ethic further emphasizes this point.

Centralities of Neuroanatomical Targets and Their Implications

The BC-values of neuroanatomical targets indicate a higher one for ALIC than for GP and a higher one for Nacc than for Vim. This may serve as another evidence for the growing importance of neuropsychiatric topics in the literature of DBS. However, this sequence changes when conducting Page-rank analysis: highest values are accredited to the STN, GP, ALIC, Vim, and Nacc. Since Page-rank puts an emphasis on the number of connections (e.g., "links"), the traditional motor targets STN and GP would be listed before ALIC within a given search result. Given the fact that GP and Vim represent historically older topics in DBS and based on the higher Page-rank values, the two are more densely linked with other topics. However, ALIC and Nacc already are more central concepts within the DBS-literature, presumably acting as mediators of information to a greater extent than GP and Vim.

MDD and Alternative Therapeutic Approaches

The execution of a Page-rank analysis also changes the sequence of the most important topics: PD clearly is attributed the highest value and MDD makes it into the "top 5." In sum, one can state that depression is the most discussed psychiatric indication in the DBS literature. In light of MDD's importance within the DBS literature, it is from a bioethical point-of-view important to emphasize that this indication has not yet received approval from the U.S. Food and Drug Administration (FDA) as a standard therapeutic treatment. Patients therefore should be well-informed about the ongoing search of optimal neuroanatomical targets, the challenging support without standardized guidelines of patients along the whole treatment and beyond as well as the complexities associated with the appropriate conduct of clinical trials (Jimenez-Shahed, 2015) and the vulnerability of patients (Bell et al., 2014).

When looking specifically at alternative therapeutic approaches such as SCS, tDCS, ECT, and VNS, it becomes obvious that they receive especially low BC. This circumstance can be explained by highlighting that we specifically selected scientific publications involving DBS. Presumably, those publications have a low interest in advocating for alternative therapeutic approaches. Furthermore, the co-occurrence analysis shows that within the DBS-literature, ablative therapeutic approaches such as pallidotomy, subthalamotomy, and thalamotomy are most frequently discussed in combination with terms from the topic side effect. While ablative therapeutic strategies appear to a greater degree to be negatively connoted, the latter also symbolize the still most direct competitors to DBS, as already outlined within the trend-analysis. Interestingly, the lesional approaches (pallidotomy, subthalamotomy, and thalamotomy) receive dramatically more weight (in the middle field) when performing Page-rank (among lowest BC). In analogy of the previous hypothesis, lesion approaches might be underestimated if incorporating BC only and seem to be interlinked to a greater extent.

Discussion of Issue-comparisons

The specific comparison involving indications and side-effects indicates that the description of side effects is clearly dominated by the ones closely associated with PD, the indication for which most publications exist ($n = 3544$, followed by essential tremor, $n = 901$). This does not mean that PD is the DBS indication where most side effects occur, but that side effects are most frequently described in the context of PD. As outlined above, the strong connection between PD and hypersexuality only reflects that within the few papers dealing with hypersexuality, the term "parkinson" is almost always present. Since the topic hypersexuality is very infrequent, this result has to be taken with caution. On the other hand, one also has to take into account that our data consist of abstracts only, i.e., terms need to have some importance within a paper in order to appear in the abstract. Side effects of other indications, especially neuropsychiatric, are to a far lesser degree discussed. Depression for example co-occurs only to a minimal extent with personality, death, and psychosocial issues. As highlighted previously, side effects in the context of psychiatric disorders are expected to be (1) much harder to be identified and (2) still have to be published as such newer indications have only recently been added to the therapeutic spectrum. OCD with its unconventional entry into the therapeutic landscape via a humanitarian device exemption (Fins et al., 2011) is also quite rarely discussed in the context of concrete side effects [probability of co-occurrence: hypersexuality (11%), impulsivity (8%), and infection (5%)]. Again, there is a duty to longitudinally follow patients in order to constantly monitor potential side-effects, besides the great need for introducing new measures in order to fully capture potential changes also in the psychosocial/psychiatric domain (Lilleeng et al., 2015).

The comparison involving indications and neuroanatomical targets highlights a further interesting result: apart from being discussed most often with the STN, PD is also quite strongly connected to the PPN, even more than to the GP—the other standard target for stimulation apart from the STN. PPN-stimulation was initially promoted for the treatment of balance impairments as well as refractory gait freezing and has been shown to be used as surgical target relatively unspecifically ("the PPN-area") and this despite largely unknown clinical usefulness (Hariz et al., 2013). The high centrality of the PPN together with such a critical stance toward its usefulness and lack of clinical evidence further corroborates an apparent tension.

Finally, when comparing side-effects and anatomical targets, we observe again a dominant description of side-effects in combination with the STN—one of the most widely used anatomical targets for the treatment of movement disorders. The most frequent co-occurrence of the GP is its connection to apathy, but this happens only in 7.5% of cases in which a possible co-occurrence is possible. This, potentially driven by stimulation of ventral and medial subterritories of the STN (for STN-subterritories see Tremblay et al., 2015; for actions beyond motor control see Zavala et al., 2015), reflects a described dominance of side-effects in the context of STN rather than other (e.g., GPi) DBS targets. Moreover, this could indicate that side-effects emanating from predominantly ventral STN-stimulation have overshadowed the description of side-effects of other anatomical targets such as the GP. Alternatively, the STN may be intrinsically more prone to (behavioral or affective) side effects due to its circumscribed connectivity to limbic areas. There is evidence for a clearer separation of motor and non-motor functions in the GPi compared to the STN (Wichmann and DeLong, 2011; Da Cunha et al., 2015). Additionally, ALIC, an anatomical target with marked BC, is rarely found in combination with specific side effects. This imbalance may be problematic or may be the result of the already mentioned problem of capturing side-effects in the context of psychiatric disorders. However, if DBS for the neuropsychiatric domain further expands, the accurate description combined with the nuanced measurement of psychological changes poses a bioethical obligation and responsibility for any researcher involved. It might be an interesting endeavor to once try to capture the implicit perception of professionals in the field of DBS regarding such issues. The numerical imbalance of how e.g., anatomical targets are discussed in relation to side-effects together with the concrete framing of such issues within the most often read articles in the literature supposedly induce unconscious preferences which do not necessarily display the situation in an accurate way based on (pre-)clinical evidence.

Bioethical Issues

As the field of bioethics is comparably subjected to a vast increase of publications, quantitative methods for obtaining a better understanding might be as important as for neuroscience. Such an approach is moreover suitable for identifying potential mismatches between what is currently being discussed and what might be important ethical topics which are less tangible or more vulnerable for being overlooked.

Motor-targets and Their Connection to Ethics

Apparently, ethical issues are to a greater extent discussed in combination with the STN rather than the GP. Is the STN therefore more thoroughly described in terms of its stimulation-based ethical consequences or is there evidence that the STN intrinsically harbors to a greater extent problematic ethical issues including the potential of inducing undesired effects? The debate of which target is most appropriate (mostly including STN and GP, Follett et al., 2010; Krack and Hariz, 2010; Odekerken et al., 2013) is an old one. But since currently, there is evidence for a statistical chance selection rather than one based on (patho)-physiological evidence for either receiving STN or GP stimulation (Christen et al., 2014; Gilbert, 2014) [besides clinical considerations such as envisaging drug reduction (STN) or preexistence of cognitive symptoms (GPi) (Da Cunha et al., 2015)], this difference might be an important one. As long as there is no proven display regarding superiority in terms of therapeutic action, there might be a duty to investigate ethical issues to a similar extent for all nuclei used for stimulation.

Depression and Its Connection to Ethics

Another interesting finding is an observed imbalance reflected in a strong connection between the issue which incorporates the topic ethics on the one hand and MDD on the other and a substantially weak connection of the former topic and the one involving the most often used anatomical targets in the context of depression. Whenever ethical issues are being discussed, MDD is most often also discussed. However, the factual co-occurrence dramatically decreases in the case of neuropsychiatric anatomical targets: ethical issues co-occur only in 6.5% of cases when discussing the Nacc, in 3.5% when discussing the ALIC and in 1.75% when discussing the SG. This apparent dissociation between indication and anatomical target is questionable and more pronounced as in the case of PD and STN. As DBS has not faced a comparably long history regarding randomized controlled clinical trials for psychiatric disorders, studies have to be continued in order to identify which nucleus (or nuclei) shows greatest potential for the treatment of MDD and other neuropsychiatric disorders but also to identify which nucleus might be especially vulnerable for (behavioral) side-effects, psychosocial maladjustments and consequently ethical issues (e.g., non-maleficence).

Hardware Related Issues

As evidenced in some publications (Kondziolka et al., 2001; Okun et al., 2005; Fins, 2009) hardware related complications do impose ethical challenges. This is also backed by our results highlighting an apparent tension between hardware and ethical issues. Concomitantly, our data set indicates a continuous decrease of the discussion of hardware related topics (evidenced in the trend analysis; data not shown) but also particularly high BC. The strong link to ethical issues, apart from the mere description of hardware-related side-effects, might be evaluated as unintuitive. However, the data suggests that hardware related issues in the context of social, ethical and moral questions apparently have already been a topic of debate (e.g., Hilimire et al., 2015; Fumagalli et al., 2015). Generally, the topic of ethical and social implications of technological devices is certainly an important one which, e.g., in the context of emerging closed-loop devices, will nourish further discussions in the future. Therefore, closely investigating ethical, social, and clinical aspects of the follow up process longitudinally, including e.g., the often challenging postoperative phase for precise DBS parameter adjustments (Ineichen et al., 2014) as well as fiscal and legal aspects of hardware replacement apart from ethical issues specifically in the context of hardware is important. In parallel, our result may emphasize not only a duty to investigate hardware related ethical issues which transcend merely and well-known technical problems (Christen et al., 2014) thoroughly, but also that ethical duties already instantiated also apply to engineers which represent key players and which are well-positioned to support the deployment of innovative hardware in order to diminish the burden of patients (Fins, 2009). In the general DBS review literature, hardware-related issues such as the ones attached to recording devices and the related implications for patients' autonomy and responsibility but also the potential use and abuse of such recorded signals in connection with privacy issues, the dependency on device manufacturers (Underwood, 2015) and conflicting interests (Clausen, 2011), the long-term risk of living with implanted hardware (Farris et al., 2008) apart from psychological issues have in comparison to surgical complications probably received less attention. The fact that hardware-related issues receive dramatically more weight in the context of ethical challenges than impulsivity, concrete side-effects and death/suicide is certainly surprising and needs further analysis. Whether this means that hardware-related issues are already sufficiently discussed in an ethical and social context or need further exploration has to be identified by a qualitative in-depth analysis.

Although DBS has alleviated patients suffering tremendously, many obstacles still remain. Recently, the development of innovative neuromodulation exemplified by current steering (Martens et al., 2011; Hariz, 2014b), adaptive DBS (Little et al., 2014) but also the potential deployment of closed-loop devices (e.g., Rosin et al., 2011; Grahn et al., 2014; Williams, 2015) have increasingly gained weight within the discussion of DBS. In the meanwhile, magnetothermal neuromodulation in translational models (Chen et al., 2015) shows potential to increase our knowledge of neuronal microcircuitries (Temel and Jahanshahi, 2015). Apart from technological as well as biological hurdles (e.g., identification of true biomarkers) also ethical issues might arise. As our data highlights a tremendously weak co-occurrence of the topics ethics and closed-loop, it might be time to think about how emerging closed-loop devices may affect already instantiated guidelines and what differences as well as implications might be identified both from a theoretical (i.e., philosophical) but also practical (i.e., what it would mean for patients) perspective.

Limitations

This study, of course, incorporates some limitations. First of all, as in any quantitative text-network approach, we are unable to make qualitative statements. This however, is within the nature of a heuristics approach. Additionally, various topics might in fact be used in a different context than used as a basis for interpretation within this study. For example, the neuroanatomical targets may in fact very well also be mentioned without referring to a target for stimulation. For example, the STN may be described within a DBS-publication not as a target for stimulation but within the context of hyper-reactivity in the case of hemiballism. Due to the fact that we have limited our analysis to abstracts, we assume this scenario to be quite infrequent and would hypothesize such a wording to be included in a general introduction rather than within an abstract. Moreover, the Web of Science database is associated with a language bias. As papers emphasizing psychosocial and philosophical issues are often published in other languages, they are likely to be underrepresented in our sample. Finally, topics which incorporated multiple terms, of course, inevitably have a greater probability of co-occurrence.

Outlook

The proposed analysis is by no means complete and has no prerogative of accuracy. It is one additional possibility to read any text in order to gain new insights about its structure and hidden messages, suitable to deal with a large number of texts. We are of the opinion that applying network approaches, visualization techniques and graph theory to a text corpus might be an innovative and promising alternative which entails fruitful and worth considering aspects. The final interpretation of the data, once visualized as a graph, is certainly open for discussions and by no means definitive.

Hariz recently wrote in his book chapter "The literature revisited" that "serendipitous discoveries and advances in functional imaging are providing 'new' brain targets for an increasing number of pathologies, and the corollary is an exponentially growing literature on DBS, such that it is simply impossible to keep track of all papers and books appearing on this subject." He then goes on by stating "While most of the literature constitutes an invaluable wealth of knowledge, a small but important part gives rise to serious concern and needs to be revisited and discussed" (Hariz, 2014a). By using a quantitative network approach, we tackled this issue from another perspective and tried to identify potentially hidden and underrepresented issues which might be relevant for further discussions and future research.

AUTHOR CONTRIBUTIONS

CI extracted the data, MC generated the final set, CI and MC analyzed the data and wrote the paper. CI furthermore confirms that he has final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnint.2015.00052

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

OPINION
published: 20 April 2016
doi: 10.3389/fnint.2016.00017

Mental Side Effects of Deep Brain Stimulation (DBS) for Movement Disorders: The Futility of Denial

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Keywords: deep brain stimulation, psychiatric side effects, suicide, moral competence, depression, Parkinson's disease

OPEN ACCESS

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Received: *01 February 2015*
Accepted: *29 March 2016*
Published: *20 April 2016*

Citation:
Cyron D (2016) Mental Side Effects of Deep Brain Stimulation (DBS) for Movement Disorders: The Futility of Denial. Front. Integr. Neurosci. 10:17. doi: 10.3389/fnint.2016.00017

The benefits of deep brain stimulation for parkinsonian patients are well documented and have established the method as mainstay in the late stages of the disease (Deuschl et al., 2006). However, early in the history of the method reports of mental side effects were published. In 1995 Limousin and colleagues reported transient confusion and hallucinations with one of their first patients (Limousin et al., 1995). Further reports with disturbing side effects accumulated over time (Krack et al., 2001; Berney et al., 2002; Herzog et al., 2003a). While cognitive squeals were studied in numerous papers (Funkiewiez et al., 2004; Contarino et al., 2007) but are generally conceived to have little impact on the quality of life (Schupbach et al., 2006), the field of psychiatric effects was more hesitantly explored. Results to the latter remain ambiguous with a tendency toward less severe side effects in the large series of experienced centers (Deuschl et al., 2006; Weaver et al., 2009). Adverse events in this domain were largely attributed to acute effects weaning over a short period (Herzog et al., 2003b).

However, over the years I have seen a considerable number of patients both operated by myself but also from other experienced centers who showed psychological symptoms that counteracted the improvements in motor function. This personal experience is in line with patients and their representatives who voice concern over these phenomena with their deleterious impact on the wellbeing of patients, their families and caregivers (personal communication, F-W. Mehrhoff, Geschäftsführer, Deutsche Parkinsonvereinigung, Nov. 2014). Such concerns also appear quite regularly in patient support group meetings. My impression is, that patients and their representatives feel their concerns not appropriately reflected in the scientific literature and expert opinions. This comment responds to such observations with the aim to reposition the defense of DBS for Parkinson's disease. Reluctance to delve into this subject may in my opinion eventually leave those who offer the procedure defenseless toward reproach from patients, referring colleagues and the general public.

One may counter such observations by outlining that, particularly in case of complex psychiatric side effects, there are no objective means of deciding when a treatment has to be considered a failure or a success. Patients and relatives have also the propensity to underestimate their preoperative disabilities (Herzog et al., 2003b). This is further complicated by the fact that PD is a disease with cognitive, affective, and behavioral symptoms and thus has a neuropsychiatric impact on the patient as well. DBS may even in some cases restore the original personality, which then is simply not fitting any more into the actual social and familial setting. Finally, also medication-based therapies for PD can have severe neuropsychiatric effects (Cools et al., 2003).

Nevertheless, there remains a substantial proportion of DBS patients with severe and lasting behavior disturbances, which were credibly not present in the ultimate preoperative phase and that also has led to critical comments in the literature (Moro, 2009). These comprise reckless driving or other forms of risk-seeking behavior and even aggressive and contemptuous behavior toward

Abbreviations: DBS, Deep brain stimulation; GPI, Globus pallidus internus; STN, Subthalamic nucleus.

relatives and spouses. In some cases this can be remedied by moving the active contacts outside the STN with subsidence of aggressive behavior within hours. This hints to a direct effect of stimulation. Unfortunately in some patients stimulation must be markedly reduced or switched off completely to ameliorate psychiatric effects. Numerous reports and case series have contributed to this issue with delineation of alarming psychiatric disturbances ranging from hypomania to suicidal ideation and suicide (Herzog et al., 2003a; Morgan et al., 2006; Schupbach et al., 2006; Witt et al., 2008). At the same time other publications failed to find relevant changes of personality and behavior (Schuepbach et al., 2013), considered significant changes as not relevant for overall quality of life (Morgan et al., 2006) or even found much higher incidence of psychoses in the control group compared to the DBS group. I will now elaborate on these issues in some more detail.

MOOD AND BEHAVIOR

A symptom that may be systematically underestimated in its frequency is hypomania. It occurs early after the intervention and may lead to apparent improvement in rating scales like the Beck Depression Inventory and scales measuring quality of life. The subjective rating by the patient may however be a result of direct stimulation of the limbic system and not a normal joyful response to the improved motor performance. Hypomania becomes dangerous though impaired judgment of the own abilities and limits. While the patient (and the surgeon) may be content or even happy with the result, the patient's family may be dismayed about disinhibited and reckless behavior.

After some weeks hypomania may subside but other alterations in mood and behavior surface. Depression and Apathy may evolve and stay for years leading to markedly reduced quality of life not only for the patient but also for his caregivers. The reasons for both remain unclear and have been attributed to the stimulation directly or the resulting changes in medication. The incidence of both is relatively well reflected in the scientific literature (Drapier et al., 2006) with a minority finding contradicting results. With few exceptions the burden resulting from altered mood and behavior on caregivers and families has not received much attention (Lewis et al., 2015).

SUICIDE

While some studies found markedly elevated incidences of suicide (Voon et al., 2008) a direct association with DBS surgery was not found in a recent prospective study (Weintraub et al., 2013). This may indicate improvements regarding selection criteria—but the observation time in latter study was however short and patients were in the close scrutiny of a prospective setting allowing early detection and intervention if suicidal ideation occurred. The issue is further complicated by the fact that suicide after DBS has occurred not only with different anatomic targets but also with other diseases than Parkinson's disease (Appleby et al., 2007). Rare events like suicide are statistically difficult to assess, however, it is alarming that even in prospective studies with close monitoring of patients these events occur (Schuepbach et al., 2013). From a laymen's viewpoint the situation remains confusing; patients and their relatives remain worried due to reports of such events in patient representative organizations that seem to be in contrast to studies and expert opinions. To my understanding, a definite proof of the safety of the procedure in this respect is at present not available and the matter may eventually only be solved by a comprehensive DBS case registry.

MORAL COMPETENCE AND PERSONALITY

These are (in my view) the issues with the most confounding ethical impact. While hypomania subsides and depression may respond to treatment, rarely measurements are taken to exclude less obvious changes in behavior and personality. Fundamental changes in personality have been relatively seldom been studied (Florin et al., 2013) although basic research documents the role of the STN in decision making (Ray et al., 2011). Relatives however report reckless and risk seeking behavior that lasts well beyond the postoperative phase. Again, these types of behavioral change may occur gradually in the natural course of the disease or as side effect of drugs—but the sudden and seemingly irreversible alteration of personally after DBS comes as a shock for families. Probably the most profound, albeit at first sight easily overlooked effects are changes in moral competences of the patients. Such changes may result in taking risks for oneself and ignoring the rights of others, exemplified by car accidents or marital conflicts (Schupbach et al., 2006). Seminars for management of such conflicts after DBS are therefore already offered with patients and spouses reporting their experiences.

Changes in personality or moral competences have so far not been an issue in recent large studies (Schuepbach et al., 2013). One reason might be that they are difficult to measure with the scales presently at hand. Scales using the patient's own perception are fated to miss deficits in his ability to cope with the needs of others. Recently, the issue has come into focus (Fumagalli et al., 2015), but more appropriate scales to detect and quantify such complex changes must be implemented in the future (Witt et al., 2013). Cooperation with specialists in the area of moral psychology should be considered to adopt scales and knowledge.

THE STN AS TARGET

One reason for the frequency of psychiatric side effects may be the stimulated target. As the standard target for DBS in Parkinson disease the STN must be foremost scrutinized.

One of the basic assumptions in defense of the safety of the STN is the assumption that it consists of three clearly separated parts and that electrodes can be reliably steered into the motor part that exclusively contains motor functions. This concept while propagated by some researchers (Temel et al., 2005) has at the same time been questioned by others (Keuken et al., 2012). Furthermore, with the assumed motor division being quite small currents from the presently used electrodes will almost inevitably spread to other parts namely the limbic subdivision (taking into account that currents spread sideways from the electrode into areas outside the intended target).

Empirically the majority of studies come to the conclusion that targeting the GPI produces less psychiatric side effects (Liu et al., 2014) while allowing for almost equal motor improvement. Only one recent study found a clear advantage for the STN (Odekerken et al., 2013). Disadvantages of GPI are a smaller reduction of medication and possibly a weaning of effect over time. The necessity to keep up a high level of dopaminergic medication may itself provoke psychiatric events (Volkmann et al., 2004). Still the GPI may serve as target for a subset of patients prone to complications by STN-stimulation as outlined in a recent comment (Krack and Hariz, 2013). As such it has been advertised as target for patients prone to psychiatric complications[1].

The evaluation search for alternative targets should therefore be continued. Other promising targets are located in the subthalamic space within the fiber connections between thalamus cerebellum and basal ganglia as proposed by Velasco and others. However, it must been kept in mind that the basal ganglia and the cerebellum are involved in the processing of cognitive and emotional tasks and with the effects of stimulation spreading far complete avoidance of mental side effects is therefore not possible.

PERSPECTIVES

In summary, the available evidence suggests to my understanding that neuropsychiatric effects may be an integral albeit unintended effect of DBS for Parkinson's diseases. The ethical issues related to these effects may be even less trivial compared with DBS for psychiatric disorders. In the latter case, DBS is used with a transparent and obvious intention to interfere with the patient's psyche (Chabardes et al., 2013). In DBS for Parkinson's disease, the neuropsychiatric effects are not an obvious "part of the deal" with the patient.

Subsequently a sober and unprejudiced discussion about how far these phenomena can be accepted should evolve. For fear of putting a well-established and beneficial procedure at peril, its disadvantages shall not be disguised.

The discussion about target points that carry a lower risk of changing the patient's personality should continue. Patients must be informed about the available targets and the risks and benefits connected with each of them.

Prerequisite for the future development of DBS are diagnostic tools that are reliably able to detect the long-term consequences of the operation on behavior, personality and moral competence. Suitable scales can be developed or integrated from other disciplines into the clinical assessment and future studies. These must concentrate on the crucial domains of social interaction and judgment of own behavior. They should also address caregivers and family's perception of the patient and the impact on their life.

In defense of the procedure a reversal in the argumentation should be considered:

- The existence of psychiatric side effects as integral part of the treatment should be conceded.
- It should be asserted that DBS is a reversible therapy and can therefore not be put on a par with irreversible surgical interventions like the lesioning of brain areas. In analogy to drug therapy it can be discontinued simply by switching it off.
- The patient should be fully informed about the intrinsic risks of psychiatric adverse events, possible changes of personality and the targets at hand. Ideally the patient's partners and next of kin are involved and informed about the possible resulting burden as caregivers. This will counter the reproach of guiding patients into a treatment with consequences he cannot foresee.

Clearly the issue of psychiatric side effects of DBS involves a legally and ethically utterly sophisticated discussion. Yet postponing it beyond the moment the lay press may cover negative events in an untoward manner will not improve our position to influence its already unforeseeable outcome.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

ACKNOWLEDGMENTS

I am indebted to Markus Christen for helpful comments and suggestions.

[1] Radio broadcast in Deutschlandfunk covering the work of a implantation center in Germany www.dradio.de/dlf/sendungen/forschak/1407092/

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author has received grants for contributing to the development of stereotactic planning systems from Medtronic and Precisis.

frontiers in Integrative Neuroscience

OPINION
published: 11 August 2015
doi: 10.3389/fnint.2015.00046

Is there still need for microelectrode recording now the subthalamic nucleus can be well visualized with high field and ultrahigh MR imaging?

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Keywords: microelectrode recording, magnetic resonance imaging, subthalamic nucleus, deep brain stimulation, Parkinson's disease

OPEN ACCESS

Edited by:
Sidney A. Simon, Duke University, USA

Reviewed by:
Hagai Bergman, The Hebrew University of Jerusalem, Israel
Ludvic Zrinzo, UCL Institute of Neurology, UK

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Received: *10 March 2015*
Accepted: *15 July 2015*
Published: *11 August 2015*

Citation:
Kocabicak E, Alptekin O, Ackermans L, Kubben P, Kuijf M, Kurt E, Esselink R and Temel Y (2015) Is there still need for microelectrode recording now the subthalamic nucleus can be well visualized with high field and ultrahigh MR imaging? Front. Integr. Neurosci. 9:46. doi: 10.3389/fnint.2015.00046

The Question

High frequency stimulation of the subthalamic nucleus (STN) is an effective treatment for patients with Parkinson's disease (PD) (Odekerken et al., 2012; Kocabicak et al., 2013; Schuepbach et al., 2013). The technique has been further refined throughout the years by improved magnetic resonance imaging (MRI) techniques, advanced neurophysiological recording possibilities, and advances in hardware and software technology (Kocabicak and Temel, 2013). There are at least two major determining factors for an acceptable therapeutic outcome: patient selection (Deuschl et al., 2006) and the accuracy of targeting of the relatively small STN (Temel et al., 2005). The latter requires a state-of-the art stereotactic approach, adequate imaging facilities, and a detailed neurophysiological mapping of the target area. The preferred area within the STN is the motor part (thought to be located dorsolaterally in the STN), which can, be to some extent, identified by intraoperative multi-unit activity analyses, and MRI-based tractography (Zaidel et al., 2010; Brunenberg et al., 2011).

While the STN could not be visualized on MRI images when modern DBS of the STN surgeries started in Grenoble in 1993, nowadays its visualization has become a routine procedure for most centers offering DBS for patients with PD. While using intraoperative electrophysiology was evident in the beginning, now it is questioned whether it still has an essential added value. In this opinion article, we aim to provide an answer on the question whether or not electrophysiology still has a clinically relevant role in this era of advanced neuroimaging technology, which enables us to visualize both function and structure anatomy.

Old Debate

The discussion of whether or not to use intraoperative microelectrode recording (MER) is not a new one (Hariz, 2002). This discussion was perhaps less vivid when modern DBS started to be applied in patients with PD. The STN was an invisible target on MR images in most centers and MER was considered very helpful to find and delineate the boundaries of the target (Pollak et al., 1993; Limousin et al., 1995; Shamir et al., 2012). Since then things have changed. However, currently the STN can be directly visualized on T2 weighed and susceptibility weighed MR images.

The imaging field progresses rapidly further with ultra-high field imaging modalities becoming now available for patients (Plantinga et al., 2014).

It is more than 15 years ago that that the visualization of the STN for DBS surgeries was described (Starr et al., 1999). Mostly, T2 weighed and inversion recovery MRI sequences have been used. In most of the patients, the predefined target on T2 weighed MR images was chosen for implantation after intra-operative electrophysiology and test-stimulation (Bejjani et al., 2000; Egidi et al., 2002; Starr et al., 2002). This meant that in most patients MRI images could reliably show the STN, except for the y axis, in which microelectrode recording (MER) indicated that the STN extended more anteriorly than suggested by MRI (Hamani et al., 2005). Detailed volumetric analysis of MER-determined borders of the STN and MRI- defined borders in 22 patients (44 STN's), showed that MER-determined borders of the STN were exceeding the MRI signal (Schlaier et al., 2011). In addition, we examined the entry and exit borders of the STN on MRI images and with MER, using the probe's eye trajectory (Kocabicak et al., 2013). We found that T2 weighed MRI could reliably predict the electrophysiological entry and exit of the STN. Although these data confirm the accuracy of MRI in visualizing the STN, there are also limitations. There are known variations between the patients with respect to the x, y, and z planes, and the borders can sometimes be less clear, mainly toward the substantia nigra pars reticulata (SNr) (Hamani et al., 2005; Kocabicak et al., 2013).

From Atlas-based to MRI Based Coordinates and from Single-electrode to Multiple-electrode Recordings

In our previous series of 55 patients with PD who underwent DBS of the STN, atlas- based coordinates were used and in about one third of the patients the predefined target (central trajectory) was used for final electrode implantation, after MER and intra-operative test-stimulation (Temel et al., 2007). With applying individually adjusted coordinates based on T2 weighed MRI, the central trajectory was chosen in about two-thirds of the patients (Kocabicak et al., 2013; Tonge et al., in press). This has resulted in a clear reduction in operation time. Similar rates have been reported by others with atlas-based (Amirnovin et al., 2006) and MRI-based targeting coordinates (Reck et al., 2012). The change from 1.5 to 3.0 T has also improved the accuracy of targeting (Toda et al., 2009; Kerl et al., 2012).

Another development has been the change of single-electrode to multiple-electrode intra-operative electrophysiological recordings (Temel et al., 2007). The latter provides more detailed information about the electrophysiological boundaries of the STN; however, implantation of several electrodes at one time might increase the risk of bleeding. We found that the simultaneous implantation of multiple electrodes did not cause more bleedings or other major intracranial complication. The use of multiple electrodes resulted in better motor results when compared with patients who underwent DBS of the STN guided with a single recording electrode. There are reports, however, suggesting increased risk of hemorrhage due to MER (Ben-Haim et al., 2009; Xiaowu et al., 2010).

Back to the Question

Is intra-operative electrophysiology necessary to find the STN? Our answer is no based on the advances in MRI technology.

In line with this experienced DBS centers have shown good outcome with a MRI-guided approach (Ostrem et al., 2013; Aviles-Olmos et al., 2014). So should we abandon MER then? In our centers, we have decided not to abandon it for a number of reasons. Even in experienced centers, in about two-thirds of the cases, the predefined target is chosen for final implantation. In one-third, an alternative trajectory is needed. With MER, alternative trajectories are immediately available. The trajectory with the second longest and, if needed, the third longest STN activity can be used as alternative trajectories. Two other less common reasons to use intra-operative electrophysiology can be an unexpected error in the stereotactic approach or a shift caused by excessive CSF leakage or a hematoma (Reck et al., 2012).

Acknowledgments

OA is an employee of Medtronic and has a scientific affiliation at Maastricht University.

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Conflict of Interest Statement: The Review Editor Dr. Hagai Bergman declares that, despite chairing meetings for the Mediterranean Neuroscience Society as well as organizing an academic course with Author Dr. Yasin Temel (as a joint collaboration between Maastricht University Medical Center and the Mediterranean Neuroscience Society) the review process was handled objectively. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

PERSPECTIVE
published: 02 April 2015
doi: 10.3389/fnint.2015.00027

Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness

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In the wake of deep brain stimulation (DBS) development, ablative neurosurgical procedures are seeing a comeback, although they had been discredited and nearly completely abandoned in the 1970s because of their unethical practice. Modern stereotactic ablative procedures as thermal or radiofrequency ablation, and particularly radiosurgery (e.g., Gamma Knife) are much safer than the historical procedures, so that a re-evaluation of this technique is required. The different approaches of modern psychiatric neurosurgery refer to different paradigms: microsurgical ablative procedures is based on the paradigm 'quick fix,' radiosurgery on the paradigm 'minimal-invasiveness,' and DBS on the paradigm 'adjustability.' From a mere medical perspective, none of the procedures is absolutely superior; rather, they have different profiles of advantages and disadvantages. Therefore, individual factors are crucial in decision-making, particularly the patients' social situation, individual preferences, and individual attitudes. The different approaches are not only rivals, but also enriching mutually. DBS is preferable for exploring new targets, which may become candidates for ablative microsurgery or radiosurgery.

Keywords: psychiatric neurosurgery, radiosurgery, gamma knife, DBS, ablative neurosurgery, cingulotomy, capsulotomy, neuroethics

OPEN ACCESS

Edited by:
Elizabeth B. Torres, Rutgers University, USA

Reviewed by:
Eduardo Fernandez, Miguel Hernández University of Elche, Spain
Dawei Li, Duke University, USA

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Received: *20 January 2015*
Accepted: *17 March 2015*
Published: *02 April 2015*

Citation:
Müller S, Riedmüller R and van Oosterhout A (2015) Rivaling paradigms in psychiatric neurosurgery: adjustability versus quick fix versus minimal-invasiveness. Front. Integr. Neurosci. 9:27. doi: 10.3389/fnint.2015.00027

Introduction

Since 2000, there is a renaissance of neurosurgical treatments of psychiatric disorders. Many researchers and clinicians hope that modern neurosurgical approaches will be established as treatment options for a growing number of therapy-refractory psychiatric disorders. About 90% of functional neurosurgeons feel optimistic about the future of psychiatric neurosurgery (Lipsman et al., 2011; Mendelsohn et al., 2013).

Modern psychiatric neurosurgery includes DBS and ablative neurosurgical procedures (thermal or radiofrequency ablation, and radiosurgery). DBS and thermal or radiofrequency ablation procedures require a craniotomy. Radiosurgery (Gamma Knife Radiosurgery) is performed without craniotomy, mostly as an ambulant treatment. In future, high intensity focused ultrasound might

Abbreviations: ALIC, anterior limb of the internal capsule; DBS, deep brain stimulation; ITP, inferior thalamic peduncule; MRI, magnetic resonance imaging; NAcc, nucleus accumbens; OCD, obsessive-compulsive disorder; SCC, subgenual cingulate cortex; slMFB, superolateral medial forebrain bundle; VC/VS, ventral capsula/ventral striatum.

become another option. The worldwide first four patients have been treated with this technique in South Korea (Na et al., 2015).

Many authors consider DBS as the most modern and superior technology, particularly because of its adjustability and high degree of reversibility. However, in the wake of DBS development, ablative neurosurgical procedures are seeing a comeback, although they had been discredited and nearly completely abandoned in the 1970s because of their frequent serious complications and their unethical practice. Since modern stereotactic ablative procedures, particularly radiosurgery are much safer and more efficient than their historical antecessors, a re-evaluation of this technique is required.

Until now, ethical discussion about non-DBS psychiatric neurosurgery is scarce, whereas psychiatric DBS is intensively discussed ethically. This blind spot in neuroethics is astonishing for several reasons: First, the fraction of ablative procedures in psychiatric neurosurgery is big: in North America, 50% of psychiatric neurosurgeons use lesioning exclusively or combined with DBS (Lipsman et al., 2011); outside of North America even 54.9% (Mendelsohn et al., 2013). Second, two expert panels have affirmed stereotactic ablative procedures as important alternatives for appropriately selected patients (Parkinsonism: Bronstein et al., 2011; psychiatric disorders: Nuttin et al., 2014). Third, a clear superiority of any procedure in all relevant aspects cannot be established. Forth, which approach is optimal, depends significantly on patients' individual medical and non-medical properties. Fifth, the much higher costs of DBS, particularly for long-term treatment, exclude this option for the majority of patients world-wide.

Therefore, a comprehensive ethical analysis of the pros and cons of the different approaches is necessary, based on clinical facts, not on ideological prejudices. Particularly, it is not justified to characterize modern lesioning procedures as successors of historical psychosurgery, while presenting DBS as something quite different. In fact, both psychiatric DBS and modern ablative psychiatric neurosurgery are significantly improved successors of the historical psychosurgery.

Different Paradigms

The different approaches of modern psychiatric neurosurgery refer to different paradigms: microsurgical ablative procedures is based on the paradigm 'quick fix,' radiosurgery on the paradigm 'minimal-invasiveness,' and DBS on the paradigm 'adjustability.'

The purpose of ablative microsurgical procedures is to disconnect limbic system circuits related to different psychiatric disorders in order to enhance brain function and reduce psychiatric symptoms (Martinez-Alvarez, 2015).

Radiosurgery is usually considered as an ablative treatment. However, recent neurophysiological, radiological, and histological studies challenge this view. Radiosurgical protocols for neurological or psychiatric disorders might have differential effects on various neuronal populations and remodel the glial environment, leading to a modulation of function while preserving basic processing. Thus, modern functional radiosurgery might be based on neuromodulatory effects (Régis, 2013).

DBS has been considered as a method to produce reversible lesions. Indeed, high-frequency DBS has a similar effect as lesions, i.e., inhibition of targets that are hyperactive in psychiatric disorders. However, its mechanism of action is unclear, and several hypotheses have been put forward to explain the blocking effect of stimulation (Lévèque, 2014). Its main advantage is that the stimulation effect can be adjusted by adapting the stimulation parameters.

Efficacy

A direct comparison of the efficacy of the different approaches is not yet possible, particularly because of the heterogeneity of the studies, the small patient numbers, and the fact that most studies are neither placebo-controlled nor double-blind. The rapid development of the methods aggravates their comparison: In psychiatric DBS, many targets (mostly overlapping for different diagnoses) are tested with different stimulation parameters. In radiosurgery, the radiation doses used decreased significantly. Randomized controlled trials would be optimal to directly compare the efficacy of the different approaches. However, this scientific standard cannot be met for practical and ethical reasons. Nevertheless, studies that directly compare different approaches with matched patients would also provide a valid efficacy comparison. In any case, this would be much better than the current practice of publishing reviews. The problem with most reviews is that they summarize only data published in medical journals in English language. However, this practice does not represent the clinical reality but presents a distorted picture. Therefore, we expect a severe publication bias (Schläpfer and Fins, 2010), leading to a systematic over-evaluation of the benefits.

The publication bias is no minor problem in psychiatric neurosurgery, but a fundamental problem, which corrupts the evaluation of risks and benefits of the different procedures. For example, we have performed a systematic literature search on psychiatric neurosurgery for treating anorexia nervosa, which yielded only 27 cases (Müller et al., forthcoming). However, from presentations on conferences we learned that a multiple of the patients reported in journals have been treated with ablative neurosurgery. Websites of private clinics in Europe as well as in Asia offer ablative surgery for a broad spectrum of psychiatric disorders as part of clinical routine. These treatments are not part of clinical studies and usually not published. Recently, a book of Sun and De Salles (2015) has been published which presents original data from several studies with ablative neurosurgery for different psychiatric disorders which had not been published in medical journals.

That being said, we summarize available data on the efficacy of the different approaches, whereby we refer to the most recent reviews as well as to the above mentioned book of Sun and De Salles.

Deep Brain Stimulation

For OCD, data from 25 papers comprising 109 patients and five targets (NAcc, VC/VS, ITP, nucleus subthalamicus, and internal capsule) have been published (Kohl et al., 2014). The responder rates ranged from 45.5 to 100%.

For depression, data from 22 papers comprising 188 patients and six targets (NAcc, VC/VS, SCC, lateral habenula, ITP, and slMFB) have been published (Morishita et al., 2014). The responder rates ranged from 29 to 92%. However, two multicenter, randomized, controlled, prospective studies evaluating the efficacy of VC/VS, and SCC DBS were recently discontinued because of inefficacy based on futility analyses (Morishita et al., 2014). The failure of two high quality studies in spite of the universally positive results of reported open-label trials could be attributable to the typical overestimation of efficacy associated with open label trials that arises from the failure to control for placebo, and biases due to lack of blinding and randomization (Morishita et al., 2014).

For anorexia nervosa, six papers comprising 18 patients and three targets (NAcc, subcallosal cingulum, and VC/VS) have been published (Müller et al., forthcoming). Remission (normalized body mass index) occurred in 61% of patients, and in 88.9%, psychiatric comorbidities improved, too. However, Sun et al. (2015) have recently published less favorable results: only 20% (3/15) of their patients treated with NAcc DBS showed improvements in symptoms. The other 80% underwent a second surgery (anterior capsulotomy), which improved eating behavior and psychiatric symptoms in all patients (Sun et al., 2015).

Generally, the current knowledge does not allow for identifying a superior target (Kohl et al., 2014; Morishita et al., 2014; Müller et al., forthcoming).

Microsurgical Ablative Procedures

For treatment-refractory depression, 40–60% of patients responded to bilateral capsulotomy or cingulotomy performed with thermal coagulation or radiosurgery (Eljamel, 2015).

For OCD, response rates between 36 and 89% have been published (Martinez-Alvarez, 2015). Martinez-Alvarez (2015) reports own data of 100 OCD patients of whom 71% responded.

For anorexia nervosa, three papers with nine patients report a remission rate of 100%, with regard to both weight normalization and psychiatric comorbidities. Different targets were used (dorsomedial thalamus, anterior capsula, NAcc; Müller et al., forthcoming). Sun et al. (2015) report 150 patients treated with capsulotomy, of whom 85% experienced an improvement in symptoms.

Radiosurgical Ablative Procedures

For OCD patients, a response rate of 70% has been reported in the literature (Martinez-Alvarez, 2015). Martinez-Alvarez (2015) reported a response rate of 100% in five own patients.

Adverse Effects

Deep Brain Stimulation

Following DBS, surgery-related, device-related, and stimulation-related side-effects have been reported. Serious adverse events during surgery were reported: seizures, intracerebral hemorrhages (in one case causing a temporary hemiparesis), a panic attack, and a cardiac air embolus (Kohl et al., 2014; Morishita et al., 2014; Müller et al., forthcoming). In anorexia nervosa patients, a high rate of severe complications have been reported: further weight loss, pancreatitis, hypophosphataemia, hypokalaemia, a refeeding delirium, an epileptic seizure during electrode programming, QT prolongation, and worsening of mood (Müller et al., forthcoming).

In several cases, superficial wound infections, inflammation, or allergic reactions occurred (Kohl et al., 2014). Device-related adverse effects comprised breaks in stimulating leads or extension wires requiring replacement, dysesthesia in the subclavicular region, and feelings of the leads or stimulators (Kohl et al., 2014).

Stimulation-induced adverse effects comprised mood disturbances, suicidality, anxiety, panic attacks, fatigue, and hypomania, partly induced either by a change of stimulation parameters, or by battery depletion. These effects were either adjustable by parameter adaption or device exchange (Kohl et al., 2014; Morishita et al., 2014; Müller et al., forthcoming). Some DBS patients report feelings of self-estrangement (Gilbert, 2013). A great problem is the high number of suicides and suicide attempts after DBS that have been reported in eight papers (Kohl et al., 2014; Morishita et al., 2014). Further side effects include vertigo, weight loss or gain, long-lasting fatigue, an increased headache frequency, and visual disturbance (Kohl et al., 2014).

Microsurgical Ablative Procedures

Adverse side effects of microsurgical ablative surgery for major depression comprised epilepsy (up to 10%), incontinence, weight gain, transient confusion, transient mania, and transient incontinence. Further side effects reported by only one or two studies are personality change (7 and 10%), lethargy, hemiplegia (0.3%), and suicide (1 and 9%) (Eljamel, 2015). Following microsurgical ablative surgery for treating OCD, a similar spectrum of adverse effects has been published. Most side effects were transient, and included headaches, urinary incontinence, impaired cognitive function, and confusion. Tardive epileptic seizures occurred in 2–9% of patients (Martinez-Alvarez, 2015). In case of anorexia nervosa, the journal papers reported only transient adverse effects: bradycardia, mild disorientation, moderate somnolence, loss of concentration, apathy, emotional emptiness and mild loss of decorum, headaches, and centric fever (Müller et al., forthcoming). However, Sun et al. (2015) report intracranial hematomas in 1.9% of the patients (4/216); one patient died thereof (0.5%).

Radiosurgical Ablative Procedures

Side-effects such as fatigue, weight gain, or apathy occurred in several patients who had received doses of more than 180 Gy. In newer studies with lower radiation doses, adverse effects did not occur (Lévèque, 2014).

Recommendations

From a mere medical perspective, none of the procedures is absolutely superior; rather, they have different profiles of advantages and disadvantages (see **Table 1**). The main advantages of DBS are

TABLE 1 | Comparison of different approaches of modern psychiatric neurosurgery.

	DBS	Microsurgery	Radiosurgery
Paradigm	Adjustability	Quick fix	Minimal-invasiveness
Adjustability	Very high	Low (through a second intervention to produce another lesion or to enlarge the lesion)	Low (second intervention to produce another lesion) to medium (through a step-by-step approach)
Addressing different targets in a single session	No	Yes	Yes
Reversibility	High (exception: permanent adverse effects due to lesions, infections, bleeding)	No	No
Invasive craniotomy	Yes	Yes	No
Onset of action	Hours to 12 months	Days or weeks	6–12 months
Appropriateness for patients with special needs	No	Patients who would not comply with long-term follow-up	Patients - Who would not comply with long-term follow-up - With higher risks of anesthesia - With higher infection risks
Time and effort of the procedure	Single surgery; several days in hospital plus visits for adapting stimulation parameters	Single surgery; several days in hospital	Ambulatory treatment, single session
Long-term treatment	Frequent consultation of specialists required (parameter adjustment, device exchange)	Not necessary	Not necessary
Costs	Very high direct and life-long costs	Medium	Low
Mortality risk	Yes	Yes	No
Short-term risks	- Anesthesia - Infection - Hemorrhage - Hardware complications	- Anesthesia - Infection - Hemorrhage	- Development of cysts - Edemas
Long-term risks	- Infection risks (due to biofilms and regular battery exchange) - Hardware complications	No	No
Possible adverse effects	- Suicidality - Mood disturbance - Anxiety - Panic attacks - Hypomania - Weight loss or gain - Long-lasting fatigue - Increased headache frequency - Visual disturbance	- Suicidality - Headaches - Seizures - Drowsiness - Urinary incontinence Cognitive impairment - Personality change	- Transient cognitive impairment - Transient apathy - Radiation dose >180 Gy: fatigue, weight gain, or apathy
Disadvantages in daily life	Device-related problems in daily life (e.g., at airport controls)	No	No
Disadvantages for further medical treatment	- Exclusion of electroconvulsive therapy - Special MRI required	No	No
Possible problems of psychosocial adaptation	Self-estrangement, feeling of being manipulated; burden of normality syndrome	Burden of normality syndrome	Improbable

its adaptability and high degree of reversibility; of microsurgical ablative procedures the rapid onset of action; and of radiosurgery its noninvasiveness and low rate of adverse effects. Furthermore, it differs individually what counts as an advantage or disadvantage: For example, the delayed onset of action of radiosurgery makes it disadvantageous for patients who need a rapid symptom reduction. However, the gradual development of effects might be advantageous since it alleviates the psychological adjustment (Lindquist et al., 1991). This may be protective against feelings of being manipulated, self-estrangement and the burden of normality syndrome.

We support further research in this area generally, but think that therapeutic adventurism cannot be justified. The current research practice in psychiatric neurosurgery does not fulfill the highest ethical and scientific standards. We plead for ethical reasons for better safeguards in research and clinical practice. Since psychiatric neurosurgery has both the goal and the potential to change core features of the patients' personalities, these interventions require a solid scientific fundament. Particularly, we recommend the following:

- Case registries should become obligatory for all clinical studies in order to avoid a publication bias and its negative consequences, namely faulty evaluations of therapies, flawed therapy recommendations, unpromising treatment attempts and unneeded clinical studies (Morishita et al., 2014). Individual treatment attempts should not be performed.

- A multi-center, randomized, controlled study should be performed that directly compares DBS, microsurgical ablative procedures and radiosurgery for different psychiatric disorders.
- Since multiple circuits seem to be involved in psychiatric disorders, targets of DBS or ablative procedures, respectively, should be selected specifically with regard to the prominent symptoms instead of using the institution-specific target for all patients.
- Since no single procedure is absolutely superior, patients should be informed comprehensively about the different treatment options and their respective benefit-risk-profiles. Individual factors have to be crucial in decision making, particularly the patients' social situation, individual preferences, and individual attitudes (e.g., whether they could tolerate implanted devices; whether they are more afraid of the irreversibility of an ablative procedure or of the medical risks of brain surgery).

We are convinced that the different approaches are not only rivals, but also enriching mutually. DBS is preferable for exploring new targets, which may become candidates for ablative microsurgery or radiosurgery.

Acknowledgment

The research of Sabine Müller has been supported by the German Research Foundation (DFG), Germany (MU 3321/1-1).

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Sun, B., Li, D., Liu, W., Zhan, S., Pan, Y., and Zhang, X. (2015). "Surgical treatments for anorexia nervosa," in *Neurosurgical Treatments for Psychiatric Disorders*, eds B. Sun and A. De Salles (Dordrecht: Springer), 175–187. doi: 10.1007/978-94-017-9576-0_15

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

PERSPECTIVE
published: 15 June 2015
doi: 10.3389/fnint.2015.00041

Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective

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The number of depressed patients treated with deep brain stimulation (DBS) is relatively small. However, experience with this intervention now spans more than 10 years at some centers, with study subjects typically monitored closely. Here we describe one center's evolving impressions regarding optimal patient selection for DBS of the subcallosal cingulate (SCC) as well as observations of short- and long-term patterns in antidepressant response and mood reactivity. A consistent time course of therapeutic response with distinct behavioral phases is observed. Early phases are characterized by changes in mood reactivity and a transient and predictable worsening in self ratings prior to stabilization of response. It is hypothesized that this characteristic recovery curve reflects the timeline of neuroplasticity in response to DBS. Further investigation of these emerging predictable psychiatric, biological, and psychosocial patterns will both improve treatment optimization and enhance understanding and recognition of meaningful DBS antidepressant effects.

Keywords: treatment resistant depression, deep brain stimulation, subcallosal cingulate, therapeutic course, emotional reactivity

OPEN ACCESS

Edited by:
Markus Christen, University of Zurich, Switzerland

Reviewed by:
Albino J. Oliveira-Maia, Champalimaud Foundation, Portugal
Marco Iacoboni, University of California, Los Angeles, USA

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Received: *26 March 2015*
Accepted: *30 May 2015*
Published: *15 June 2015*

Citation:
Crowell AL, Garlow SJ, Riva-Posse P and Mayberg HS (2015) Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective. Front. Integr. Neurosci. 9:41. doi: 10.3389/fnint.2015.00041

Introduction

Deep brain stimulation (DBS) is being investigated as a potential therapy for treatment-resistant depression (TRD). The DBS target with the most experience is the subcallosal cingulate white matter, alternatively referred to as subgenual or Area 25 DBS (SCC; Mayberg et al., 2005; Lozano et al., 2008, 2012; Bewernick et al., 2010; Kennedy et al., 2011; Holtzheimer et al., 2012; Puigdemont et al., 2012; Merkl et al., 2013; Ramasubbu et al., 2013). Therapeutic response has also been reported with DBS of the nucleus accumbens (NAC)/medial forebrain bundle (MFB; Schlaepfer et al., 2008, 2013; Bewernick et al., 2010, 2012), and ventral capsule/ventral striatum (VC/VS; Malone et al., 2009; Dougherty et al., 2014). While studies of DBS at these targets vary in design and rationale, small trials have demonstrated clear benefit, including long-term sustained antidepressant response (Kennedy et al., 2011; Bewernick et al., 2012; Holtzheimer et al., 2012). However, pivotal industry-sponsored trials have not demonstrated efficacy (Dougherty et al., 2014; closure of the BROADEN trial).[1] For DBS to be validated as a reliable treatment strategy for depression, each

[1]http://www.sjm.com/broaden

independent approach must clearly define the precise surgical target, appropriate patient selection, time course of antidepressant response, and symptom specificity of that response. Given the small number of researchers with firsthand experience with DBS for depression, open dialog to maximize our collective experiential knowledge of this treatment is encouraged. Towards this goal, we offer a single lab perspective (Emory University, Atlanta GA, USA) from 8 years of studies of SCC DBS for TRD, highlighting the key clinical features of patient selection and the DBS-mediated therapeutic response in this target (**Table 1**; clinicaltrials.gov NCT00367003, NCT01984710).

Patients

Screening and evaluating hundreds of participants with in-depth assessments (**Table 1**) has shaped our view that three factors characterize a DBS responsive patient: (1) history of clear antidepressant response in early depressive episodes with evidence of inter-episode functional recovery (job, family, activities); (2) transformation from treatment-responsive to treatment-resistant depression; and (3) lack of emotional reactivity at presentation.

A typical history for those participants who respond to DBS starts with a depressive episode in their 20s that responded to antidepressant medication with symptomatic and functional recovery. In subsequent episodes, more aggressive antidepressant treatment was required and more medication failures were experienced. Most underwent electroconvulsive therapy, with an initial good response that could not be recaptured when symptoms later returned. Puigdemont et al. (2012) reported a similar pattern of disease progression. Patients' descriptions of their depression often include themes of psychic pain, darkness, being weighted down, or being in a hole. This is accompanied by pronounced psychomotor slowing, non-fluent, monotonous speech, and limited affective range. Consequently, these qualities have taken on the most weight in our assessments of potential new subjects.

All subjects must meet a minimum severity score on a standardized rating scale for study inclusion (**Table 1**). However, disease severity cannot be solely defined this way. While a severity score on a depression rating scale can be informative and is important for research metrics and study integrity, assumptions about severity scores may be a confound in this chronically ill population (Bech et al., 1975; Snaith, 1977; Bagby et al., 2004). Chronicity, treatment resistance, and functional impairment define overall disease severity in addition to total symptom burden.

DBS Lead Placement

Intraoperative testing of DBS contacts is conducted in awake subjects to explore acute stimulation effects, assess safety, and confirm electrode placement. In the SCC target, acute effects to stimulation including "lightness" and "connectedness" were initially reported and replicated in subsequent studies (Mayberg et al., 2005; Lozano et al., 2008; Holtzheimer et al., 2012; Merkl et al., 2013), but are not universal (Puigdemont et al., 2012; Ramasubbu et al., 2013). Our subjects have not experienced adverse events during intraoperative testing, although stimulation of many contacts produce no discernable behavioral effects. While the experiences reported by patients are highly personal and thus idiosyncratic, the predominant characteristic is relief from negative rather than induction of positive mood. Return of negative mood is noted soon after discontinuation of the stimulation. Acute behavioral phenomena to stimulation have been reported at other DBS targets and generally fall into categories of decreased negative mood; increased positive mood, interest, and motivation; autonomic changes including increased heart rate, sweating, or flushing; and unpleasant sensations of anxiety and mental or physical slowing (Mayberg et al., 2005; Lozano et al., 2008; Schlaepfer et al., 2008, 2013; Malone et al., 2009; Bewernick et al., 2010; Holtzheimer et al., 2012; Merkl et al., 2013; Riva-Posse et al., 2014a). Possible explanations of these phenomena include: site-specific behavioral biomarkers of antidepressant response, epiphenomena that may or may not have clinical relevance, or simply side effects of the spread of electric current to adjacent structures. In some cases, as in double vision with stimulation of the MFB (Schlaepfer et al., 2013), the specificity, predictability (based on local anatomy), and reproducibility of the effect would point toward this being a side effect. In contrast, smiling has been reported as asymmetric and time-locked to stimulation of the VC/VS target (Okun et al., 2004), but may also represent a positive affective response to the sudden absence of mental pain (Malone et al., 2009; personal observation). Such an effect would seem to blur the line between side effect and spontaneous expression of mood change.

Our observations led us to take a more systematic approach to intraoperative testing, which confirmed predictable, reproducible, contact-specific responses in most subjects (Riva-Posse et al., 2014a). The use of tractography has led us to optimize electrode placement based on the ability to engage key white matter tracts within the stimulation zone (Riva-Posse et al., 2014b). We have observed increased heart rate and skin conductance with stimulation of appropriately-positioned contacts, which have greater connectivity to the dorsal anterior cingulate and subcortical regions (Riva-Posse et al., 2014a). These autonomic effects are predictable based on the putative targets of the white matter tracts stimulated, but can tell only part of the story as additional tracts appear necessary for the antidepressant response to DBS.

The acute behavioral effects seen with intraoperative stimulation and described above are typically reproducible within the immediate post-operative period. In the days following intraoperative stimulation, it is not uncommon for our patients to experience some persisting symptom relief even though stimulation is off. This effect is strongest in the days after surgery and fades within 3 weeks. Repeating acute stimulation 1 month after surgery may reproduce the effects in attenuated form, or they may be absent. These intraoperative responses are now being evaluated as initial antidepressant effects, as biomarkers to confirm proper electrode placement, and as a probe of initial antidepressant physiological responses.

TABLE 1 | Emory SCC DBS for depression experience.

Subjects[1]
- 2080 potential subjects contacted
- 524 completed phone screens
- 274 medical records reviewed
- 76 in-person assessments
- 40 subjects enrolled
  - 8 failed to meet pre-surgical depression severity criteria[2]
  - 1 declined surgery
  - 1 comorbidity exclusion
- *N* = 30 implanted
  - 17 published in Holtzheimer et al. (2012)
  - 11 manuscript in preparation
  - 2 in current protocol

Standardized Assessment
- Primary outcome measure: 17 question Hamilton Depression Rating Scale (HDRS-17)
  - Response = 50% decrease from baseline; *N* = 17/30 at one year
  - Remission = 7 or less; *N* = 11/30 at one year

Time Course
- Clinical assessment weekly × 8 months, then tapered to semi-annual assessment by year 2
- 8 years since first subject enrolled
- 1527 subject-months (127 patient-years)

[1]*As of 5/2015,* [2]*HDRS-17 ≥20 averaged over 4 weeks prior to surgery.*

Post-Operative Course

A 1-month post-operative recovery period, during which stimulation is off, is followed by 6 months of continuous stimulation during which no medication changes are allowed and only limited adjustments to stimulation parameters are made. In our observations, the full antidepressant response evolves through stereotypic early and late subacute phases before settling into stable long-term recovery.

Out of the Rut . . .

In the first weeks of chronic stimulation, patients generally report minimal change, though outside observers notice more dynamic affect, movement, and speech. Anecdotally, family members comment that the patient "looks younger" or "is more like her old self." Within the first month, patients report an increase in activity and may notice more things in their environment. They report little subjective change in mood, although depression ratings are usually decreasing. Patients begin to notice that they are having more emotions, including brief positive moods, before endorsing any significant or lasting lifting of their depression. Others have similarly observed that significant subjective improvement in mood may not be reported for several weeks of active stimulation (Lozano et al., 2008; Merkl et al., 2013).

Having chosen the contacts for chronic stimulation on the basis of tractography and intraoperative effect, we typically do not make changes to stimulation parameters as this clinical process unfolds. While it is not uncommon for programming changes to be required over time in neurodegenerative diseases like Parkinson's disease, it is not clear that this level of tuning is necessary or helpful in depression (Bewernick et al., 2012; Dougherty et al., 2014). Over time, we have focused on the subtle signs of improvement, particularly with regard to a patient's reactivity. In the absence of a clear biomarker for depression or DBS treatment effect, it is necessary to rely on clinical judgment to make such decisions. This task is more difficult in depression, where a key feature of the illness, negative mood, is not always pathological nor always attributable to major depressive disorder. With chronic stimulation, patients learn to differentiate normal negative emotions from the depressive state. However, learning to make this distinction and trust one's ability to emerge from a sad situation appears to take time and practice and likely is affected by a patient's premorbid personality and life experience.

. . . And Into the Rough Patch

The relatively smooth and progressive improvement in depressive symptoms seen in the first weeks tends to destabilize roughly 10–12 weeks after initiation of chronic stimulation. What follows is a temporary period of subclinical emotional dysregulation characterized by increased negative affect, especially flares of anger and irritability, mood swings, and disproportionate negative emotional reactivity to environmental stressors. This is often concurrent with increased activity outside the home and increased frequency and complexity of interpersonal interactions. This period tends to last around 4 weeks. During this time, patients may report a return of depressive symptoms with increases in depression rating scores, although generally they no longer meet criteria for a major depressive episode. In the Emory experience, these fluctuations resolve without changes in stimulation parameters. At a similar time point after starting DBS, Puigdemont et al. (2012) reported a depressive recurrence in some of their patients, as well as one suicide attempt. This underscores the importance of close monitoring of patients during the first several months of DBS treatment, as this is an expected period of vulnerability. This phase may also coincide with the timing of outcome measurements in double-blind controlled clinical trials (Dougherty et al., 2014), thus confounding a normal reemergence of emotional bandwidth with return of true depressive symptoms as both load onto standard depression severity scales. Failure to establish clear distinctions between what appears to be a normal plastic process and the presumed pathological state has clear implications for evaluating efficacy and for the design of future trials. In our own studies, once this stage was recognized, parameter adjustments were halted and psychotherapy was engaged in earnest.

Recovery Takes More than Stimulation: Chronic Response and Non-response

After 6 months of chronic stimulation, emotional hypersensitivity usually abates. Depression rating scale scores again decrease. Global Assessment of Function scores increase, as patients become more active and connected with others. They are able to imagine life further into the future and entertain longer-term goals, such as a return to employment or other productive activities. Relationships with loved ones, especially partners, change in response to the patient's decreased dependency. Patients report an increased ability to tolerate setbacks in life and relationships. We see gradual improvement in mood and resilience through the first year and beyond, suggesting ongoing plasticity effects. Long-term follow-up studies have typically shown that the response at 1 year may continue to improve in subsequent years (Kennedy et al., 2011; Holtzheimer et al., 2012). All available evidence suggests that ongoing stimulation is necessary even in those who have been in remission for years. With device failure the euthymic state may hold for a period of time, but usually within weeks depressive symptoms gradually return. These symptoms are familiar to patients from previous episodes, although they rarely have the melancholic features characteristic of the pre-operative state. When device function is restored, therapeutic benefit returns, but it may take weeks to fully reach the previous level of wellness (Kennedy et al., 2011; Merkl et al., 2013).

Interestingly, even those considered non-responders by study criteria may nevertheless report meaningful improvement in their lives and choose to continue the treatment even when offered discontinuation and device removal, as has been the experience with other stimulation targets (Bewernick et al., 2010; Dougherty et al., 2014). In the case of SCC DBS, such a partial response may be attributable to a failure to stimulate all the white matter tracts necessary for a full response (Riva-Posse et al., 2014b). Alternatively, non-response or partial response may occur as a function of individual disease, biological, or personality characteristics. It may be that specific depressive symptom clusters that predominate in an individual may respond preferentially to stimulation of one DBS target over another. As with all psychiatric treatments, personality is bound to play a role in the nature and timing of therapeutic response or lack thereof. It is important to note that the core personality traits of patients who are accepted into DBS studies may be masked by their chronic depressive illness, such that a full understanding of their character structure can only be seen after the depressed state is lifted and the patient returns to previous behavioral patterns.

Once therapeutic contacts and parameter settings have been established, they are typically maintained over the years. Medications are generally not changed significantly once stimulation is initiated. In some instances, doses have been reduced, but generally not eliminated. However, since the protocol does not allow medication changes until after 6 months, it is possible that DBS becomes entrained with the pharmacological milieu instantiated at the time that DBS effects evolved. That said, patients do not appear to require medication to enable a DBS effect as patients on no medications can achieve clinical response and remission, although this is uncommon.

Discussion

In our experience, patients with the best response to SCC DBS are those who have a history of treatment-responsive depressive episodes with good inter-episode recovery, but undergo a malignant transformation and no longer respond to standard therapies. The antidepressant response to SCC DBS may be best described in acute, subacute, and chronic phases. Acute stimulation of appropriately positioned electrodes is frequently associated with feelings of relief or increased awareness. These responses are specific to each individual and highly reproducible with repeated testing in the intraoperative and perioperative period.

That said, with chronic stimulation, initial changes are noticed first by others. Patients notice increased activity and become more aware of their environment before they notice improved mood. As patients experience more sustained improvement in mood and more critically, increased emotional range, they move from a state of relative stability around a low negative to relative instability, with heightened emotional sensitivity and reactivity. Close follow-up and reassurance during this period of emotional recalibration is warranted, though frequent stimulation parameter adjustments are not. This intermediate stage of recovery, generally lasting several weeks, gives way to increased stability and resilience manifest by progressive improvement in depressive symptoms that are maintained over months and years. While the steepest improvement tends to be seen in the first 6 months, DBS responders report continued gradual improvement over one or more years of treatment. Discontinuation of stimulation during this recovery phase nonetheless leads to a gradual return of symptoms over several weeks. Current studies are exploring how rehabilitative strategies may best synergize with these distinct phases of recovery.

The gradual and predictably bumpy recovery curve in SCC DBS for depression stands in contrast to the response to DBS observed in Parkinson's disease and essential tremor, where the effect is apparent immediately, maximal effect is reached within hours, and with discontinuation, primary symptoms return immediately (Hristova et al., 2000). The response to DBS for dystonia is more similar to that of depression, as it develops gradually and maximum effect is seen only after months of stimulation (Yianni et al., 2003). In dystonia and depression, neuroplasticity and CNS remodeling may be critical to the long-term treatment response to DBS (Ruge et al., 2011; Gibson et al., 2014). Indeed, changes in serum levels of brain-derived neurotrophic factor are abnormally low and increase with antidepressant treatment (Brunoni et al., 2008, meta-analysis) and in response to chronic DBS in an animal model (Hamani et al., 2012). DBS-induced plasticity may allow for changes in regional and network activity that ultimately result in a normalization of depression-related pathology. PET scans 3 and 6 months following DBS implantation show activity changes in depression-relevant regions, including normalization of hyperactivity in the SCC (Mayberg et al., 2005; Lozano et al., 2008; Bewernick et al., 2010). Prior to PET scan changes, autonomic changes accompany the behavioral response to acute stimulation (Riva-Posse et al., 2014a), and changes in EEG frontal theta concordance after 1 month of stimulation predict 6 month response to DBS therapy (Broadway et al., 2012). The time course varies for different regions, which may reflect both direct and indirect actions on these networks by acute and chronic stimulation. Comparable findings have been demonstrated using EEG, suggesting a differential time course of changes with long-term stimulation. These findings are consistent with the clinical observations of phase response characteristics and further they work toward understanding the mechanism of DBS treatment.

It is hoped that knowledge gained from these small, open-label, mechanistic investigations will inform the design of larger scale efficacy trials for DBS. Those who would design such trials face significant challenges. The heterogeneity of depression may be obscuring subsets of patients who are the most appropriate candidates for DBS at each anatomical target. Inability to effectively quantify the desired patient characteristics creates a problem for clinical trials, where everything must be operationalized. Allowances must be made in treatment decision algorithms for discrepancies between clinical impression and standardized rating scores. During the transient period of emotional hypersensitivity in the subacute phase, depression ratings may worsen, which may trigger protocol-defined parameter changes that interrupt the natural course of recovery thus confusing the clinical picture and ultimately, the demonstration of efficacy. Development of next-generation closed-loop DBS systems that are capable of monitoring and responding to changes in neuronal signals may further improve the conduct of future clinical trials (Afshar et al., 2013; Hosain et al., 2014; Smart et al., 2015). Such systems will be critical to identifying biomarkers of DBS-mediated antidepressant response and hence guide treatment optimization.

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Conflict of Interest Statement: Dr. Crowell has received funding from the American Psychiatric Association's Psychiatric Research Fellowship Award funded by Eli Lilly and Company and the National Institutes of Health Loan Repayment Program. Dr. Mayberg has received funding from the Dana Foundation, Woodruff Fund, Stanley Medical Research Institute, and the Hope for Depression Research Foundation and consulting and intellectual licensing fees from St. Jude Medical Inc. All other authors report no commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

HYPOTHESIS AND THEORY
published: 08 June 2017
doi: 10.3389/fnint.2017.00011

Autonomy in Depressive Patients Undergoing DBS-Treatment: Informed Consent, Freedom of Will and DBS' Potential to Restore It

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According to the World Health Organization, depression is one of the most common and most disabling psychiatric disorders, affecting at any given time approximately 325 million people worldwide. As there is strong evidence that depressive disorders are associated with a dynamic dysregulation of neural circuits involved in emotional processing, recently several attempts have been made to intervene directly in these circuits via deep brain stimulation (DBS) in patients with treatment-resistant major depressive disorder (MDD). Given the promising results of most of these studies, the rising medical interest in this new treatment correlates with a growing sensitivity to ethical questions. One of the most crucial concerns is that DBS might interfere with patients' ability to make autonomous decisions. Thus, the goal of this article is to evaluate the impact DBS presumably has on the capacity to decide and act autonomously in patients with MDD in the light of the autonomy-undermining effects depression has itself. Following the chronological order of the procedure, special attention will first be paid to depression's effects on patients' capacity to make use of their free will in giving valid Informed Consent. We suggest that while the majority of patients with MDD appear capable of autonomous choices, as it is required for Informed Consent, they might still be unable to effectively act according to their own will whenever acting includes significant personal effort. In reducing disabling depressive symptoms like anhedonia and decrease of energy, DBS for treatment resistant MDD thus rather seems to be an opportunity to substantially increase autonomy than a threat to it.

Keywords: deep brain stimulation, depression, autonomy, informed consent, decision making, neuromodulation, neuroethics

Edited by:
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Received: *29 March 2017*
Accepted: *22 May 2017*
Published: *08 June 2017*

Citation:
Beeker T, Schlaepfer TE and Coenen VA (2017) Autonomy in Depressive Patients Undergoing DBS-Treatment: Informed Consent, Freedom of Will and DBS' Potential to Restore It. Front. Integr. Neurosci. 11:11. doi: 10.3389/fnint.2017.00011

INTRODUCTION

The introduction of the minimally invasive and highly precise stereotactic method, which is also the basis of deep brain stimulation (DBS), has most certainly been helped by the desire to overcome the often gruesome practice of frontal lobotomy (Gildenberg and Krauss, 2009). In 1947, the American neurologist Ernest A. Spiegel and neurosurgeon Henry T. Wycis were the first to use the stereotactic apparatus on humans and described dorsomedial thalamotomy for depression and anxiety disorders (Gildenberg, 2002[1]). Due to its tendency to induce cognitive deficits, the dorsomedial thalamus was soon replaced by other target regions for lesion surgery that have just recently been investigated for their distant connectivity (Schoene-Bake et al., 2010). Lozano and Mayberg first applied DBS technology on treatment resistant major depressive disorder (MDD) with a formerly unknown efficacy in 2005 (Mayberg et al., 2005). Over the years, other target regions were tested (see, **Table 1**), all with strikingly similar anti-depressant effects[1]. Whereas one recently published multicenter study on DBS of the Ventral Capsule/Ventral Striatum failed to reproduce the remission rates of the initial studies (Dougherty et al., 2015), a pilot study using the superolateral medial forebrain bundle (slMFB) as new target reported heretofore never achieved anti-depressant efficacy of 85%. Remarkably, this latter target has been developed in a hypothesis-guided way (Coenen et al., 2011). Stimulation of this region, which is until today mostly known for its role in motivated behavior and addiction research (Panksepp, 1998), required even significantly less energy than for all previous targets (Schlaepfer et al., 2014).

Up to one third of patients with MDD do not show significant symptom reduction in standard treatment and therefore have to be considered as treatment-resistant (Rush et al., 2006). Given the high prevalence of treatment-resistant major depression (TR-MDD), DBS-treatment of MDD is only performed in relatively rare experimental instances, which are generally included into clinical studies. Patients thus necessarily are research participants at the same time, highlighting the importance of preoperative valid informed consent. In the above studies, all included patients had a long history of chronic depression neither responding to pharmacological treatment, nor to psychotherapy or electroconvulsive therapy. For instance, the average length of the current depressive episode of patients included in one of the largest studies amounts to 10.8 years (Bewernick et al., 2010). Experimental treatment with DBS, although not yet approved for depression by the US Food and Drug Administration (FDA), thus can be considered a *last hope* for many patients, if the widely dismissed ablative neurosurgery is not taken into consideration due to its irreversibility.

Patient selection for DBS is always preceded by an extensive multi-professional screening process. The most important inclusion criteria, apart from diagnosis and treatment resistance, are the length of the current episode and severity of symptoms, typically measured with the Hamilton Depression Rating Scale (HDRS) or the Montgomery Åsberg Depression rating Scale (MADRS). The main exclusion criteria are current or past psychotic disorders, abnormal Magnetic Resonance Imaging (MRI) of the brain and any comorbid psychiatric, neurological or medical condition that could interfere with patients' safety or compliance during treatment (Mayberg et al., 2005; Lozano et al., 2008; Malone et al., 2009; Schlaepfer et al., 2013).

In the light of DBS target regions associated with higher efficacy, continuous refinement of DBS-technology and novel applications on the horizon (Deeb et al., 2016), increasing medical interest in DBS correlates with a growing sensitivity to ethical questions raised by the use of invasive neuromodulation on psychiatric diseases. Accordingly, a consensus guideline on ethical and scientific conduct for psychiatric surgery has recently been published by an interdisciplinary group of experts (Nuttin et al., 2014). One of the principal concerns is that

[1]For a current review see Schlaepfer et al. (2014).

TABLE 1 | Previous studies on deep brain stimulation (DBS) for major depressive disorder (MDD) with three or more participants (Original table).

Study	Target structure	Patients treated	Results
Lozano et al. (2008)	Subgenuale cingulate gyrus (Brodmann-Areal 25, Cg25)	20	6 months follow up: response[a] 12/20, remission 7/20[b]
Malone et al. (2009)	Anterior limb of internal capsule (ALIC)	15	6 months follow up: response 7/15, remission 3/15
Schlaepfer et al. (2008)	Accumbens nucleus (NAC)	3	6–23 weeks follow up: response 1/3
Bewernick et al. (2010)	NAC	10	12 months follow up: response 5/10
Holtzheimer et al. (2012)[c]	Subcallosal Cingulate Gyrus (SCG)	17	2 years follow up: response 11/12, remission 7/12
Puigdemont et al. (2012)	SCG	8	12 months follow up: 5/8 response, remission 4/8
Merkl et al. (2013)	SCG	6	24–36 weeks follow up: 2/6 remission
Ramasubbu et al. (2013)	SCG	4	6 months follow up: response 2/4
Schlaepfer et al. (2014)	Superolateral branch of the medial forebrain bundle (slMFB)	7	up to 6 months follow up; 6/7 response[d]
Dougherty et al. (2015)	Ventral Capsule/Ventral Striatum	15	3/15 response within 16 weeks
Accolla et al. (2016)	Posterior gyrus rectus region/(Cg 25)	1/(4)[e]	1/1 response; (0/4 response)
Bergfeld et al. (2016)	ALIC	25	12 months follow up: response 10/25
Fenoy et al. (2016)	slMFB	4	26 weeks follow up: response 2/3[f]

[a]*Response is commonly defined as a reduction of more than 50% of baseline depressive symptoms, measured either with Hamilton Rating Scale for Depression (HRSD) or Montgomery-Åsberg Depression Rating Scale (MADRS).*

[b]*Every Patient in remission counts at the same time as a responder. Thus remission and response-numbers cannot simply be added.*

[c]*In addition to 10 patients with MDD, seven patients with bipolar II Disorder were enrolled.*

[d]*In a recently published long time observation over the course of 4 years including one more patient, a stable anti-depressant effect was found in 6 out of 8 participants (Bewernick et al., 2017).*

[e]*In the complete sample of 5 patients, 3 were identical with patients of the study published by Merkl et al. (2013).*

[f]*One patient withdrew from study participation.*

DBS could interfere with the ability of patients to make autonomous decisions and execute their free will. Consequently, the goal of this article is to evaluate the impact DBS might have on the capacity to decide and act autonomously for patients with treatment-resistant MDD. Special attention will be paid to the possibly autonomy-undermining effects depression has in itself, thus also potentially endangering valid Informed Consent—a key prerequisite for the procedure. Our approach is based on the conviction that with respect to the large differences between effects and side-effects of DBS, depending on the target of stimulation and the condition treated, a proper ethical evaluation of DBS-treatment should aim to be performed separately for every single indication, the target region used and the specific characteristics of both.

ARE PATIENTS WITH MDD COMPETENT TO GIVE INFORMED CONSENT TO INVASIVE TREATMENT?

The autonomy of patients undergoing DBS-treatment is not exclusively a matter of postoperative care. Since autonomy is one of the key principles of medical ethics and modern medical practice is widely based on it, autonomous decisions are supposed to stand at the very beginning of every medical intervention. Informed Consent was originally implemented to ensure that no patient would be harmed by unethical experiments or treatment against his or her will. From a rather defensive approach mostly aiming to protect participants of medical experiments, Informed Consent subsequently evolved into the main instrument to safeguard autonomous choices for patients in all matters of personal healthcare (Beauchamp, 2004). As such it has to be respected in the ethical evaluation of DBS-treatment for MDD as well. Since it is obvious that no person capable of expressing preferences can undergo neurosurgery against his or her will, the most relevant ethical question at this stage is, whether patients with MDD can be considered as autonomous agents in the sense that they are effectively able to provide valid Informed Consent. This is especially critical since there are good reasons to consider impaired autonomy as a key feature of severe psychiatric illness (DeGrazia, 1994). Also, it seems worth noting that DBS is not yet approved as a treatment for MDD in the United States, nor in Europe, implying that DBS in this case can only be performed within the framework of clinical trials. In giving consent to being treated, potential patients would also have to authorize a *research procedure*. This would require a certain appreciation of the experimental nature of this intervention and its partially unclear risk-benefit-ratio, posing an additional challenge to both the patient's understanding and the quality of disclosure provided by healthcare professionals.

A wide consensus can be found among ethicists that at least three criteria have to be fulfilled for valid Informed Consent (Schöne-Seifert, 2007). First of all, healthcare professionals have to provide patients with all the information required for decision-making, including disclosure appropriate for the patient's level of comprehension. Second, patients have to be competent to fully understand the information provided and must be able to decide on this basis. Finally, their decision has to be voluntary and free from manipulative influence or coercion. Assuming that good medical practice is at least likely to fulfill condition one and three and it is not ethically controversial that DBS is to be performed in such a context, our considerations will primarily focus on whether depressed patients are indeed competent to consent. This will also help clarify in which way patients with MDD are able to act autonomously and in which they are not. New efforts to discuss Informed Consent in the broader perspective of patients' vulnerability will not be discussed here as for the focus of this article. For a concise overview of this recent attention-gaining approach, we recommend Bell et al. (2014).

According to the seminal work of Beauchamp and Childress, competence can be defined by four essential criteria:

> *"Patients or prospective subjects are competent to make a decision if they have the capacity to understand the material information, to make a judgment about this information in light of their values, to intend a certain outcome, and to freely communicate their wishes to caregivers or investigators" (Beauchamp and Childress, 2009, p. 113).*

Inability to give Informed Consent because of mental disorders is a very common problem in psychiatric practice and ethics (van Staden and Krüger, 2003). Several tests have been developed to assess patients' competence, among them such well-established instruments as the MacArthur Competence Assessment Tool for Treatment (MacCAT-T; Grisso et al., 1997; Dunn et al., 2006). All in all, in psychiatric literature there has been little doubt about depressive patients' competence to consent. In a line of thought reaching back to Jean-Étienne Esquirol, one of the fathers of modern psychiatry in the early 19th century, depression is perceived as a disorder which characteristically affects *the mood* and not the mind (Ehrenberg, 2009). Consequently, it is deemed unlikely to impair cognitive features like understanding material information or the ability to communicate freely in a way relevant to patients' competence (Elliot, 2006). In fact, clinical experience shows that MDD might be associated with a slight decline in overall cognitive performance due to lack of concentration and general tiredness. However, only in the case of psychotic features, is it common to classify depressive patients as incompetent. Empirical research points in the same direction. Studies focusing on understanding and reasoning showed impairment in only 5.4% (understanding) respectively 7.6% (reasoning) of depressive inpatients consenting to treatment (Grisso and Appelbaum, 1995). Depressive inpatients asked to volunteer for research reached relatively high scores in the MacArthur Competence Assessment-Tool for clinical research and were found to be able to distinguish the levels of risk between studies (Cohen et al., 2004). In a similar vein, two studies on Informed Consent for ECT could not find any correlation between depression severity and decision-making capacity measured with the MacCAT-T (Lapid et al., 2003, 2004). Furthermore, it can be assumed that patients with MDD would also benefit from strategies to improve understanding and thus enhance the Informed Consent process in general. As a metaanalysis points out, research participants' understanding of the information disclosed in the Informed consent process can be improved by either the use of multimedia or, most effectively, additional person-to-person contact between participants and healthcare professionals (Flory and Emanuel, 2004).

Hence, ethical concerns are raised mainly over the non-cognitive dimension of decision-making. For instance, it has been argued that MDD could significantly bias the evaluation of possible treatment results towards neglecting the likelihood of a positive outcome while overrating negative outcomes and treatment risks (Rudnick, 2002). In this case, one could assume patients' judgment to depend on their overall negative perspective caused by depression rather than their true values. However, this argument overemphasizes the role of rational thinking and consciousness in decision-making. Most individuals do not decide exclusively by rationally weighing up pure facts. For the acceptance of a certain treatment, it can be crucial whether a physician seems trustworthy or if it just "feels right" to do it. Even if anxiety, a generally pessimistic perspective and maybe even desperation might have some influence on decision-making in the case of MDD, it seems questionable why this should be especially problematic in this context, while decisions in "normal" daily contexts led by the same irrational motives are considered adequate. Furthermore, anxiety and desperation are not at all specific traits of depressive patients, but in fact—understandably—a common feature of severe illness in general (Dunn et al., 2006). Thus, excluding patients from treatment or research *primarily* because of their desperation or anxiety could lead to the contradiction, that people who are the most in need of ultima-ratio interventions are the least likely to receive them. Apart from that, recent studies on depressive patients considering enrollment into DBS-treatment programs indicate that they rather tend to overrate their personal benefits and underestimate the likelihood of risks than vice versa (Leykin et al., 2011; Fisher et al., 2012). This widespread bias, known among ethicist and clinicians as *therapeutic misconception*, arises from individuals' difficulties to distinguish between regular clinical care and research procedures with unclear therapeutic benefits (Appelbaum et al., 1982). Interestingly, depressive patients did not score worse than average non-psychiatric patients. In a small sample, severity of depressive symptoms even seemed to correlate with a more precise evaluation of risks and benefits (Fisher et al., 2012).

In a similar vein, it has been argued that MDD itself can change patients' values, preferences and goals in a way that their decisions are not authentic (Rudnick, 2002; Elliot, 2006). There are several reasons to be skeptical of this argument. A general problem concerning authenticity as a criterion for the competence to consent is that it is only applicable ex-post, which means that patients' competence would be verified after they have already decided. Assuming that this judgment would mainly depend on the content of the decision made, it is probable that physicians might tend to disrespect non-conforming choices by judging them to be inauthentic. For this reason, many ethicists argue that authenticity as a criterion for autonomous decisions runs the risk of promoting paternalism (Schöne-Seifert, 2007). Furthermore, severe illness as an extreme experience clearly has the potential to change someone's goals or preferences in a relatively short amount of time. Authenticity, thus, cannot mean to expect patients to stick to their old opinions while their whole life is turned upside-down. Given that it is very natural to change one's perspective on life in reaction to extreme situations, authenticity as a criterion becomes rather useless as a safeguard for competence. It seems neither theoretically plausible nor practically feasible to separate legitimate changes of mind from inauthentic shifts of preferences in the light of severe illness (Bielby, 2008). However, there is a third argument questioning MDD patients' competence to consent, which seems to be more appropriate than the preceding ones. One main symptom of MDD is a general loss of interest in living, culminating in the worst case in suicide attempts or completed suicide. An often-cited example of how a weakened will to live can influence decision-making in medical matters is presented by Roth et al. (1977). The authors report a 49-year old woman who was asked to consent to electroconvulsive therapy because of MDD. When told that this treatment carries a risk of 1–3000 to die from complications, she articulated a surprising motivation to be treated by replying that she hoped to be the one (Roth et al., 1977). Whereas patients refusing treatment out of fear or by overrating negative outcomes at least show some concern for themselves, the patient in this extreme case displays an alarming lack of this fundamental interest in her own wellbeing. Choosing a treatment just because of the chance to die from adverse effects thwarts the very idea of Informed Consent. A patient using an instrument established to prevent harm *in order to get harmed* is not just executing his right of autonomous choice in a very uncommon way. He is rather refusing to act autonomously at all and therefore has to be considered incompetent to consent.

As a result, no argument seems strong enough to exclude patients with treatment-resistant MDD *collectively* from giving Informed Consent to DBS-treatment. Also, empirical data supports that autonomy in its sense of capacity to consent commonly seems not to be significantly impaired by MDD itself. We should take into consideration that expecting depressive patients to fulfill higher standards than mentally healthy patients would not only establish unfair access to regular or experimental treatment, but also reinforce stigmatization of this already disadvantaged group (Bell et al., 2014). The well-meant wish for special protection, when not reflected adequately, can easily relapse into old-fashioned (medical) paternalism.

On the other hand, regarding the invasiveness of DBS, the necessarily experimental character of treatment and as a concession to the current limitedness of empirical data, MDD-patients' competence to give valid consent cannot simply be taken for granted. Individual evaluation of cognitive function, as should be part of every surgical or experimental treatment of psychiatric illness, is recommended in this context as well as extensive psychiatric evaluation, neuropsychological testing and multi-professional assessment including a thorough look at possible therapeutic misconception. Additionally, as shown in the example by Roth et al. (1977) it has to be ensured specifically that depressive patients' decisions are motivated by the fundamental interest in their own wellbeing, which is the very essence of Informed Consent.

IS DBS *per se* AN AUTONOMY-SUBVERTING TREATMENT?

As the ongoing popularity of literature and movies connected to the topic shows, the very idea of technical devices implanted in the human brain seems to cause discomfort to a considerable amount of people. Although general concerns towards DBS are by no means comparable to those fears famously expressed in novels like "The Manchurian Candidate" or "The Terminal Man", similar questions are touched upon. Far from fictional scenarios of technically driven mind- and behavior-control, DBS also has to deal with the preoccupation that it might affect patients' behavior in a way that their actions would no longer count as self-governed (Klaming and Haselager, 2013; Grant et al., 2014; Unterrainer and Oduncu, 2015). The goal of the following passage is to evaluate whether evidence can be found that DBS *for therapeutical use* could be a threat to patients' autonomy. Due to a lack of empirical studies dedicated explicitly to this topic, our main focus will lie on a philosophically informed critical evaluation of cases of altered behavior during DBS-treatment. Although some cases at first sight suggest that DBS might influence decisional capacity, we hypothesize that it is in fact more likely for patients with MDD to benefit from DBS-Treatment with respect to their autonomy, given that MDD itself is a highly autonomy-subverting condition (see, **Figure 1**). A similar claim has recently been made for the treatment of obsessive-compulsive disorder, in which the overall positive effects of neuromodulation also seem to increase autonomy (De Ridder et al., 2016).

Philosophical Background: Harry G. Frankfurt's Hierarchical Model of Free Will

Going back to ancient philosophy and as a key concept of philosophical enlightenment, autonomy is a traditional issue of philosophy, recently discussed in the debate on free will and neuronal determinism. Among a variety of largely overlapping positions, the most prominent modern attempt to specify the characteristics of autonomous actions has been developed by US-philosopher Harry G. Frankfurt (Frankfurt, 1988). Frankfurt's *hierarchical model of free will* belongs to the so called *internalist* wing of the debate. According to internalists' point of view, the key feature of autonomous agency is that the agent's motives leading to particular actions somehow cohere with a framework of more general higher motives and attitudes. The latter can be called *internal* in the sense that they are mental states belonging to the agent, which are closely bound to his or her personality (Buss, 2014)[2]. They have been referred to as *higher-order desires* (Frankfurt, 1988), evaluational judgments (Watson, 1975), long term plans (Bratman, 2007) or character traits (Dworkin, 1988). Following this train of thought, a person who acts in accordance with her own—however labeled—higher-order attitudes, ultimately acts in accordance with herself, thus literally being *autonomous* in the original ancient Greek translation of *self-governing*. While internalists focus on the two-level structure of basic desires or actions and corresponding higher order desires or attitudes, taking *coherence* between the two levels as the benchmark of autonomy, *externalist* approaches, representing the other prominent wing of the debate, place much more emphasis on rationality of the agents and their higher motives themselves. According to their shared intuition, agents can only be autonomous, if they are conscious of and able to articulate logical, sound reasons for their doing (Fischer and Ravizza, 1993; Nelkin, 2007) or are at least potentially able to reason about it in an appropriate way (Christman, 1991, 1993; Mele, 1993). Consequently, for these authors autonomous action is not primarily a matter of personal preferences, but most importantly has to fulfill certain *external* criteria: to match the objective world and to follow the laws of logic.

There are several reasons to favor internalist approaches like Frankfurts' hierarchical model of free will. Generally speaking, externalists' main interest lies in identifying the conditions under which an agent can be held responsible for his or her actions, while neglecting engagement with the process of autonomous decision and action itself. As it is necessary to have at least a minimal theoretical understanding of how autonomous actions really take place in order to evaluate possible autonomy-subverting effects of DBS, it is evident why externalist approaches are of little use for our purpose.

Frankfurt's concept of autonomy is not only the most established internalist approach, it also best matches the requirements of our endeavor and the kind of data we have to deal with. Frankfurt suggests a clear and comprehensible model of autonomous agency, which is remarkably close to the everyday-experience of self-governed agency. It allows a clear focus on agents' behavior and their attitudes towards it. This is especially important given that we have no other option than drawing inferences from literature without knowing the individuals involved personally, thus being unable to verify the logical soundness of their motives or their ability to reason. Since there are no specific studies on DBS and autonomy, our aim is to take a close look at harmful or otherwise abnormal behavior which occurred under DBS-treatment and then question it for signs of the agents' underlying higher-order attitudes.

According to Frankfurt, persons can be distinguished from other living beings who are not persons by being capable of having two different classes of desires and to reflect on them. Whereas first-order desires have the structure "A wants to X" with X representing a certain action, second-order desires refer back to first-order-desires a person does or does not want to have. A person is acting autonomously when her first-order desires expressed in effective action are fitting to the framework of her second-order desires. The key feature of free will, therefore, is that a person *identifies* with her actions, meaning that she truly wants to do what she effectively does and, on the other hand,

[2] http://plato.stanford.edu/archives/win2014/entries/personal-autonomy/ (accessed October 12, 2016).

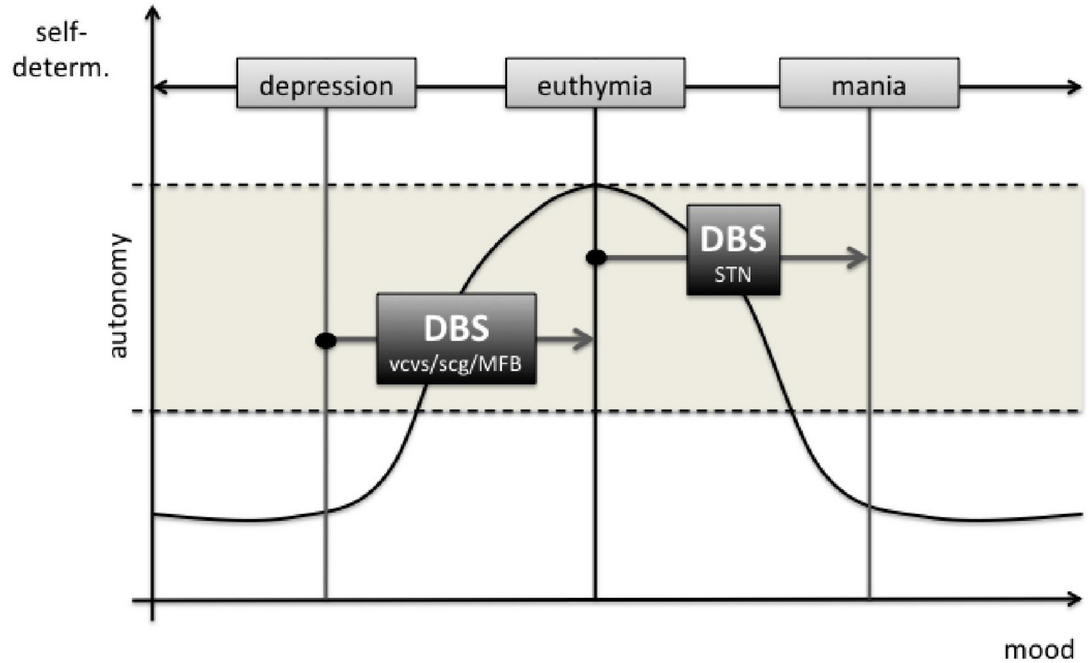

FIGURE 1 | The potential effects of deep brain stimulation (DBS) of the different target regions on patients' autonomy. In STN DBS mania is a rare (*ca*. 4%) side effect. Legend: vcvs, ventral capsule ventral striatum; scg, subgenual cingulate gyrus; MFB, medial forebrain bundle; STN, subthalamic nucleus.

really does not want to do what she passes by. According to Frankfurt, an action is hence autonomous, only if it coheres to the acting person's preferences, values and goals as represented by her second-order desires.

Autonomy Under DBS: A Critical Review of Empirical Data

Due to a lack of systematic empirical research on autonomy-subverting effects of any kind of neuromodulation, evaluating the risks of DBS-treatment to patients' autonomy in the case of MDD naturally faces a major difficulty: the only available data containing information about behavior under DBS indicating impaired autonomy originate from patients receiving treatment for different conditions. The predictive power of any evaluation thus relies on careful selection of cases which are at least in some respect comparable. The majority of studies and case reports dealing with troubled decision-making and abnormal behavior under the influence of DBS are derived from treatment of Parkinson-Disease (PD). The most relevant subgroup of patients for our purpose are those receiving DBS of the Subthalamic Nucleus (STN), which is embedded in similar neuronal circuits as DBS for MDD aims to modulate. Among several known side effects of STN-stimulation, the second most frequent psychiatric side effect (after depression) is hypomania with an estimated rate of 4% (Temel et al., 2006). According to ICD-10, core symptoms of hypomania are abnormally increased energy and activity under persistent elevation of mood, becoming manifest in behavioral changes such as heightened sociability, talkativeness, overfamiliarity, increased sexual energy or decreased need for sleep. Correspondingly, Mandat et al. (2006) report two cases of hypomania under STN-DBS leading to detrimental behavior of two male PD-patients. Seventy-two-year-old patient 1 purchased a new car, ignoring that he would never be able to drive it as he had been physically disabled for years. He also arranged to be visited by a prostitute, clearly disregarding the rules of his nursing home. Forty-five-year old patient 2, lacking any history of psychiatric disorders or criminal behavior, broke into a parked car in the middle of a crowded street. Similarly, Romito et al. (2002) report two male PD-patients with STN-DBS displaying behavioral changes associated with general symptoms of mania. Whereas patient 2 showed a wide range of abnormal sexual behavior, most remarkably inappropriate seductive behavior toward female staff, patient 1 started writing religious poems despite never having shown any interest in religion. He also began to purchase items he did not need, to plan hazardous business investments and to drive his car in a reckless manner (Romito et al., 2002, p. 1372).

Although it seems evident that the patients in these cases are not acting autonomously while in a hypomanic state, the application of Frankfurt's model to such reports is quite difficult. According to Frankfurt, the most important criterion for autonomy is coherence of the performed actions with the second-order desires of the agent. Knowing the patients only by case report, we have no access to the framework of their second-order desires. For instance, it is hard to tell whether Romito's patient 2, when writing religious poems, is just driven by some spontaneous manic fantasy or if he might be giving in to suppressed wishes. Nevertheless, we can assume that at least some of the abnormal actions displayed contradicted the higher-order desires of the agents. Wasting money on unneeded items, risking to die in a car crash or being charged with sexual harassment are very unlikely to correspond with the preferences of virtually anyone. Given that this behavior did not occur before, it appears that patients acting this way thus apparently have serious problems to act in accordance with their higher-order desires, following random impulses instead. Mandat's patient 2, who broke into a parked car, was later found unable to explain why he did it. Taking this lack of adequate reasons as a sign for a lack of second-order desires in favor of breaking into cars, the best explanation for this patient's behavior is that he was unable to resist a sudden impulse. According to Frankfurt, it is the key feature of personal autonomy to evaluate first-order desires in the light of second-order desires, which usually leads to actions compatible with a person's higher-order desires. In the cases mentioned, this mechanism seems to be impaired by impulses bypassing rational assessment. Patients tending to give in to impulses triggered by external factors (e.g., an empty highway, attractive medical staff, opportunities for spontaneous purchases) without evaluating them, thus carry a high risk for non-autonomous actions.

Having identified decreased impulse control as a possible autonomy-subverting adverse-effect of DBS, further evaluation needs to assess, if there are also examples of impaired autonomous decision-making during DBS-treatment other than manic or hypomanic states. Indeed, several cases of abnormal behavior under DBS have been reported which evidently were associated with impaired impulse control. Sensi et al. (2004) describe a patient showing explosive-aggressive behavior undergoing STN-DBS, which they explicitly relate to disturbed impulse control. On the second day postoperative, the 64-year old male exhibited spontaneous aggressive outbursts including physical attacks towards medical staff and his own family. Furthermore, he displayed kleptomaniac behavior trying to steal electric wires and bath towels. After they had found out that his aggressive behavior correlated with the strength of neurostimulation, the treating physicians eventually gained control of psychiatric symptoms through a moderate dose of antipsychotic medication (Quetiapine 100 mg/d). Supporting Sensi et al.'s (2004) interpretation, both ICD-10 and DSM-IV rank kleptomania and intermittent explosive disorder among impulse control disorders. Another kind of abnormal behavior belonging to this category is pathological gambling, which has also been found in PD-Patients undergoing DBS-treatment. According to Frankfurt, who uses the figure of the *unwilling addict* as the prime example of deficient autonomy (Frankfurt, 1988), it is highly plausible to consider pathological gambling an almost paradigmatic example of non-autonomous behavior. Typically, pathological gamblers not only act *against* their assumed second-order desires. In a certain sense one could argue that they rather act *at the expense of their second-order desires as such*, successively destroying their financial well-being and putting at stake all kinds of interpersonal relationships. In this regard, Smeding et al. (2007) report a 63-year old male patient who developed pathological gambling under the impact of STN-Stimulation. According to his family, the patient previously was "as stingy as a Dutchman". Within 1 month of his treatment, he started to gamble away considerable amounts of money, which resulted in increasing debts, the sale of his house and his wife wanting divorce. His desperate situation finally culminated in three suicide attempts, prompting his admission to the neurological ward, where his urge to gamble ceased after modification of his Parkinson medication. Apart from these rather extreme cases of impaired impulse control, STN-DBS might also impair decision-making in a less obvious way. A study based on neuropsychological tests suggests that STN-DBS can interfere with the patients' ability to stop and think when confronted with difficult decisions, thus leading to suboptimal choices (Frank et al., 2007). However, given that patients tended towards impulsive decisions especially in win-win-situations, in which only slight extra-benefits could be gained by careful selection, it seems questionable if this study actually indicates a severe threat to autonomy in any relevant sense.

Although there seems to be a wide range of autonomy-subverting side effects associated with DBS-treatment at first sight, the role of DBS in all these cases remains controversial. At least two more factors need to be taken into account for a proper evaluation. First, every patient mentioned was suffering from advanced PD and thus from a condition which severely affects dopaminergic transmission in the brain. PD itself can—at a certain disease stage—have exactly the same symptoms. Second, every patient had a history of dopamine replacement therapy and in the majority of cases medication was still being used in addition to DBS. The combination of these two factors was identified as a potential risk for impulse control disorders years ago (Voon et al., 2011). Dopaminergic dysregulation syndrome, resulting both from neurodegenerative effects of PD and longtime dopamine replacement therapy, has been discussed as a possible explanation for behavioral changes and reduced impulse control emerging independently of DBS-treatment (O'Sullivan et al., 2009; Katzenschlager, 2011). Correspondingly, Smeding et al. (2007) patient's pathological gambling eventually resolved after pergolide treatment was stopped, while DBS was continued. However, there have even been several cases in which impulse control disorders improved under DBS (Ardouin et al., 2006). All in all it is hence plausible to regard STN-DBS as just one of several factors, which, in combination, can possibly cause impairment of impulse control in *some* individuals. The same applies to manic or hypomanic states, which also occurred mainly among patients who had already been suffering from conditions affecting the limbic dopamine system. Also taking into account that the vast majority of patients undergoing DBS did not show any kind of autonomy subverting complications, it thus seems appropriate not to generally criticize DBS as a threat to autonomy. Taking seriously the examples of impaired decision-making rather should result in raising overall awareness for this category of adverse effects, including them into Informed Consent procedures and advancing standards of postoperative care.

Whereas it is questionable which role DBS has played in the mentioned cases and to which extent results originating from

STN-DBS on PD-patients can be applied to DBS of patients with MDD, the few pilot studies already indicated widespread positive effects of DBS on the autonomy of depressive patients. According to Frankfurt's concept, patients with MDD can be considered non-autonomous in a very distinct sense: although depression does not affect most patients' capability to make rational decisions, reflected in depressive patients' ability to give valid Informed Consent, it is a general feature of MDD that patients are unable to act as they truly want to. This has to do with its main symptoms, which are lowering of mood, loss of interest due to general anhedonia and reduction of energy with a decrease in activity. A typical patient therefore might actually wholeheartedly wish to leave his bed, go to work or meet with friends etc., but still none or just very few of these desires will lead to goal directed action. For this reason, patients with MDD can be conceptualized as persons with an intact framework of second-order desires, who have a significantly reduced ability to convert them into effective first-order desires and thus to act autonomously. This very impairment often entails loss of work, financial problems, damaged partnerships and social isolation. Given that there is a negative correlation between depression and autonomy, response or remission of patients undergoing DBS-treatment can be regarded as strong indicators for an increase in autonomy as well. In fact, about half of the patients included in the main pilots responded to treatment with a decrease of at least 50% on HDRS. Even non-responders have been reported to show signs of improving goal directed action (e.g., increase of activity, making new acquaintances, resuming part-time work; Bewernick et al., 2010). Thus, in the case of patients with MDD, DBS is more likely to partially restore autonomy than to subvert it, re-enabling patients to put their desires into action and leading a life which corresponds at least more closely to their own preferences than years of depressive stagnation presumably did.

CONCLUSION: AUTONOMY AS GRADUAL

As a result of our considerations, we propose to regard the majority of patients with MDD as likely to be capable of autonomous decision-making but very unlikely to be fully able to effectively act according to their own will, whenever acting includes significant personal effort. Taking into account that MDD is a highly autonomy-subverting condition, DBS thus rather seems to be a chance to restore some sovereignty in everyday life than a threat to autonomy. Though there have been some cases of partially impaired autonomy among PD-patients, potential risks of DBS in this respect seem to be overcome by anticipated benefits indicated by the pilot studies of MDD-treatment.

From a strictly clinical point of view, it is worth noting that significant improvements in daily and social life (e.g., increase of activity, establishing a daily structure, reengagement in gainful employment), which can be seen as major contributions to an overall increase of autonomy, might not be displayed adequately in standard outcome measurements. Improvements of this kind are poorly reflected in commonly used symptom-based rating scales like HRDS or MADRS. These instruments have been designed originally to monitor the effects of pharmacotherapy on "everyday" depressive patients, but not for the extreme case of treatment-resistant MDD (Bewernick et al., 2010). Exclusively measuring the effects of DBS with symptom-based scales thus could result in a paradoxical situation: patients who subjectively experience benefits of high personal relevance might be nonetheless considered objective non-responders (Bewernick et al., 2017). In a similar vein, minor but relevant improvements might be noticed best by close relatives and consequently also not be reflected in outcome measurement (Crowell et al., 2015). In line with the recently published consensus guideline for psychiatric surgery, this highlights the importance of quality-of-life measurement for the general outcome assessment of DBS for MDD (Nuttin et al., 2014). Furthermore, these findings support the claim to include individually defined treatment goals—which can of course be diverse and continually evolving—in the evaluation of overall effects of DBS-treatment (Kubu and Ford, 2012). A shift towards the individualization of outcome assessment by using more sensitive tools for improvements in daily living as well as personally defined treatment goals would facilitate the proper assessment of a possible increase of autonomy due to DBS-treatment too. Autonomy in its broadest and maybe most relevant sense means the capacity to live a self-governed life which accords as much as possible with the preferences of the agent, making it a life, which is subjectively worth living. Therefore, undergoing DBS-treatment in order to increase quality of life and to reach certain self-defined goals would not only overlap with the idea of autonomy but can in itself already be seen as a first step of regaining autonomy.

From a philosophical point of view, the example of severely depressive patients being able to decide autonomously while heavily impaired in their performance of autonomous actions, underlines that autonomy should be regarded as *gradual*. Autonomy cannot be appropriately conceptualized as an ability which is either completely lacking or fully intact. Both extremes are located at the very ends of a broad continuum. Persons reaching one of these extremes presumably are rare exceptions, given that normal, healthy agents also regularly perform actions which contradict their second-order desires. For our case, insisting on autonomy as gradual has two important implications. First, it would be more accurate to discuss DBS and its wanted or unwanted effects in terms such as "*reducing*" or "*increasing*" than "threatening", "losing" or "restoring" autonomy, which all implicitly refer to autonomy as a whole. Second, acknowledging the striking deficits in autonomy caused by MDD, the main therapeutic goal of DBS relative to patients' autonomy can only lie in *maximizing* their ability to lead a life according to their own will (Beeker, 2014). Assuming that severe motor impairments due to PD undermine self-determined living in a similar way as MDD does, the treating physicians in the cases analyzed therefore did right to continue stimulation despite the observed side effects. Having achieved significant motor benefits, they carefully adjusted stimulation parameters, optimized additional medication or just waited for adaption by way of neuronal plasticity, instead of immediately ending DBS. Remarkably, in all cases a lasting gain of overall autonomy finally achieved through successful treatment of motor symptoms thus was preceded by an episode of partially diminished autonomy. The same could apply to DBS-treatment of MDD. An evaluation of the outcome of patients always has to take into consideration that MDD itself—and therefore the condition every treatment result has to be compared to—is a condition which impedes patients living autonomously in any meaningful sense. For treating physicians, maximizing patients' autonomy in this context would mean primarily to aim for remission of depressive symptoms while carefully managing possible adverse effects. If patients are clinically benefiting from stimulation, effects which might reduce autonomy to some degree should be tolerated as long as there is reasonable hope of eventually reaching overall and long-term gains of autonomy. Even moderate persistent side effects could be tolerated, if in accordance with the will of a patient or if negligible from a broader quality-of-life perspective on autonomy. A slight overall increase in impulsiveness or a tendency towards suboptimal choices in win-win-situations might look like small disturbances to most patients, if in exchange chronic symptoms remit and theses patients are enabled to lead a relatively normal life again.

AUTHOR CONTRIBUTIONS

TB drafted the manuscript, TES and VAC substantially contributed to the conception of the work as well as its critical revision for important intellectual content. All authors approve the final version to be published and agree to be accountable for all aspects of the work, its accuracy and integrity.

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Conflict of Interest Statement: TB has no conflict of interest. TES was supported in the last five years in part by a grant from Medtronic, Inc., a manufacturer of DBS devices and the Hope for Depression Research Foundation and the Institute for Affective Neuroscience. VAC has occasionally received travel support and honoraria for lecturing and consulting from Medtronic (USA, Europe) and Boston Scientific (USA). VAC has ongoing IIT's with Medtronic and Boston Scientific unrelated to this work.

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TECHNOLOGY REPORT
published: 22 November 2016
doi: 10.3389/fnint.2016.00038

Proceedings of the Fourth Annual Deep Brain Stimulation Think Tank: A Review of Emerging Issues and Technologies

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Received: *23 May 2016*
Accepted: *01 November 2016*
Published: *22 November 2016*

Citation:
Deeb W, Giordano JJ, Rossi PJ, Mogilner AY, Gunduz A, Judy JW, Klassen BT, Butson CR, Van Horne C, Deny D, Dougherty DD, Rowell D, Gerhardt GA, Smith GS, Ponce FA, Walker HC, Bronte-Stewart HM, Mayberg HS, Chizeck HJ, Langevin J-P, Volkmann J, Ostrem JL, Shute JB, Jimenez-Shahed J, Foote KD, Wagle Shukla A, Rossi MA, Oh M, Pourfar M, Rosenberg PB, Silburn PA, de Hemptine C, Starr PA, Denison T, Akbar U, Grill WM and Okun MS (2016) Proceedings of the Fourth Annual Deep Brain Stimulation Think Tank: A Review of Emerging Issues and Technologies. Front. Integr. Neurosci. 10:38. doi: 10.3389/fnint.2016.00038

This paper provides an overview of current progress in the technological advances and the use of deep brain stimulation (DBS) to treat neurological and neuropsychiatric disorders, as presented by participants of the Fourth Annual DBS Think Tank, which was convened in March 2016 in conjunction with the Center for Movement Disorders and Neurorestoration at the University of Florida, Gainesveille FL, USA. The Think Tank discussions first focused on policy and advocacy in DBS research and clinical practice, formation of registries, and issues involving the use of DBS in the treatment of Tourette Syndrome. Next, advances in the use of neuroimaging and electrochemical markers to enhance DBS specificity were addressed. Updates on ongoing use and developments of DBS for the treatment of Parkinson's disease, essential tremor, Alzheimer's disease, depression, post-traumatic stress disorder, obesity, addiction were presented, and progress toward innovation(s) in closed-loop applications were discussed. Each section of these proceedings provides updates and highlights of new information as presented at this year's international Think Tank, with a view toward current and near future advancement of the field.

Keywords: deep brain stimulation, Parkinson's disease, Alzheimer's disease, closed-loop, depression, post-traumatic stress disorder, Tourette syndrome, DARPA

INTRODUCTION

The Fourth Annual Deep Brain Stimulation (DBS) Think Tank convened in Gainesville, FL, on March 9–11, 2016. In this summary we provide the meeting topics and expert updates, as well as important highlights in each area. DBS use has expanded in many neuropsychiatric areas and there is a need for an interdisciplinary approach incorporating neurologists, neurophysiologists, neuroscientists, neurosurgeons, psychiatrists, rehabilitation specialists, ethicists, members of industry, and engineers. The DBS Think Tank aims to be an annual forum that facilitates sharing, discussing, and debating the latest innovations and challenges in the field. This year's Think Tank focused on the regulatory process and advocacy; innovative techniques and indications; updates in the field of responsive DBS (closed-loop systems), as well as updates on associated advances in electrophysiology and sensor technology.

The overarching goal was not to produce an evidence-based summary or practice guidelines, but rather to engage participants toward addressing and solving unresolved issues that impede current and near-term research and translation of DBS. This approach has the potential to expand collaborative research, improve care and strengthen the field. The meeting, conducted in a think-tank style, afforded equal time to key speakers' presentations, and group roundtable discussions. The current proceedings of the Think Tank provide a summary and review of the developments, challenges, and opportunities in DBS research and its clinical translation.

DEVELOPMENT OF AN INTERNATIONAL REGISTRY AND DATABASE OF DBS FOR TOURETTE SYNDROME

Update

Tourette Syndrome (TS) is a complex neuropsychiatric disorder with multiple motor and vocal tics that can incur difficulty with social engagement and communications that can often be debilitating (Cheung et al., 2007; Kenney et al., 2008; Hanks et al., 2015). DBS has been explored in a subset of TS subjects with severely disabling symptoms. An international TS DBS registry and database was established in 2012 by investigators in the TS DBS field and the Tourette Association of America (TAA; previously the Tourette Syndrome Association, TSA; Deeb et al., 2016). The need for the registry and database was based on the relatively low number of cases of TS patients who have received DBS. The registry and database were therefore developed to facilitate pooling information on these cases to define and refine anatomical targets, develop management strategies, improve therapeutic outcomes, inform, and support regulatory agency approval, and ultimately, improve the quality of patient care.

Data are registered and securely stored at the University of Florida, which serves as the hub site. The registry and database enable collaborators to safely access and use the data for research and practice improvement. The project collects cases of TS who receive DBS from network sites, and encourages investigators to submit complete treatment and follow up data on every case. Data from multiple domains, including demographic

Abbreviations: 3-D, Three dimensional; AD, Alzheimer's disease; ADD, Attention deficit disorder; BCI, Brain computer interface; BLn, Basolateral nucleus of the amygdala; CM, Centromedian thalamus; CMS, Centers for Medicare and Medicaid services; CUA, Cost Utility Analysis; DARPA-SUBNETS, Defense Advanced Research Projects Agency - Systems-based Neurotechnology for Emerging Therapies; DBS, Deep brain stimulation; DTI, Diffusion tensor imaging; ECoG, Electrocorticogram; EQ-5D, European quality of life 5 dimensions; FDA, Food and Drug Administration; FDG, Fludeoxyglucose; GDP, Gross Domestic Product; GTS-QoL, Gilles de la Tourette Syndrome quality of life; HDE, Humanitarian device exemption; HFS, High frequency stimulation; HR-QoL, Health related quality of life; ICER, Incremental cost effectiveness ratios; IDE, Investigational device exemption; IIR, Investigator initiated research; IRB; Institutional review board; LFP, Local field potential; LFS, Low frequency stimulation; MCID, Minimal clinically important difference; mPFC, Medial Prefrontal cortex; NINA, Neurological information non-discrimination act; NNTI, National neurotechnology initiative; OCD, Obsessive-Compulsive disorder; PET, Positron emission tomography; PTSD, Post-traumatic stress disorder; QALY, Quality adjusted life year; QoL, Quality of Life; RNS, Responsive neurostimulator; ROR, Right of Reference; SCC, Subcallosal cingulate; SF-36, Short-form 36-item; STN, Subthalamic nucleus; TAA, Tourette Association of America; TRANSFORM DBS, Transdiagnostic Restoration of Affective Networks by System identification and Function Oriented Real-time Modeling in Deep Brain Stimulation; TRD, Treatment resistant depression; TS, Tourette Syndrome; TSA, Tourette Syndrome Association; UCSF, University of California at San Francisco; VNS, Vagal nerve stimulator; YGTSS, Yale Global Tic Severity Scale.

information, pre- and post-operative clinical measures, surgical measures, lead placement, DBS programming, and adverse events are registered.

Multiple brain sites have been targeted for DBS in TS (**Figure 1**; Malaty and Akbar, 2014).

By March, 2016 there have been 149 cases from 16 different institutions registered. There were 94 cases targeting thalamic regions (centromedian, parafascicular nuclei); 23 cases with anteromedial pallidal targets; 41 cases with posteroventral pallidal targets; and 2 cases with nucleus accumbens/ventral capsular/ventral striatum targets. Interestingly, the age at the time of surgery has been decreasing for TS DBS. This has been reflected in development of revised guidelines, which now no longer advocate that TS patients be a minimum age of 25 in order to be considered as viable candidates for DBS. Indeed, TS patients younger than 18 years of age have had good clinical outcomes following DBS treatment (Schrock et al., 2015). However, data also reveal that multiple co-morbidities, including obsessive-compulsive disorder (OCD), major depressive disorder and attention deficit disorder (ADD), exist in the TS population, and it is intended that the database and registry will provide further information to elucidate how these conditions affect, and are affected by DBS intervention.

To date, one of the most significant barriers to accruing a relatively complete evidence base has been difficulties in acquiring longitudinal datasets. Many records are missing information regarding co-morbid conditions and motoric and phonic tic follow-up scores at 6, 12, and 24 months. Additionally, sub-score collection has been incomplete for tic scales (Yale Global Tic Severity Scale YGTSS), and more data are required on the actual DBS settings and their changes over longitudinal follow up.

Developing a more finely grained understanding of the problems with the technology, physiological effects, and adverse events will be critically important to map the future of DBS therapy, and new forms for effect and event recording matching the Food and Drug Administration (FDA) standards have been implemented. Adverse event reporting has included surgical, psychiatric, cognitive and general events. Preliminary data have revealed a higher than anticipated number of device explantations and issues precipitating device removal and these need to be further explored. Servello et al. (2016, 2011) have shown TS DBS to be associated with increased infections and hardware issues, but in some cases, the devices were removed due to resolution of symptoms. In a limited number of cases, post-operative lead location measurements have been made available, and increasing such data will be important to the registry. Multiple approaches have been suggested and implemented to improve the collection of data across the numerous centers and groups that provide DBS treatment for TS. For example, quarterly reminder messages will now be sent to contributors in order to acquire heretofore-missing data fields, and a dashboard has been developed to allow secure, multi-site access to data.

The registry and database effort has been initially successful in collecting information on safety of DBS in the TS population, understanding preliminary effectiveness, and in driving better outcomes. A planned objective is to explore if and how the database could—and should—be utilized to inform and support more a more facile method for obtaining of humanitarian device exemptions (HDE), or other approval for DBS use from other international regulatory agencies. Here a number of key questions were posed that were regarded as important to leveraging DBS in other potential areas of clinical application, as well. These questions included: What obtaining HDE approval would mean to scope and extent of research in the field. What lessons can be learned from the OCD HDE experience? If HDE approval does not prove to be a viable next step, how might the registry and database be employed to help refine large randomized clinical trials? What types of metrics [e.g., predisposing features; clinically response measures; quality of life (QoL) indicators] will be important to characterize a good responder? Is there a role for subjective narrative input from each participating subject?

Highlights

- The TS DBS registry and database effort started in 2012 to bridge the knowledge gap in the use of DBS in TS subjects.
- More consistent and extensive data collection is needed to improve clinical outcome assessments, lead locations, programming parameters and adverse event reporting.
- Future areas of effort include:
    - Studying the viability and impact of obtaining HDE approval in TS DBS and its implications.
    - Characterizing TS subject phenotypes and meaningful clinical metrics.
    - Comparing outcomes of different surgical targets and stimulation paradigms.

Registering Lead Locations and How to Use the Data

The registry and database can serve as an expansive resource of diverse types and levels of information that will be essential to further define and refine the possible use(s) of DBS. For example, there is an important role for data from functional magnetic and diffusion tensor and kurtosis-imaging studies to further systematically depict lead location(s), and changes in the activity of anatomical nodes and tracts that may be involved in, and/or subserve observed clinical outcomes and effects.

There are several laboratory-based tools for predicting and reconstructing DBS effects. However, these tools are often difficult to use and incur a relatively steep user-learning curve. Developing simple systems to disseminate three-dimensional (3-D) interactive models could provide means toward more useful and user-friendly toolkits. One proposed approach toward this objective is to incorporate plotting and predictive functions into an interactive 3-D model. The method would employ a visualization component that provides volume rendering as well as surface renderings. The results would reveal the effect-size on specific clinical outcomes (such as bradykinesia) and would represent results as a function of stimulation-location. The informatics component allows the user to use a widget to query a position in space that will reveal

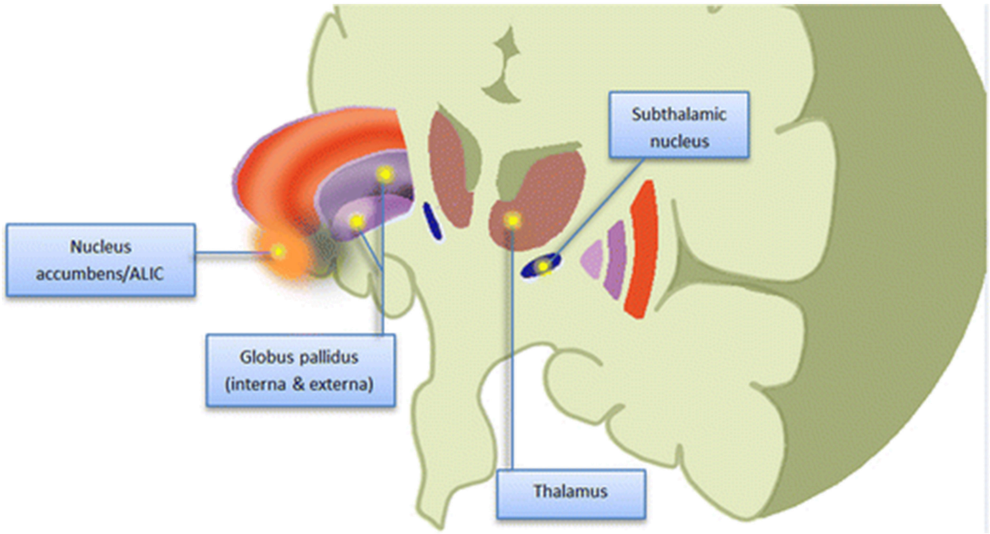


FIGURE 1 | Schematic (cartoon) representation of potential therapeutic targets of DBS for Tourette Syndrome. Figure is not drawn to scale. ALIC, anterior limb internal capsule (From Malaty and Akbar, 2014; with permission).

different visualizations of the outcome data associated with stimulating a specific point in space. Clinical effect sizes for various effects can also be extracted from the data obtained.

A composite figure of actual lead locations in the subthalamic nucleus was produced using data from a multi-center DBS clinical trial. It revealed significant variability in lead location and trajectory across the different centers, despite targeting the same structure, and region (subthalamic nucleus). Analyzing the variability in lead location will be critical, as it will allow more accurate site specific correlation of lead placement and clinically relevant (objective and subjective) effects of DBS in treating different signs and symptoms of various disorders.

Future steps in developing imaging databases include measures for insuring patient (and clinician) anonymity, consideration of a data-use embargo period, and defining the terms of use of information in the database. Participants in the Think Tank proposed the possibility of a central data repository of images and lead locations, to which practitioners could upload individual scans to be used for comparisons and benchmarks.

To be sure, the collection and assimilation of various types and extent of data represent challenging tasks, and opportunities. At present, a number of computational tools are available to facilitate data collection and sharing. One such tool, developed by the Center for High Performance Computing at the University of Utah, enables use of a protected data environment platform to allow collection of sensitive, personal health information. This organized, scalable infrastructure can be used to host RedCap® and imaging software that enable differing types of data from providers, patients, and caregivers to be entered and analyzed. Ongoing efforts will be focused upon developing this and other big data platforms to optimize collection, integration, use, and modeling of diverse information.

Highlights

- Any database effort needs to establish the short-term, medium term, and long-term goals.
- Lead location in the TS DBS database effort is a bedrock in understanding outcomes.
- Steps are needed to improve collaboration and eliminate obstacles.
    - Tools are available to facilitate sharing of interactive and predictive 3-D models.
    - The think tank participants recommended the development of a central data repository of lead location images.

Quantifying Economic Impacts of Deep Brain Stimulation

Since 1999, a small number of patients worldwide have received DBS for severe TS (Ackermans et al., 2008). Although, clinical results have been promising, establishing clinical effectiveness is not always sufficient to ensure investment in new medical technology.

The Center for Movement Disorders and Neurorestoration at the University of Florida maintains an international database of patients with severe TS who have received DBS ($n \approx 150$). While clinical data is collected pre- and post-DBS, to date economic data have not been collected. When medical treatments must compete aggressively for a limited pool of healthcare resources, well-designed economic evaluation is essential to ensure that necessary resources are directed toward treatments that offer the best outcomes. In light of this, a comprehensive economic evaluation of DBS for TS is planned.

A survey of patients and treating medical practitioners will be undertaken to collect data necessary for economic evaluation. Patients will be surveyed for indirect medical costs, including workforce participation and health related quality of life (HRQoL) using a validated instrument (e.g., SF-36 or EQ-5D). The treating medical team will be asked to report direct medical costs and relevant post-operative clinical data (e.g., verification of the neuroanatomical location of the DBS electrodes, etc.). Direct medical costs will include the costs of DBS hardware, surgery, inpatient stay, neurostimulator titration, and post-operative complications. Quality-adjusted life years (QALYs), a generic metric of HRQoL, is routinely used as a summary measure of health outcomes in cost-utility analyses (CUA) (Drummond et al., 2015). A QALY of one denotes a year of life lived in perfect health. Years lived in less than perfect health are scored less than one. Health policy analysts deem cost per QALY ratios, less than some designated threshold, as being cost effective. Thresholds between nations will vary, and can be approximated by the gross domestic product (GDP) per capita (Marseille et al., 2015). For example, ratios of US $50,000 per QALY (Grosse, 2008) and £20,000–£30,000 per QALY (McCabe et al., 2008), are used in the United States and United Kingdom, respectively. Post-operative QALYs will be derived from reported HRQoL sub-item scores. Pre-operative QALYs will be hindcast, using coefficients obtained from statistical analysis, which regress clinical variables on post-operative QALYs (Dodel et al., 2010; Müller-Vahl et al., 2010). Costs and QALYs will then be analyzed and incremental cost effectiveness ratios (ICERs) reported. Other methods of analysis, such as the Minimal Clinically Important Difference (MCID) may be valuable. We believe that such findings will represent an important first step to elucidating health outcomes' afforded by DBS, and to informing appropriate investment in DBS technologies and practices.

Highlights

- It is planned that economic data should be collected to establish the cost-effectiveness of DBS as a treatment for severe TS.
- Technical (e.g., post-operative electrode placement), as well as direct and indirect health costs plus a generic measure of HRQoL data should be collected.

Regulatory Processes and Translational Viability: Time for a Change?

Investigational Use of DBS in Clinical Practice

The overarching goal of the US Food and Drug Administration (FDA) regulation process is to establish that any and all drugs and devices provided for medical care are safe and technically sound. In the United States, device trials utilizing either a non-approved or an approved device to be used for a non-approved indication require an investigational device exemption (IDE) to be granted from the FDA. Failure to obtain an IDE will preclude most Institutional Review Boards (IRBs) from approving prospective studies of off-label use of devices. Both the IDE and HDE entail considerable detail in scope, application, review and guidance, and such stringency is necessary and important to determine and to assure probity in applications of technology. Moreover, whereas IDEs can be obtained (by industry) for industry-sponsored device trials, investigators are required to obtain the IDE in non-industry sponsored trials; this can be- and frequently is—an arduous, and time- and cost-expensive process.

In recent years, IDE and HDE applications, review and approval have become considerably more facile and efficient; this is a notable improvement—and a step in the right direction. However, as regards to DBS, it may be that aspects of the overall structure and certain specifics of the IDE and HDE are not well suited to meet the contingencies (and exigencies) of actual clinical use, particularly in light of interest in exploring if and how DBS may be of clinical benefit in the treatment of an expanding number of neuropsychiatric conditions (as detailed elsewhere in this report). For example, the current regulatory framework necessitates filing and securing an IDE as a first step in investigator-initiated research (IIR) and/or other off-label use of DBS in those cases where other approaches have been shown to be ineffective or untenable, and for which DBS may prove to be viable as "humanitarian care." In such instances, it may be that the proverbial cart precedes the horse, and the HDE might be more practical and valuable given both the nature of the disorder and treatment, and the value of the HDE in establishing a basis for further (and/or expanded) application, as supportable by an IDE.

Moreover, while both IDE and HDE establish parameters for using DBS in practice, neither regulatory mechanism establishes or enforces a basis for provision of economic support necessary for right and good use-in-practice. As recent work has demonstrated, non-payment of insurance costs for pre-certified DBS interventions has been, and remains a problem of considerable concern (Rossi et al., 2016a,b). Absent resources to provide: (1) DBS as a demonstrably-important or necessary treatment option for those subjects with conditions that are non-responsive to, or not candidate for other therapeutic options, and (2) continuity of clinical services as required, the sustainability of this neurotechnology may become questionable (Rossi et al., 2014). We see this as contrary and counter-productive to recent federal incentives to maximize benefits of translating extant and new neurotechnologies into clinically-relevant and affordable care and to implementing precision medicine.

In the main, we applaud actions taken by the FDA to date that have streamlined the IDE and HDE process. Yet, while certain aspects of the IDE and HDE mechanisms may be in order, apt, and valuable for regulating use of DBS, others may require re-examination, revision or replacement, so as to remain apace with developments in the field, and needs and necessities (of both subjects and clinicians) in practice. In this vein, we recommend further study of: (1) the scope and tenor of the IDE and HDE mechanisms to determine their independent and interactive benefit (as noted above); (2) whether and which aspects of the current IDE/HDE process are effective and efficient, and which are not; (3) what aspects need to be retained and fortified, revised or replaced; (4) what is entailed in these revisions/replacements; and (5) if and how regulatory, policy and legal processes can and should be aligned with, directive toward, and supportive of and by concomitant changes in standard of care guidelines and federal insurance structure (Fins et al., 2012). A number of possible alterations to the IDE process were addressed, which may streamline application and granting of regulatory approval. These include: removal of the right of reference letter (ROR) requirement; improved alignment of federal grant mechanisms and regulatory process, and institution of mechanisms for Centers for Medicare and Medicaid Services (CMS) and private insurance payment to support costs incurred by patients involved in these trials. Proposed alternatives to IDE-sponsored trials were also addressed, including the viability and value of retrospective analyses of multiple case series, and large scale, multi-site single case analyses, which could be facilitated through the use of currently available computational tools (e.g., the *AvesTerra* System; see: http://osvpr.georgetown.edu). that enable massive data assimilation and integration, both in concert with, and independently of a registry mechanism. Important to this effort would be the development of both a governmental-commercial enterprise to guide industrial efforts in neurotechnology (e.g., a National Neurotechnology Initiative; NNTI), as well as the establishment and enactment of federal laws (e.g., a neurological information non-discrimination act; NINA) to govern potential use(s) of information obtained through DBS and related neurotechnologies together with extant and novel big data initiatives (Kostiuk, 2012; DiEuliis and Giordano, 2016). We believe that while establishing this "translational estate" will require significant effort; it represents a worthwhile endeavor toward the achievement of genuine and durable progress in the development and use of neurotechnology in clinical practice.

DBS INNOVATIONS

Tourette Syndrome

As noted, much of the more innovative work to date has (and remains) focused upon studying the viability and value of DBS for the treatment of Tourette syndrome. While the exact causes of TS remain unknown, recent neuropathology neuroanatomical investigations have collectively implicated dysfunction of corticostriatal and thalamocortical circuits thought to play a role in the generation of abnormal motor programs, possibly due to aberrant thalamic disinhibition (Albin and Mink, 2006). The collection of neural activity from the awake and behaving human TS patients will offer new and vital insights to the underlying neurophysiology of tic generation. To this end, next generation DBS devices, such as the *Neuropace RNS* and Medtronic *Activa PC+S* enable recording of electrophysiological signals from both the implanted depth electrodes, as well as acutely placed electrocorticography (ECoG) strips.

An unpublished study was presented that examined the effects of DBS on two patients with severe, medication refractory TS. Patients were implanted with bilateral Medtronic *Activa PC+S* devices. Depth leads were placed in the centromedian-parafascicular nucleus of the thalamus (CM) and ECoG strips were placed over the precentral gyrus to cover the hand primary motor cortex (M1). Experiments consisted of separate interleaved trials in which patients were instructed to: (1) tic freely, (2) suppress tics (baseline), and (3) execute volitional movements (e.g., shaking hands rapidly, opening and closing hands, raising arms up, and down, talking). Post-operatively recorded data suggested that M1 yields a general motion detector (15–30 Hz), whereas CM yields tic-specific features (1–10 Hz). A human tic detector, based on support vector machines was constructed during each post-operative visit (for a period of 6 months). Three types of tics were recorded including simple, complex, and long complex tics. Long complex tics were shown to be concurrent with a consistently detectable thalamocortical signature. Short complex tics were more difficult to detect than long complex tics, and simple tics were the most difficult to detect. Acute trials of closed loop stimulation using the Medtronic Nexus-E platform are currently underway. The proposed system is presented in **Figure 2**.

Highlights

- The initial RNS study in TS patients revealed that good benefit in tic control can be achieved with scheduled stimulation as compared to continuous stimulation.
- LFP-ECoG neurophysiological testing identified a correlation between tic activity and appearance of a 10 Hz narrow band signal.
- Targeted stimulation using the 10 Hz band as signal resulted in tic improvement (preliminary results).

Summary of Use of DBS to Treat Epilepsy

Epilepsy, the result of the hyper-synchronization of firing of neurons, creates "fragile" neurological networks that tend to cycle. Multiple modalities of neurostimulation have been developed to modulate burst and cycling activity in epileptic patients (Krishna et al., 2016). In addition to DBS, techniques such as vagus nerve stimulation (VNS), which engages afferents of peripheral nervous system input to activate vagal pathways, can alter firing patterns of brain networks involved in ictal discharges and cycling. As well, the use of other neuromodulatory techniques, such as responsive neurostimulation (RNS), has been explored (Chang et al., 2015).

These approaches differ in their modulatory effects upon cycling time, burst duration, frequency, and amplitude. In addition, the locations of the VNS and DBS electrode placement (at the anterior nucleus of the thalamus) are the same in all patients while RNS employs a variety of possible placement sites. The site of RNS is dependent upon identifying the epileptogenic locus of nodes involved in a specific patient. In most cases, this has been shown to be cortical gray matter. However, patients with long-standing refractory epilepsy have been shown to develop areas of secondary epileptogenesis, possibly through kindling. To better manage multiple epileptogenic loci in this population, stimulation of the affected circuitry (white matter) rather than the epileptogenic gray matter is being considered (Girgis and Miller, 2016). In these studies, it has been shown that microelectrode recording and modification of the area of stimulation can achieve differential, acute and chronic effects on the involved neurocircuitry. Chronic effects appear to be related to stimulation-induced plasticity, and may engage trophic mechanisms in that they subserve (at least some component of) the therapeutic outcomes of neurostimulation in this patient population.

Highlights

- Studies of the mechanisms and effects of DBS in treating epilepsy can be useful to both an expanded understanding of

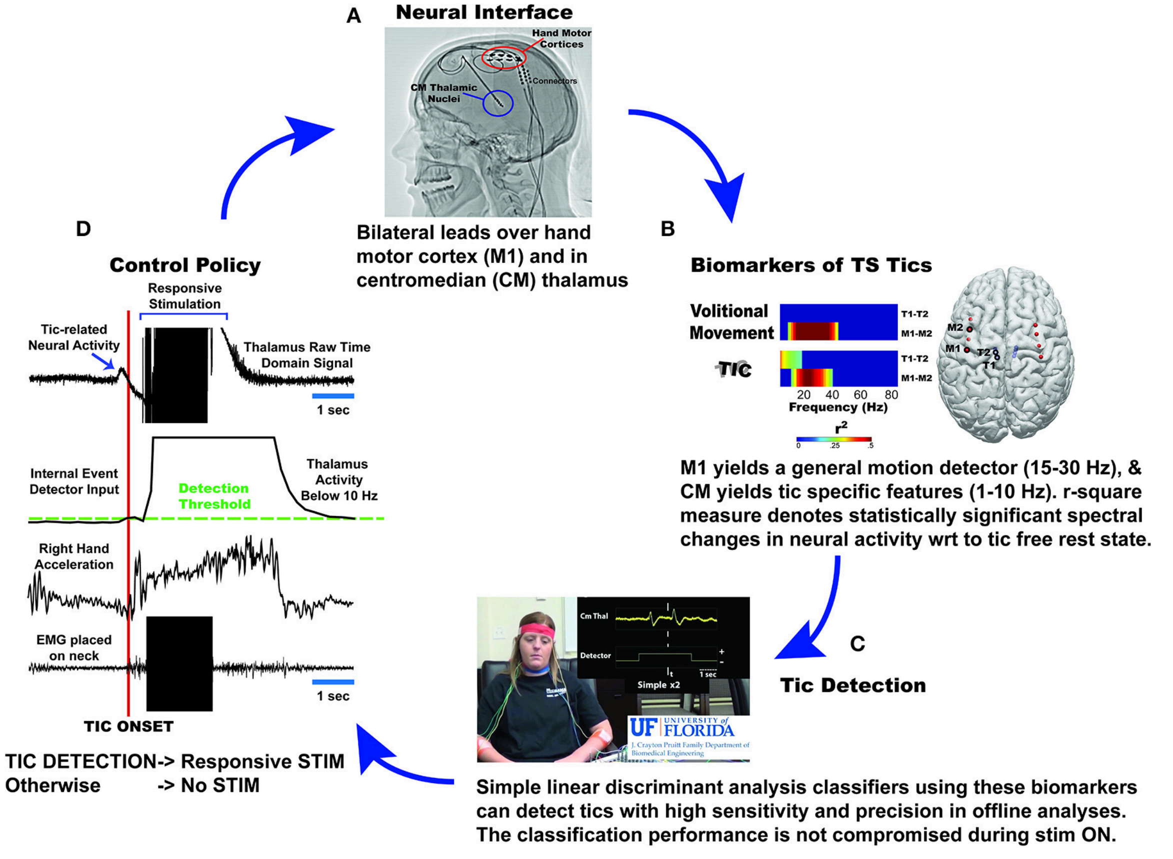


FIGURE 2 | Diagrammatic depiction of the University of Florida approach to implementing chronic responsive DBS therapy for Tourette Syndrome. Current experience with two patients with TS, who received bilateral centromedian (CM) thalamus depth leads and bilateral subdural grid implantation over their hand motor cortex **(A)**, led to the discovery of tic specific features in CM thalamus (1–10 Hz) and motion detection features in hand motor cortex (15–30 Hz; beta rhythm) **(B)**. A combination of these two features yielded highest detection of tics and differentiation from voluntary movements in linear discriminant analysis classifiers **(C)**. These classifiers are embedded in PC+S and send control signals to Nexus- E stimulation engine **(D)**. Once the detectors sense presence of tic related activity, stimulation will be activated to deliver stimulation to optimize therapeutic effects/outcomes.

DBS and brain pathology, and can synergize the development of other types of neuromodulation.

- Studies of DBS (and VNS and RNS) reveal the importance of determining and identifying anatomical targets (gray matter) vs. circuit targets (white matter).
- Brain stimulation can exert acute and chronic effects, the latter being related to neuro-plasticity and trophic effects.
- The role of multi-site, multi-electrode pre- and intra-operative recording is essential to advancing understanding and improvement of neuromodulation approaches to the treatment of epilepsy; however, how findings from studies of the use of DBS, VNS, and RNS may translate to broader applications of these techniques remains a subject of continuing speculation.

Novel DBS Settings—Biphasic Pulses and Beyond

DBS signal delivery is a rapidly progressing field. Recent innovations in DBS signal delivery (Fasano and Lozano, 2015) include regulated current vs. regulated voltage waveforms (Lempka et al., 2010; Preda et al., 2016), differing stimulation waveforms (Foutz and McIntyre, 2010; Wongsarnpigoon and Grill, 2010), and different temporal patterns of stimulation (Brocker et al., 2013; Adamchic et al., 2014).

Studies have repeatedly demonstrated the enhancement of the therapeutic window with lower DBS pulse widths (Moro et al., 2002; Volkmann et al., 2014). High frequency stimulation (HFS; >100 Hz) has generally been considered to be effective for mitigating certain signs and symptoms of Parkinson's disease (PD), but low frequency stimulation (LFS; <100 Hz) has yielded contradicting results. LFS <50 Hz has been shown to be harmful resulting in worsening bradykinesia and tremor (Moro et al., 2002). Stimulating at individualized gamma frequencies (30–90 Hz) improved PD symptoms, with outcomes that were similar to those produced by HFS (Tsang et al., 2012). These findings suggest that LFS can be effective provided that it is appropriately matched to subject's individualized gamma frequency patterns associated with movement. Irregular patterns of stimulation have also been studied in computational models, non-human primates, and human patients. While there are some irregular patterns that seem to be as effective as—or more effective than—regular HFS, evidence for human testing remains limited. A recent randomized, blinded pilot study of nonconventional

DBS patterns and pulses—the first reported study of its kind—tested 3 essential tremor and 8 PD clinically-optimized patients in a clinic setting (Akbar et al., 2016). Of the settings tested, the nonconventional biphasic pulse (equal and opposite, active recharge phase) was shown to be more effective than the clinically optimized settings. Of course, it may be premature to draw firm conclusions about the effectiveness of this pulse shape based upon the results of this small pilot cohort, but such findings are both of great interest and promising in their implications for the viability and effectiveness of novel pulse and pattern parameters. Additional studies to further investigate these possibilities and to address the potentially short washout interval are underway.

Highlights

- A number of techniques of stimulation are available including differing stimulation waveforms and current.
- There is a differential therapeutic effect of the various stimulation parameters in DBS that appears to be related to the underlying disease process (e.g., PD, dystonia). A recently published pilot trial to assess different stimulation parameters in PD and essential tremor subjects revealed significant improvement induced by symmetric biphasic pulse stimulation.
- Ongoing unresolved issues include the effect of differing pulse and pattern settings on battery drain, requisite washout time, and biophysical changes induced in affected neural nodes and circuits.

Development of DBS Sensors

DBS surgery provides an investigational opportunity for use of electrophysiological and/or neurochemical recording techniques. Such approaches can: (1) aid in DBS lead placement, (2) provide additional information about disease states, and (3) potentially enable future development of techniques to better control and fine-tune DBS therapies including closed-loop control (Herrington et al., 2016). In addition, DBS surgery provides a vector to introduce stem cells, autologous transplants, and/or gene modification. We have termed the conjoined use of these approaches *DBS Plus*.

Future directions in DBS have been proposed to incorporate real-time monitoring of field potentials/unit activity, and *in vivo* assessment of neurotransmitter release and turnover (Paek et al., 2013). Such combinatory approaches could be used to further define brain networks affected in disease processes, which could serve to elucidate target sites for current and future applications of DBS (including closed-loop systems) to more effectively—and automatically—program, control, and modify stimulation parameters (Grahn et al., 2014).

These iterations are currently under development. For example, RNS for epilepsy and a new DBS variant manufactured by Medtronic, the Brain Radio, implement simultaneous field potential recordings that are coupled to neural stimulation. The use of simultaneous DBS and neurotransmitter measurement is being studied by Lee and coworkers in a Phase I investigation using fast-scan cyclic voltammetry recordings coupled to carbon fiber or boron doped diamond-like carbon microelectrodes (Bennet et al., 2016). Gerhardt, van Horne and colleagues are investigating (personal communication) the possible use of glucose and glutamate as chemical biomarkers for control of DBS. Current preclinical studies support that oxygen and glutamate measures can be used to reveal both tonic and phasic changes in neuronal systems that may be indicative of trait- or state-dependent properties (Stephens et al., 2014). A persistent technical impediment to these types of studies is the difficulty of long term monitoring of neurochemistry *in vivo*. As well, it remains unclear if and how *in vivo* neurochemical monitoring can be durably yoked to DBS. The combined use of electrophysiological recordings and real-time neurochemical monitoring show considerable value for closed-loop control of RNS technology for epilepsy, and for closed-loop control of DBS therapy for PD. Nevertheless, given the early stage of these developments, it will be important to continue studies of real-time neurochemical monitoring for use in both open- and closed loop DBS applications pursuant to advancing these approaches toward more broadly applied clinical translation.

Highlights

- We introduce the concept of *DBS Plus* to describe the incorporation of additional treatment and recording modalities (e.g., stem cells, gene modification, neurochemical monitoring, etc.) during DBS surgery.
- Multi-modality monitoring can be important to identifying neural circuity involved in various pathologies and DBS effects, and in these ways can facilitate more accurate electrode target placement.
- These *DBS Plus* approaches show promise in the further development of closed-loop systems.

DBS for Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia worldwide (Scheltens et al., 2016). Current focus of treatment for AD treatment has pharmacotherapy aimed at modifying acetylcholinesterase activity, N-methyl D aspartate receptor activation, and more recently, production or deposition of beta-amyloid or tau proteins. The limited evidence for symptomatic benefit or slowing of disease progression from these approved and investigational treatments, as well as the side effects reported, support pursuing other avenues of intervention (Winblad et al., 2016).

The importance of developing approaches to modulate cortical and hippocampal circuits affected in AD was the impetus for a phase I study of DBS targeting the fornix (Laxton et al., 2010). The choice of the fornix as the target was based upon serendipitous observation of improved spatial and verbal learning and memory functions in patients who received DBS leads in the hypothalamus for obesity management. In the phase I study, continuous fornical stimulation produced sustained increases in cortical metabolism at 1 month and 1 year post-operatively. Further, increased functional connectivity was observed in two orthogonal networks: a frontal-temporal-parietal-striatal-thalamic network and a frontal-temporal-parietal-occipital-hippocampal network. These increases in functional connectivity were greater than effects produced by 1 year of pharmacotherapy (with cholinesterase inhibitors) and were in contrast to metabolic reductions and decreased functional connectivity seen in the 1 year course of AD. Higher cortical metabolism prior to initiation of DBS, as well as increased metabolism after 1 year of DBS, were correlated to better outcomes in global cognition, memory, and quality of life indices (Smith et al., 2012). A multi-center, double-blind, randomized, and controlled Phase II trial of 42 mild probable AD patients—the *ADvance trial*—was conducted (Lozano et al., 2016). In this study, the mean age of subjects was 68.2 ± 7.8 years (younger than the AD population, but similar to the age range of AD patients enrolled in clinical trials; Leinonen et al., 2015). Average disease duration since diagnosis was 2.3 ± 1.7 years. Electrodes were implanted in all patients, but half of the patients did not receive stimulation for the first 12 months, and were subsequently crossed over to active stimulation. The trajectory was trans-ventricular and implantations of Medtronic hardware were bilateral (Ponce et al., 2016). Stimulation was applied using extant PD protocols, with a frequency of 130 Hz, pulse width of 60 μs, and voltage set at 50% of that at which side effects (e.g., autonomic or cognitive changes) were seen, with a maximum test voltage set at 7 V and maximum continuous voltage of 3.5 V. There was no noted acute decline in cognition after 1 month of surgery. Consistent with results of the prior Phase I study, persistent increases in metabolism were observed in the group receiving stimulation (i.e.,- the ON group) after 6 and 12 months of DBS of the fornix, in contrast to the OFF group that showed decreased metabolism (7–13%) across all regions assessed. The primary goal was safety; the safety profile of the procedure was acceptable and comparable to pharmacologic therapies. There were some short-term side effects related to the surgery, as well as some psychiatric side effects (as expected following DBS). None of the subjects had persistent side effects or complications at 12 months follow-up.

Secondary goals were to evaluate the preliminary efficacy of therapy. These secondary end points were not met, although *post-hoc* analysis of subgroup evaluations based upon age showed that when patients 65 years of age or older were analyzed separately, greater increases in metabolism were observed in the ON group compared to those under age 65 (14–20% across regions over age 65). The subgroup aged <65 years had worsening clinical scores, while the subgroup aged >65 years showed improvement in clinical scores. The clinical scores used for this analysis included the Clinical Dementia Rating (CDR) and Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-Cog). In this older cohort, increased metabolism with fornical DBS was observed in the temporal and parietal cortices and hippocampal regions affected by AD, as well as in sensory and motor cortical regions that are relatively spared in this disorder. Functional connectivity and correlational analyses are currently in progress to determine the networks affected by DBS that are involved with clinical improvement, and the relationship between the metabolic and structural brain alterations associated with DBS to the fornix.

Other potential targets for DBS treatment of AD have been assessed and include the nucleus basalis of Meynert and the entorhinal cortex. Further studies are needed to: (1) clarify stimulation parameters for various brain regions and networks that can be targeted to mitigate signs and symptoms of AD; (2) define mechanisms through which DBS produces therapeutic and side effects in AD patients, and (3) to enable more accurate subject identification and selection.

Highlights

- DBS of the fornix has been shown in phase 1 studies to be associated with metabolic and clinical changes.
- The *ADvance* trial, a recently completed phase 2 study, assessed the safety of fornix DBS in AD, that demonstrated:
  - No significant long-term complications,
  - No acute cognitive decline after DBS surgery,
  - Age-dependent effects with patients over age 65 achieving better outcomes,
  - Concerns about bilateral simultaneous implantation,
  - The need to further identify "optimal" stimulation parameters,
  - Need for further study before considering fornical DBS as a viable treatment for AD in clinical practice.

CLOSED-LOOP DBS

Introduction

Existing DBS devices continuously stimulate their target structures regardless of the actual level of pathological activity. This can result in stimulation induced adverse effects, habituation, short battery life, and the need for labor-intensive programming sessions by a neurologist. Closed loop DBS enables simultaneous feedback and feedforward control of stimulation parameters that can afford a high level of precision and individual modification to variations in brain state. A major consideration of closed loop DBS is determination of the input signal. Recording brain signals in different therapeutic conditions (on and off DBS; on and on medication) has led to a better understanding of pathophysiology underlying PD, TS (discussed above) and major depression. This work results in the identification of disease markers that might be used as control signals for closed-loop DBS algorithms.

Parkinson's Disease

Published work has focused on the use of a beta-band signal (13–30 Hz) as a control signal (Little et al., 2013). However, the beta band is somewhat limited as a control signal by the influence of normal movement upon the signal fidelity. In light of this, current work is aimed at identifying oscillations that are outside of the beta-band that may be useful as markers. One, a narrow band gamma signal that has been defined as between 60 and 90 Hz, has been previously assessed as a surrogate signal using local field potential measurements (LFP) of the subthalamic nucleus (STN) (Brown et al., 2002; Cassidy et al., 2002). However, further study is required to more fully define the value of this, and other signals that can be utilized for optimized closed-loop control. Pursuant to such study, extensive neurophysiological work will be required. Work currently underway involves cortical recording with ECoG at the precentral gyrus/primary motor area and depth electrode recording at the level of the basal ganglia.

For example, to assess control signals in PD subjects with dyskinesia, researchers at the University of California at San Francisco (UCSF) group have implanted 5 patients with Medtronic Activa PC+S neurostimulators attached to a DBS lead (Medtronic 3389) in the STN and a 4-contact cortical ECoG strip (Medtronic Resume paddle) placed over the M1. Cortical and subcortical signals were collected over 2 years while patients were on and off therapeutic DBS as well as on and off dopaminergic therapy. During these recordings patients were resting with eyes open or engaged in a cued arm-reaching task (de Hemptinne et al., 2015). M1 and STN signals were recorded in a bipolar configuration at 800 Hz, stored and the PC+S downloaded non-invasively via telemetry and analyzed in the frequency domain.

Using this unique data set (unpublished data), they found that periods of dyskinesia are associated with an increased neuronal synchronization in the gamma band (60–90 Hz; **Figure 3**). This excessive synchronization is reflected as a narrow band peak in the spectral power density of both M1 and STN signals, although less reliably detected in the latter. The emergence of this excessive synchronization occurs only in the presence of dyskinesia suggesting it as a marker of dyskinesia rather than a marker of the dopaminergic state. Interestingly, the cortical narrow-band gamma signal was shifted to half of the stimulation frequency when DBS was turned on, in the presence of dyskinesia only, which might be explained by a partial entrainment of axonal activity to stimulus pulses (Li et al., 2012). Contrary to broadband gamma activity, a non-oscillatory signal strongly affected by movement, the narrow-band gamma signal studied here was independent of the subject's "normal" voluntary non-dyskinetic movements. Other markers were studied including the coherence between the cortical and basal ganglia signal, as well as phase-coherence (unpublished data).

Narrow gamma band signals are part of a normal motif in brain connectivity allowing communication between multiple brain areas and alteration of these oscillations might results in dyskinesia as suggested by this study. Recordings in the motor cortex of a rodent model of PD identified a remarkably similar phenomenon in dyskinetic rats versus non-dyskinetic animals (Halje et al., 2012).

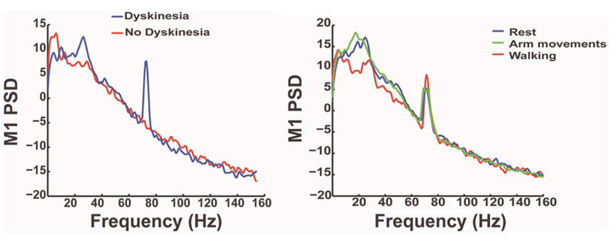


FIGURE 3 | The graphs depict the results of analysis of the M1 signal in the frequency domain in PD patients with dyskinesia. It shows, in the graph on the left, that dyskinesia is associated with an increased neuronal synchronization in the gamma band (blue line) reflected as a narrow band peak. The graph on the right shows that this gamma-band signal is related to dyskinesia and independent of the functional state (rest, walking, or voluntary arm movement).

Given the predictable frequency at which this marker occurs, the simple method used to calculate it and the small impact of stimulation artifact of cortical signals, this biomarker is the ideal candidate to develop a closed-loop DBS algorithm. Therefore, the next step of this study is to develop closed-loop paradigms using this narrow-band gamma signal as a control signal and test it in PD patients with dyskinesia using the Medtronic Activa PC+S with the Nexus-D and E updates that allow for real time sensing and stimulation updates.

Highlights

- The use of beta-band subcortical oscillations in PD as a control signal is limited by the effects of voluntary movements and stimulation.
- Narrow gamma-band signal (60–90 Hz) appears to correlate with the dyskinetic state in PD subjects, is less affected by stimulation artifact and is independent of voluntary movements.
- Ongoing study to use the identified narrow gamma-band as a control signal for closed-loop DBS in PD patients for better control of dyskinesia.

Depression

It has been ∼10 years since the first proof-of-principle report supporting the efficacy of subcallosal cingulate (SCC) DBS to reduce signs and symptoms of treatment resistant depression (TRD; Mayberg et al., 2005). Initial selection of the SCC as a putative DBS target was principally based on converging findings from resting-state positron emission tomographic (PET) imaging studies of conventional antidepressant interventions, localization of depression-related circuits, and nodes using standard structural imaging methods, and trial-and-error behavioral testing of chronic stimulation at individual contacts on each implanted DBS electrode. As testing of DBS for treatment resistant depression has matured and expanded, neuroimaging continues to play a crucial role, with recent work now focused on refinement and optimization using multimodal methods combined with real-time behavioral and physiological metrics. These combinatory approaches afford more precise identification of optimal target locations in real time (Smart et al., 2015).

One proposed mechanism of DBS in reducing features of treatment resistant depression is modulation of a multi-region network converging at the SCC (**Figure 4**). Structural connectivity analysis of SCC DBS confirms the SCC as a critical node within this specified "network," as small differences in stimulation location can generate substantial differences in activated fibers. Recent studies have further confirmed which of these pathways are necessary for clinically significant effects of DBS. These pathways can now be prospectively characterized in individual patients using DBS parameter models coupled to structural connectivity analyses (Riva-Posse et al., 2014; Choi et al., 2015).

Close clinical monitoring and systematic long-term follow-up using small experimental cohorts outside of industry-sponsored trials have further provided new perspectives on the time course, trajectory and sustainability of DBS-mediated effects (Crowell

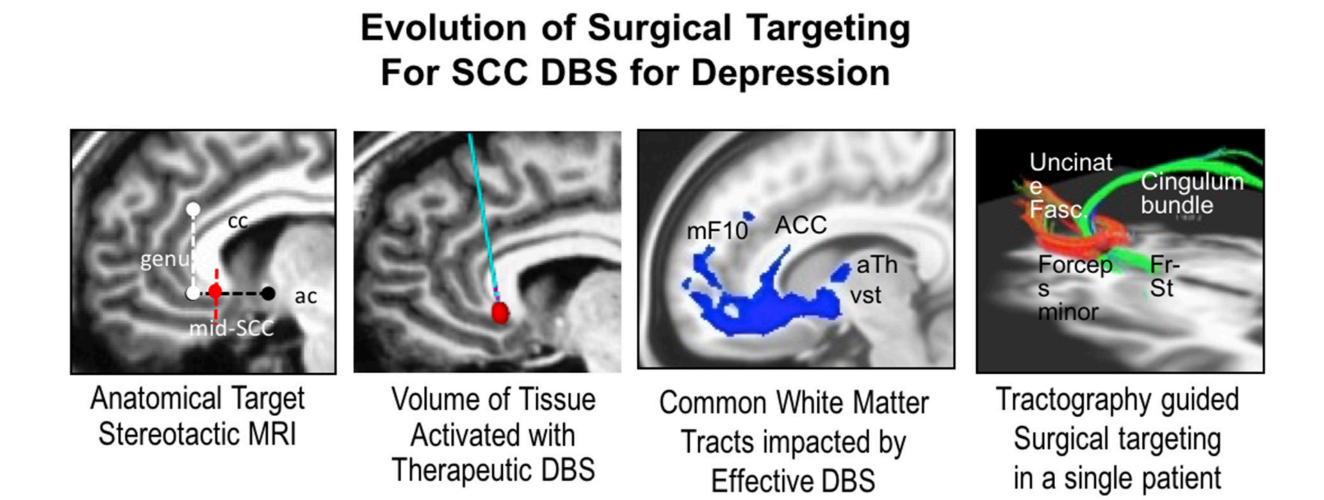


FIGURE 4 | The panes depict (from left to right) the evolution of surgical targeting of SCC in depression from, an anatomical "gray matter" target to identification of the "white matter" tracts activated, and finally tractographic data allowing identification of the involved pathways that elicit differing effects when targeted by DBS. This approach allows individualized target refinement and produces improved therapeutic outcomes. Genu, genus of the corpus callosum; Mid-SCC, mid subcallosal cingulate; Ac, anterior commissure; mF10, medial frontal Brodmann Area 10; ACC, anterior cingulate cortex; aTh, anterior thalamus; vSt, ventral striatum; Fr-st, frontal striatal fibers.

et al., 2015). Notably, patients often experience contact-specific changes in mood, attention, psychomotor speed, and autonomic reactivity with initial testing during electrode implantation surgery. Importantly, these acute behavioral effects appear predictive of long-term response. Recent implementation of real-time recording of SCC LFP during acute testing and ongoing therapeutic DBS using the prototype Activa PC+S DBS system is providing a first-in-human view of differential SCC LFP changes mediating immediate, sub-acute, and chronic DBS-induced antidepressant effects at the neural level. LFPs measured at the site of stimulation combined with concurrent high density EEG will further enable characterization of clinically relevant network-wide effects. Findings from this small exploratory study will potentially provide new metrics to further improve precision of surgical targeting as well as new algorithms for DBS delivery beyond current methods. Validation of relationships between local and network-wide changes with the differential time course of recovery in specific clinical features will lay the foundation for sensing signals for next generation neurostimulation systems.

Highlights

- Initial selection of the SCC as a putative DBS target was principally based on converging findings from resting-state PET imaging studies of conventional antidepressant interventions.
- Recent work now is focused on refinement and optimization using multimodal methods combined with real-time behavioral and physiological metrics, providing a more precise identification of the optimal target location in real time.
- Modulation of a multi-region network converging at the SCC is a proposed mechanism of action for DBS in reducing features of depression.
- Validation of relationships between local and network-wide changes with the differential time course of recovery in specific clinical features will lay the foundation for sensing signals for next generation neurostimulation systems.

Clinical Assessment and Management of Tremor

Tremor-dominant PD patients have been shown to have a functional correlation of their tremor and beta-band signals as measured by LFP. The resting state beta band may be attenuated during periods of tremor in PD. Resolution of tremor results in re-emergence of the beta band (Little and Brown, 2012). This suggests that beta band power may be viable as a kinematic control variable to drive closed loop DBS for tremor, as diminished beta band power during tremor could be assumed to signal a decrease in closed loop DBS. However, the activity-dependent fluctuations in the beta-band power limit its use a sole control for closed loop DBS in PD tremor. Bronte-Stewart and colleagues (Malekmohammadi et al., 2016) reported the efficacy of closed loop STN DBS to control resting tremor, using a kinematic measure of tremor power from use of a wearable Bluetooth enabled smart watch (LG G-watch; **Figure 5**).

In their study, baseline tremor recordings were performed, from which maximum tremor power was calculated. Closed loop DBS was driven by real-time measurement of tremor: when tremor intensity exceeded 50% of the maximum baseline tremor power, the control policy algorithm commanded an increase in DBS voltage at a predetermined safe ramp speed; when tremor intensity fell below 25% of the maximum tremor power, voltage was decreased. Using this model it was noted that the rate of change in stimulation voltage (if decreased quickly) could

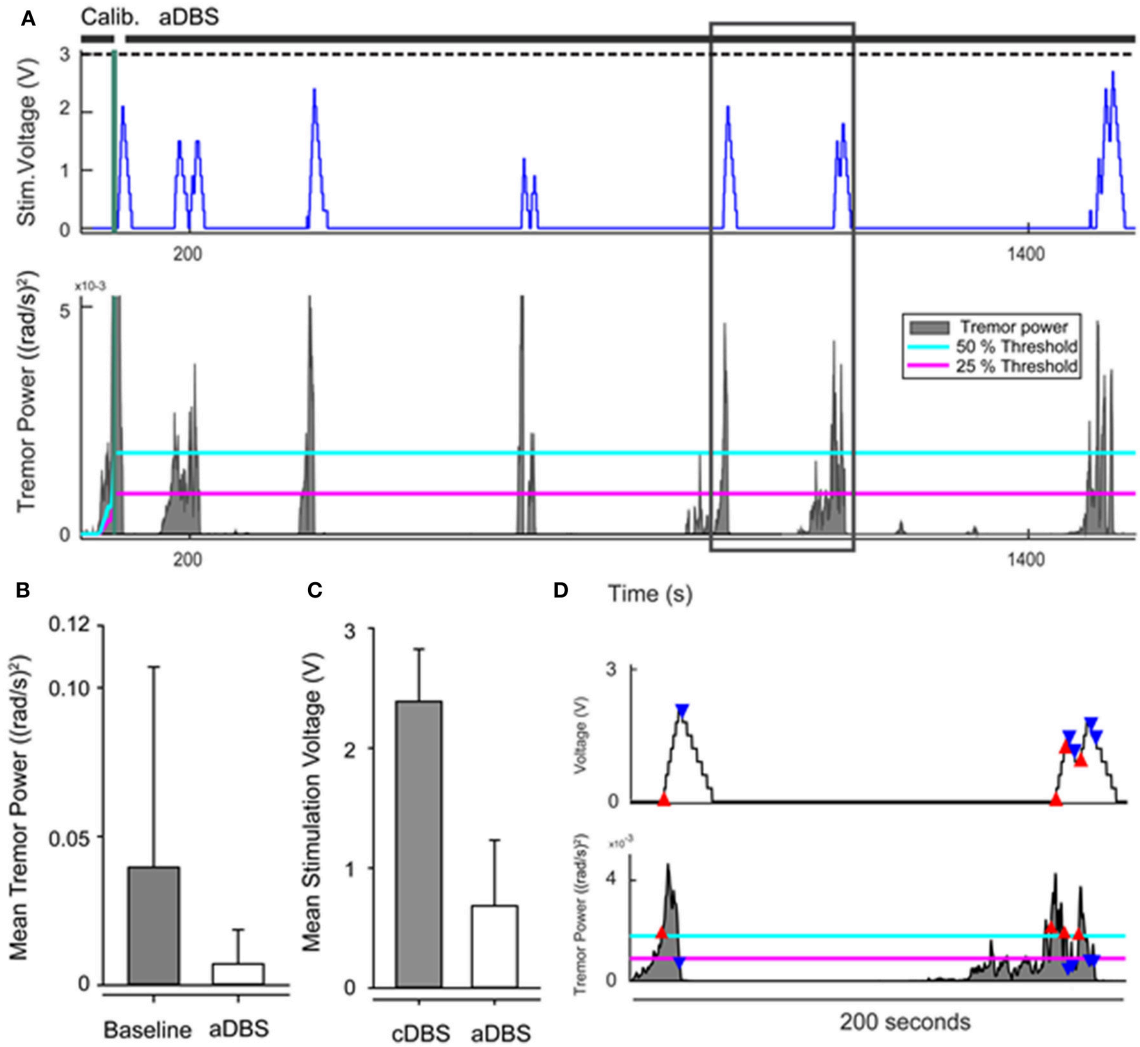


FIGURE 5 | (A) Example of adaptive stimulation voltage (top row) and tremor power with 25% (magenta) and 50% (cyan) thresholds of the control policy algorithm (bottom row). Black horizontal lines above upper panel indicate timing of calibration and closed loop DBS (aDBS). Dashed black line shows level of clinical stimulation voltage. **(B)** Comparison of mean tremor power at baseline and during aDBS across the group. **(C)** Comparison of average stimulation voltage during open loop continuous (cDBS) and aDBS for the group. **(D)** Insert to **(A)** showing the timing of the aDBS decision tracking. When tremor power exceeded the upper threshold (red triangles), the stimulation voltage increased. When tremor power fell below the lower threshold (blue triangles), stimulation voltage decreased. Stimulation voltage remained unchanged if the tremor power level remained between lower and upper thresholds.

be correlated to occurrence of rebound tremor. Consequently the rate of decreasing voltage was set at 0.5 times the ramp (or increase) rate. Overall, the mean tremor power significantly decreased by 36.6% ($p = 0.014$) during closed loop DBS, and the mean voltage used was 76.4% lower than that used during continuous open loop DBS ($p = 0.02$). On average, closed loop DBS was "on" for only 51.5% of the time ($p = 0.002$), but there was a significant variation among subjects in the duration and average voltage required for effective stimulation.

This study provided proof of concept that real time kinematic measurement of tremor represents a safe, tolerable and efficacious method to drive STN DBS for tremor in PD. This strengthens prior findings of pilot trials using a neural control variable to drive closed loop DBS in the treatment of PD (Little et al., 2013; Rosa et al., 2015), and provides further support for the use of kinematic controls to supplement LFP input in developing personalized closed-loop DBS systems.

Development and Use of Algorithms in Closed Loop Systems—A Focus on Tremor

In current clinical practice, DBS treatment involves open loop control. The stimulation parameters are pre-set for each patient, and do not automatically adjust to the presence or absence of symptoms, side effects or other patient-specific variables. The result is excessive battery consumption, as well as the possibility for undesirable side effects. Work by Chizeck and colleagues has produced a platform for investigating the control of DBS (Herron and Chizeck, 2014), which has now being employed by other groups. One mobile, wireless version consists of a set of worn inertial and electromyography sensors that communicate via Bluetooth to a host application running on a smartphone, smart watch or laptop. Using sensed data, the host application initiates control decisions, including enabling or disabling stimulation or modifying individual stimulation parameters (voltage, pulse width, frequency). These control signals are then transmitted by Bluetooth to a Medtronic Nexus™ system, which relays packets and control on a hardware and software modification of the clinician programming unit, driving a FDA approved and implanted DBS system (the Medtronic Activa PC+S)™ (Herron et al., 2015; Houston et al., 2015; Malekmohammadi et al., 2016). An alternative, fully implanted system that is currently under development uses implanted cortical electrodes (connected to the DBS) to measure local field potentials (along with the deep brain electrode), as indicators of tremor and/or patient intentions and stimulation adjustment requests. These systems are being evaluated on patients with essential tremor and PD (Houston et al., 2015). This represents a practical implementation of a brain computer interface—BCI (i.e., which can be used for voluntary BCI-triggered stimulation adjustment by the patient; Thompson et al., 2016). These platforms also provide an opportunity for collection of tremor and stimulation data for extended periods of time, which will be vital toward gaining further insight to both the neurological basis of tremor, and issues related to the long term viability and use of these devices (Brown et al., 2016).

Highlights

- Activity-dependent fluctuations in the beta-band power in STN limit its use a sole control for closed loop DBS in PD tremor.
- Kinematic input can be processed by a laptop or smartphone that produces control signals that are then transmitted via Bluetooth to a Medtronic Nexus™ system, which relays packets and control on a hardware and software modification of the clinician programming unit, driving a FDA approved and implanted DBS system.
- Combination of kinematic input in a closed-loop DBS system resulted in tremor control, but there was considerable variation among patients.
- Future directions include the development of fully implanted closed loop DBS systems.

Development of a Closed Loop System for Tourette Syndrome

(See Section Tourette Syndrome).

DARPA SYSTEMS BASED NEUROTECHNOLOGY FOR EMERGING THERAPIES (SUBNETS) RESEARCH PROGRAMS UPDATES

Introduction

The goal of the Defense Advanced Research Projects Agency (DARPA) Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) project is to develop closed-loop DBS projects that will address the multiple neuropsychiatric problems occurring in the veteran and general population, including post-traumatic stress disorder (PTSD), traumatic brain injury, depression, anxiety, chronic pain, and substance abuse. In a recent article, Vigo and colleagues estimate from published data, that the global burden of mental illness is 32.4% of years lived with disability (Vigo et al., 2016).

Currently available treatments (e.g., pharmacological and psychological therapies) can be helpful for some patients. However, some patients are left with partial or no response to such intervention(s). Brain stimulation offers notable promise in treating these patients, as there are already FDA approved indications for the use DBS in treating other neuropsychiatric conditions such as OCD (see: http://www.accessdata.fda.gov/cdrh_docs/pdf5/H050003b.pdf). To address this clinical problem, DARPA currently supports East Coast and West Coast Research Teams that are engaged in key projects focusing upon one or more areas of state-of-the-art DBS techniques and technologies. Sections East Coast Research Team Updates and West Coast Research Team Updates summarize their unpublished work.

East Coast Research Team Updates

Transdiagnostic Restoration of Affective Networks by System identification and Function Oriented Real-time Modeling in Deep Brain Stimulation (TRANSFORM DBS), the DARPA 5 year, funded program at Massachusetts General Hospital (MGH) is currently in its second year.

A recurring concern when attempting to categorize neuropsychiatric disorders is that most patients have co-morbid conditions that present with considerable variability. To decrease the effects of co-morbidity on analysis, the TRANSFORM DBS group employed a trans-diagnostic

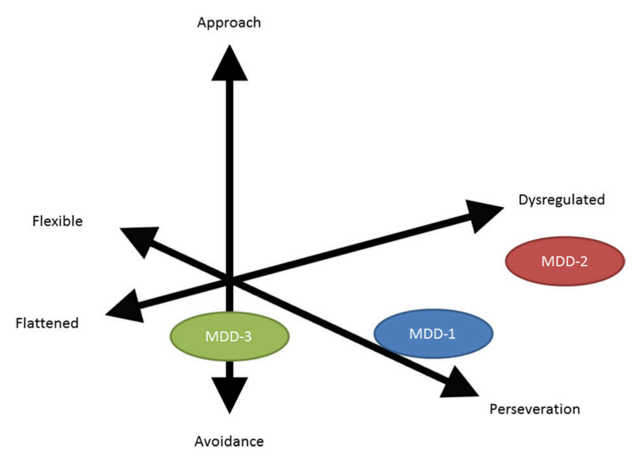


FIGURE 6 | Vector diagram illustrating the difference between a categorical diagnosis (in this instance MDD or major depressive disorder) and a symptom based or behavioral based domain assessment. The limitation of the categorical diagnosis analysis is that it can average and thereby diffuse genuine subgroup (behavioral domain) therapeutic effects.

approach that focuses on behavioral domains rather than categorical diagnosis or co-morbidity assessments (**Figure 6**). Behavioral tests were developed to quantitate the severity of each domain, and these findings were used to guide treatment.

In collaboration with Draper Laboratory (Cambridge, MA), the group developed a modular, flexible implantable system that allows 320 simultaneous recordings. The identification of the deep electrode implantation site is determined by structural and functional assays relating to the different behavioral components. Studies thus far have been on non-human primates, with plans to extend investigations to humans in the epilepsy-monitoring beginning in summer 2016.

West Coast Research Team Updates

Recent animal and human studies of brain connectivity have fostered a mesoscale network approach to interpreting and understanding mechanisms of neurocognitive function and dysfunction (Yuste, 2015).

This network-based construct suggests that psychiatric disorders may be related to changes in the function and/or structure of particular neural nodes and inter-nodal connectivity. Given the plasticity that has been demonstrated in neural circuity, a basic premise of SUBNETS is that DBS can be employed as a tool to facilitate re-modeling of brain architecture on micro to mesoscales.

The West Coast Team—at the UCSF—presented their initial work "mapping" the frontal and pre-frontal cortical areas by advancing an electrode grid under intra-operative fluoroscopy in PD patients undergoing DBS. At each cortical area, they stimulate and record the electrophysiological and clinical changes (mood states). The results show significant variability among patients, but indicate a possible correlation between the recorded signals and different mood states.

The next phase of this DARPA project will focus on chronic recording and stimulation in PD patients who have moderate psychiatric co-morbidities.

Highlights

- The goal of the DARPA's SUBNETS project is to develop closed-loop DBS projects for multiple high-burden neuropsychiatric disorders: PTSD, anxiety, depression, substance abuse, and pain.
- Two projects were discussed with different approaches in identifying DBS closed-loop systems:
  - East Coast Group
    - Using behavioral domains (avoidance, perseveration, etc.) rather than categorical diagnoses (depression, anxiety, PTSD, etc.) as endpoints.
    - Using a custom-built modular and flexible implantable system allowing 320 simultaneous recordings.
    - Work so far has been on non-human primates with human studies planned to start in summer 2016.
  - West Coast Group
    - Using intra-operative grid mapping of the frontal and pre-frontal cortical areas to assess their effect on affective states in patients with PD undergoing DBS.
    - Noted significant variability among the different patients.
    - Work so far has been on intra-operative recording, next phase will use chronic recordings.

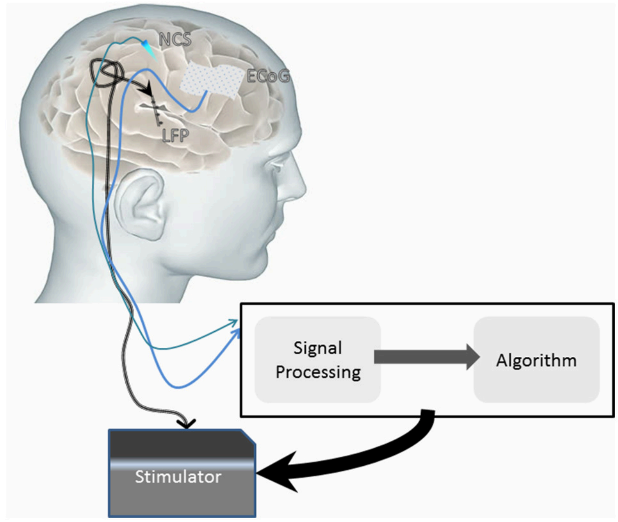


FIGURE 7 | Diagrammatic representation of a possible closed-loop DBS system comprised of sensors (e.g., - ECoG, neurochemical sensors and local field potential sensing through the implanted electrodes) that influence the stimulator (actuator) signal. The sensed signal is classified, and with use of an implementation algorithm, can influence the stimulator output to induce therapeutic effects.

DEVELOPMENT IN TECHNOLOGY AND APPLICATION

Closed-Loop DBS

Much of the hardware of DBS technology has been adapted from the cardiology field. A major limitation to ongoing refinement of DBS technology is a somewhat limited understanding of its mechanism(s) of action (Herrington et al., 2016). As noted in Section Introduction, open loop DBS does not respond to variations in the patient's state and disease progression but rather produces a pre-programmed output stimulation. This can result in a suboptimal outcome as optimization of the output stimulation has to be done by separate visits to provider clinics, usually many weeks apart. The closed-loop DBS system offers a solution by allowing integration of feedback signals to continuously modulate the output stimulation using an algorithm. The development of these advanced systems involves the construction of a number of components that are reliant, at least in part, upon feedback and feed-forward integration. The system comprises sensors that are connected to an actuator through a classifier and control policy (**Figure 7**).

Recent technological advances allow multi-modality sensing. Many of these modalities were discussed in prior sections and include LFP, ECoG, and neurochemical sensing modalities.

There are multiple limitations to the current recording/sensing implantable technology. One, the signal sensed and recorded by implantable sensors has a lower quality than the one measured by stand-alone devices that are non-implantable and can be used only intra-operatively for a short period of time. Two, the signal measured is of relatively low amplitude. Three, identification of the appropriate signal to sense is still evolving and not clear for most indications (refer to Sections Tourette Syndrome, Development of DBS Sensors, Parkinson's Disease, Clinical Assessment and Management of Tremor). Four, there is a need to develop mechanisms to distinguish between the feedback and stimulation signals.

The feedback signal is transmitted from the sensors to a classifier system. The role of this system is signal processing, converting the raw signal into classified data that will be recognized by the algorithm. The latency of the signal transmission for analysis, though improving, is still a limiting factor in building closed loop DBS systems. The most complex component of developing algorithms for closed loop DBS is to modulate the output signal from the actuator (DBS stimulation) in order to affect the outcome toward the desired state. This is an area of considerable research. Section Clinical Assessment and Management of Tremor exemplifies the development of a classifier system based on the amplitude of the tremor and a relatively simple algorithm that modulates the output signal.

As with any biomedical technology, safety is an important aspect of closed loop DBS, and therefore a first objective is determining safety limits for the algorithms. A second and related consideration is the development of facile mechanisms to allow the patient and/or clinician to deactivate the closed-loop system, and/or engage a "default—safety mode" open loop system.

Highlights

- The DBS field is moving from the use of systems of continuous stimulation to more adaptive, closed-loop systems.
- To facilitate such progress, it will be important to address and resolve a number of issues, including:
  - Improving recording and feedback signal acquisition.
  - Improving latency time from signal sensing to analysis.
  - Developing classifier systems that allow signal processing.
  - Generating valid and safe algorithms of closed-loop function(s).
  - Identifying markers of neural response.
  - Identifying appropriate stimulation responses.
  - Understanding and developing patient specific parameters for precision closed-loop DBS.

Electrical Current Shaping

The most commonly used lead design in DBS systems includes four (4) ring-shaped contacts. In monopolar settings, each of these contacts produces a spherical electrical field. This can be problematic in cases when the lead is not optimally positioned in the target zone, as resultant stimulation induces side effects evoked by stimulation of off-target tissue(s) (Deuschl et al., 2006). To maintain clinical benefit while minimizing side effects, practitioners tend to modify the shape of the electrical field. Different approaches have been used, including bipolar stimulation, double monopolar stimulation, and/or interleaving settings.

Given the demonstrated importance of site and directional specificity of DBS electrical fields, new lead designs that allow current shaping/steering have been developed. The "directSTIM" lead, a design by Aleva Neurotherapeutics (Lausanne, Switzerland), divides each contact ring into 3 sub-compartments that can be individually stimulated (Hariz, 2014). Another, "SureStim," developed by Sapiens (Eindhoven, the Netherlands), has 32 contacts distributed evenly (Contarino et al., 2014). A third, Vercise PC, produced by Boston Scientific and recently approved for use in Europe (September 2015), uses an 8-contact directional lead—the VANTAGE study (Timmermann et al., 2015). These designs allow current to be shaped away from unintended targets while maintaining a larger therapeutic window to the intended target site(s). Some limitations to these designs arise from the electrical properties of the system. For example, decreasing the surface area of the active contact will result in increased impedance and therefore increased power consumption. As well, impedance variation between different smaller contacts will passively dictate current distribution when more than one contact is simultaneously active if independent current sources are not employed.

To date, published data, as derived from use of the commercially available Vercise PC, has been limited to acute intraoperative settings, with only limited information available about the effects and efficacy of current steering in clinical care. However, unpublished data were presented at the Think Tank that illustrated the feasibility and improved therapeutic window of steered current, STN DBS in PD patients using the Vercise PC system in the clinic setting.

We posit that current steering/shaping approaches offer promise to improve the clinical outcomes of DBS, by allowing a wider therapeutic stimulation window, especially in those cases where lead placement may be difficult, and/or less than precise. For example, if a lead is targeting the STN in a PD patient but was noted post-operatively to be more lateral than initially planned, conventional stimulation will not only stimulate STN but also the adjacent internal capsule. This will produce a low threshold of stimulation to side effects thus providing only sub-optimal control of PD symptoms. By steering the current away from the internal capsule, a higher threshold of stimulation can be tolerated resulting in a better clinical outcome (Hariz, 2014).

Highlights

- A challenge facing the use of conventional DBS leads is delivery of the electrical current to the desired region while avoiding side effects by stimulating undesired areas.
- One approach proposed to decrease the undesired area stimulation is by using current steering
  - Multiple lead designs are now being investigated.
- Unpublished results of prospective in-clinic current steering testing were presented that showed improved outcomes with STN current steering.

Neurosurgical Technique Updates in DBS

The accuracy of surgical placement of the DBS electrode(s) at the specified anatomical targets is important. Although stereotactic techniques combining preoperative image-based planning with intraoperative recording and test stimulation are well-developed, these approaches carry risks including intracranial hemorrhage (1–3% both symptomatic and asymptomatic with <1% symptomatic), seizures (∼1%), leak of cerebrospinal fluid (1–2%), and infection (2–3%) (Videnovic and Metman, 2008; Patel et al., 2015). While rates of adverse events appear to be quite low, in reality, these rates have been shown to increase to ∼5% when data are prospectively and systematically collected (Burdick et al., 2010). Innovations in the surgical delivery of DBS include the use of intraoperative magnetic resonance imaging (Ostrem et al., 2013; Chabardes et al., 2015) to identify and guide electrode placement, and the use of frameless stereotaxy to enable more accurate surgical access and reduce burden and risks incurred by the operative hardware (Khan and Henderson, 2013). These are yet nascent, and the benefit and effect(s) of such innovations remains unknown.

Another surgical innovation in DBS lead implantation is the development of intravascular DBS electrodes. The feasibility of intravascular electrodes for both neural stimulation and recording and stimulation has been demonstrated. Electrodes positioned temporarily within intracranial vessels enabled recording of both spontaneous and evoked EEG-like electrical activity (Driller et al., 1969), and this work was recently extended to multi-electrode recordings using a chronically implanted stent-like device (Oxley et al., 2016). Stimulation through the blood vessel wall is also possible, an example being endovascular stimulation of the vagus nerve (Nabutovsky et al., 2007), and a recent simulation analysis demonstrated comparable patterns of model nerve fiber activation between an intravascular electrode and traditional stereotactically-positioned DBS leads (Teplitzky et al., 2014). This is not to suggest that intravascular methods are without risk; however, such innovations may provide a less-invasive approach to both record and stimulate deep in the brain and thus, represent new way to deliver DBS.

Highlights

- Significant advances have improved neurosurgical techniques of DBS implantation, but the complication rate remains ∼5%.
- Intravascular stimulation may prove to be a viable, alternate method for delivering DBS.

NEW CLINICAL APPLICATIONS OF DBS

DBS for Treatment of Addiction

This year, a case was presented at the Think Tank of a female patient with severe OCD (displaying excessive cleaning behavior) who gained appreciable therapeutic benefit (i.e.,—reduction of compulsive behaviors and obsessive ideation) following nucleus accumbens DBS (Mantione et al., 2010). Of particular note however, was that this patient also was able to quit smoking and lost an appreciable amount of weight (she was obese) following DBS implantation. Although, it remained unclear whether these latter two effects were directly due to DBS or were artifacts, it was speculated that DBS may have effected change in neural circuitry mediating obsessive ideation and/or compulsive-type behaviors that subserve over-eating and smoking. The effect of the nucleus accumbens stimulation on addiction (cigarette smoking) in this OCD patient prompted interest in considering this target for treatment of addiction without co-morbid OCD. This has been reinforced by the identification of nodes and networks in the brain associated with addiction (Volkow et al., 2016).

This has prompted a funded trial of DBS targeting the nucleus accumbens to treat 8 heroin-addicted patients. Multiple cortical and deep brain recording sessions were performed while exposing the patients to either neutral or addiction-themed images. Change in signal intensity with cortico-basal coherence was used to identify the appropriate stimulation contact. Identifying the appropriate stimulation setting was achieved by asking the patient to engage in heroin "freebasing" behavior (using real heroin), and to rate his/her experience with each of the different settings used. At this writing, two patients have been treated, and decreased addiction behavior was noted in both patients with DBS stimulation. To be sure, these results are preliminary, and continued work in this study—and others—will be required to more accurately address and define the role and value of DBS in treating addition disorders.

Highlights

- The "optimal" target for DBS in addiction is not established; however, given extant data supporting the efficacy of nucleus accumbens-directed DBS in treating OCD, and similar cognitive and conative features of compulsive and addictive behaviors, the nucleus accumbens has been considered as a possible target.
- A study in the Netherlands that employed bilateral nucleus accumbens DBS implantation to treat heroin addiction demonstrated possible therapeutic benefits. At this point, results are preliminary, and continued work in will be required to more accurately address and define the role and value of DBS in treating addition disorders.

Use of DBS to Treat Post-Traumatic Stress Disorder

Dis-inhibition and propagation of fear responses appear to be cardinal neuro-cognitive features of PTSD (Furini et al., 2014). Extinction of fear responses involves engagement of the basolateral nucleus of the amygdala (BLn) and the medial prefrontal cortex (mPFC) (Marek et al., 2013). Fear responses (to even inert stimuli) can become heightened if this network is compromised. In this event, progressive psychotherapeutic approaches, such as progressive desensitization and/or stimulus immersion are less likely to succeed. Pharmacotherapy using benzodiazepines, while somewhat effective, is burdened by side effects (inclusive of sedation, tolerance, and withdrawal), and other pharmacological approaches (e.g., azapirones; beta-receptor antagonists) have been shown to be only nominally effective (Ravindran and Stein, 2010). In these cases, DBS of the amygdala may be useful to suppress abnormal activity within amygdalar-prefrontocortical circuits, and "re-set" the inhibitory tone necessary for fear extinction and reduction of PTSD symptoms.

Langevin presented results of a 1-year study of a patient with treatment-resistant PTSD who received BLn DBS. The patient exhibited and reported significant improvements in all domains of PTSD assessed (Langevin et al., 2016). In particular, the patient reported and evidenced improved quality and quantity of sleep (without nightmares), overall reduction in anxiety, fear and irritability, and improvement in interpersonal interactions with family members and work colleagues. Patient scores on the clinician administered PTSD scale decreased in excess of 40%. There have been no treatment-related adverse events and, in particular, monthly EEG studies have shown no evidence of seizure or epileptiform activity. In addition, the monthly EEG has shown progressively more sleep activity and improved sleep architecture, with the patient showing increased deep sleep that consistently occurs earlier in the patient's sleep cycle. Pre-operatively, the patient had undergone a fludeoxyglucose (FDG) PET imaging studies, both at rest and under symptomatic conditions during an exposure therapy session. These studies revealed increased metabolic activity in the amygdala during the symptomatic phase, as compared to the resting phase (Langevin et al., 2016). The FDG PET study was repeated 1 year after initiation of BLn DBS; post-treatment PET showed no difference in amygdalar metabolic activity between the resting and the symptomatic phase. This finding is consistent with patterns of amygdalar activity during fear extinction, suggesting the efficacy of BLn DBS in restoring a more normal pattern of activity in amygdalar networks involved in cognitive and behavioral aspects of fear that are representative of PTSD. The study is continuing, with ongoing recruitment toward a target enrollment of six patients.

Highlights

- A case was presented to support the possibility of using DBS targeting the amygdalar BLn to reduce signs and symptoms of PTSD
    - Prior to DBS, the patient had disrupted sleep quality and quantity, night terrors, OCD-like symptoms, and manifest social disturbances. Following BLn DBS, the patient reports feeling calmer, evidences improvement in sleep architecture and quality (as demonstrated by EEG and described through self-report), and describes improvement in social interactions.
- FDG PET studies revealed post-DBS normalization of metabolic activity in the amygdala metabolism.

Use of DBS to Treat Clinical Obesity

Clinical, morbid obesity is a significant public health problem, both in the United States, and worldwide (Nangunoori et al., 2016). The current standard of treatment for morbid obesity that is not responsive to dietary and lifestyle modification, or pharmacotherapy is bariatric surgery. However, bariatric surgery although certainly of clinical value, also poses a number of risks, and is not uniformly successful (Ho et al., 2015). In seeking alternatives to gastro-intestinal surgery, DBS has been proposed as a viable approach to affect hypothalamic mechanisms of hunger and satiety that may be dysfunctional in morbidly obese patients (Nangunoori et al., 2016).

To explore this possibility, three (3) patients with a history of bariatric surgery were recruited; each with a current body mass index (BMI) greater than 40 Kg/m^2. The DBS target was the bilateral lateral hypothalamus and post-operative images confirmed successful electrode implantation in all cases. The patients were followed for 2.5 years. The primary goal of this study was to assess safety. There were no serious adverse effects reported and no evidence of autonomic dysfunction. There was a subjective report of decreased urge to eat. Although, the study was not designed to assess efficacy, the resting metabolic rate was measured using a metabolic chamber. It was noted that contacts centered in the lateral hypothalamus were associated with an increase in the resting metabolic rate. This, however, did not correlate with a consistent weight loss (Whiting et al., 2013).

Long-term follow-up data were presented; one patient dropped off due to delayed bariatric surgery complications. During the long-term follow-up period, multiple DBS settings (9 settings/day) were used to determine the optimal stimulation parameters required to elicit the greatest increase in resting metabolic rate. In one patient, BMI decreased from 46 to 38, while the other patient did not show any weight loss or change in BMI. However, both patients showed an increase in their resting metabolic rate. The effects of any stimulation paradigm were short-term. This was attributed to the "hedonic component of food seeking and the motivational processes that drive eating" (Whiting et al., 2013).

Future directions for studying the potential viability and value of DBS to treat certain forms of clinical, morbid obesity are centered upon the identification of other neurological targets (e.g., the nucleus accumbens; see also Section DBS for Treatment of Addiction, above; either singularly, or in combination with stimulation of the lateral hypothalamus), and the potential utility of employing closed-loop systems.

Highlights

- DBS to treat clinical morbid obesity has targeted the lateral hypothalamus in an attempt to restore balance in hunger and satiety states.
- In a limited study ($n = 3$), obese patients who had previously undergone bariatric surgery and still maintained a BMI > 40 Kg/m^2 underwent DBS surgery targeting the lateral hypothalamus.
- The procedure was noted to be safe in the 3 patients tested.
- Two years post-operatively, assessments indicate an increase in the resting metabolic rate though this did not translate to consistent weight loss.
- Future directions are focusing upon identification of other and/or additional neuroanatomical targets for DBS to treat clinical, morbid obesity.

CONCLUSION

Herein we have summarized the presentations and discussion(s) of the Fourth Annual DBS Think Tank. Policy and regulatory issues and proposed optimizations were discussed, multiple advances in the field were addressed, including updates on the state of research, database and data registry, developments in closed-loop DBS, the most current and novel applications of DBS, and advances in electro-neurochemical sensing systems. In sum, the field and applications of DBS are expanding, and to some extent this expansion may represent a change in the status and trajectory of DBS research and use in clinical practice. To assess participants' perspectives and attitudes toward the current and near-term future development in the field, an anonymous 40 question poll was sent online at the conclusion of the Think Tank. The questionnaire assessed the respondent's perceived position of DBS applications in disease states, neurotechnological principles, and emerging applications on the hype cycle graph.

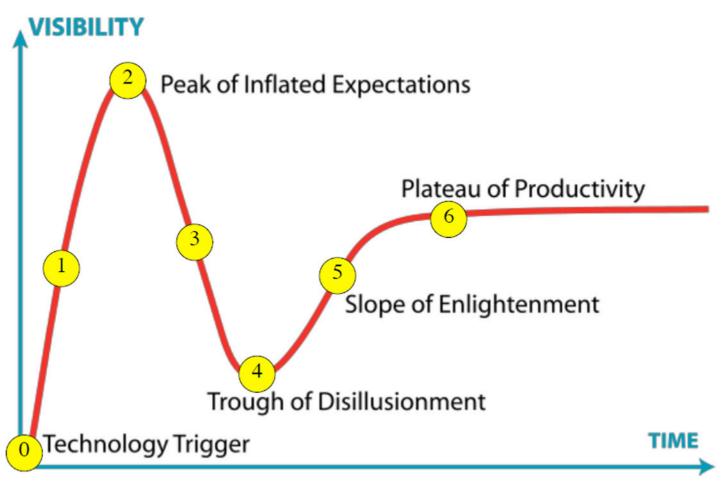
Thirty-six participants responded to the poll. These responses are depicted in **Figure 8**. Of note is in contrast to last year, participants' current perception of some uses/indications for DBS have slipped from the plateau of productivity to the slope of enlightenment (e.g., Parkinson's disease), others moved from the trough of disillusionment to the contraction phase (e.g., Depression), still others moved from the expansion slope to the peak of inflated expectations (e.g., Obesity).

In conclusion, the fourth Annual DBS Think Tank provided a nexus for the presentation of new developments and findings, discussion about the technology, research and practice of DBS, and speculation about—and proposals for—the future of the field. The future of DBS therapy will rely on continuing innovation and cooperation of key stake and shareholders, inclusive of scientists, engineers, physicians, ethicists, administrators and policy makers. The aim of the DBS Think Tank is to remain an important component of, and resource for contributions to this process and progress.

AUTHOR CONTRIBUTIONS

AM, AG, AWS, BK, CB, CH, CV, DD, DDD, DR, FP, GG, GS, HW, HB, HM, HC, JL, JJ, JV, JO, JJS, KF, MR, MO, MP, PJR, PASi, PASt, TD, USA, WG fulfilled the authorship criteria by substantial contributions to the conception of the work, providing data for the work, revisiting it critically for important intellectual content, approving the final version, and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

WD, JG, PJR, JS, MSO fulfilled the authorship criteria by substantial contributions to the design of the work and the acquisition, analysis and interpretation of data for the



Maturity	Neurotechnology	Survey
Plateau of Productivity		
Slope of Enlightenment	DBS for Parkinson's	5.18
	Cochlear implant	5.17
	DBS for essential tremor	5.03
Trough of Disillusionment	Spinal cord stimulation for pain management	4.18
	Imaging post DBS implant	4.08
	Imaging to guide surgical targeting	3.51
Contraction Slope	DBS for epilepsy	3.38
	DBS for depression	3.26
	MRI safety for neurotechnology implants	3.18
	Transcranial magnetic stimulation	2.83
	Modeling to guide surgical targeting	2.80
	DBS for OCD	2.74
Peak of Inflated Expectations	FES for SCI-bladder control	2.48
	DBS for Tourette's	2.43
	DBS for chronic pain	2.40
	FES for foot drop	2.40
	Retinal implant	2.15
	FES for SCI-limb control	2.08
	Microelectrodes in the CNS for decoding limb movement (chronic use)	2.03
	DBS for Alzheimer's	1.99
	EEG for decoding limb movement (chronic use)	1.98
	Neural stimulation for stroke symptoms	1.90
	ECoG for decoding limb movement (chronic use)	1.69
	Microelectrodes in the CNS for encoding sensory feedback (chronic use)	1.60
	Closed-loop feedback	1.59
	Wireless power for implants	1.57
	Microelectrodes in the PNS for decoding limb movement (chronic use)	1.57
	DBS for obesity	1.54
Expansion Slope	ECoG for encoding sensory feedback (chronic use)	1.48
	Bi-directional wireless telemetry	1.47
	Low intensity focused ultrasound	1.45
	Microelectrodes in the PNS for encoding sensory feedback (chronic use)	1.45
	DBS for addiction	1.32
	DBS for TBI	1.28
	Reliable implantable high-channel count connectors	1.12
	DBS for PTSD	1.06
	Optogenetics for clinical neural interfaces	1.05
	Neuromagnetic interfaces	0.93
Technology Trigger		

FIGURE 8 | Schematic results of an anonymous poll of ThinkTank participants to assess perceptions and attitudes about the current and near-term state of the DBS field. On the left is a representation of the stages of technological development, known as the "hype cycle" graph. Participants in the Think Tank were asked to rank different DBS applications and other neurotechnologies on the "hype cycle." Their responses were averaged and categorized, as depicted in the table on the right. Categories were assigned by rounding to the nearest whole number. Details in text. Figure adapted from: Jackie Fenn, "When to leap on the hype cycle," Decision Framework DF-08-6751, Research Note, GartnerGroup RAS Services, June 30, 1999.

work, drafting the work and revising it critically for important intellectual content, approving the final version to be published and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

National Institutes of Health, National Parkinson Foundation, Michael J. Fox Foundation for Parkinson's Research and the Tourette Association of America provided funding for the previous studies presented in this paper.

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Conflict of Interest Statement: AM: Consulting fees and honoraria from Medtronic; AG: Research agreement with Medtronic; BK: Receive research support from Medtronic and Boston Scientific; CB: authored intellectual property related to deep brain stimulation and other neuromodulation therapies. CB: has served as a consultant for St Jude Medical, Functional Neuromodulation, and Boston Scientific. DDD: Research support from Medtronic, Inc. FP: Consulting Fees: Consultant for Medtronic. GG: Sole proprietor of Quanteon, LLC, which makes electrochemical recording instrumentation for measures of neurotransmitters and metabolic molecules in the brain of laboratory animals; GS: Grant support from Functional Neuromodulation as Director of the Imaging Core Laboratory for the ADVANCE trial; HW: Receives funding for research from Medtronic; HM: Consultant and licensor of intellectual property to St. Jude Medical, Inc.; JG: serves as an appointed member of the Neuroethics, Legal and Social Issues Advisory Panel of the Defense Advanced Research Projects Agency (DARPA) working on the Systems Based Neurotechnology for Emerging Therapies (SUBNETS) and Restoring Active Memory (RAM) projects. He does not receive any financial compensation in this role; his views expressed in this manuscript do not necessarily represent those of DARPA or the United States Department of Defense. JG: has previously received research grants from the Department of Defense; United States Air Force Office of Scientific Research; Department of the Navy, Bureau of Medicine and Surgery and Office of Naval Research; JV: Fulbright Foundation; and the Nour Foundation. He has received royalties from Cambridge University Press, Linton-Atlantic Press, and CRC Press (for books on neuroethics and brain science). JG currently serves as Editor-in-Chief of the BioMed Central Online journal Philosophy, Ethics, and Humanities in Medicine, and Associate Editor of the Cambridge Quarterly of Health Care Ethics. In the past 12 months, he has received funding from an unrestricted research grant from Thync Biotechnologies; however, this grant terminated in in early 2016 also receives funds from the National Center for Advancing Translational Sciences (NCATS, UL1TR001409), National Institutes of Health, through the Clinical and Translational Science Awards Program (CTSA), a trademark of DHHS, part of the Roadmap Initiative, "Re-Engineering the Clinical Research Enterprise"; JL: Inventor on a patent application for DBS in PTSD; JV: Grants and personal fees from Medtronic Inc., Grants and personal fees from Boston Scientific, Personal fees from St. Jude, outside the submitted work; JO: Research Grant Support from Boston Scientific, St. Jude Medical; JJS: Consulting activities for Medtronic and St Jude Medical; KF: Research and fellowship support from Medtronic. Research support from St. Jude, Boston Scientific, NeuroPace, and Functional Neuromodulation. No personal remuneration from industry sources. MO: Funding in part from Medtronic; MP: Consulting fees from Medtronic, Inc., and St. Jude Medical; MSO: serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. MSO: DBS research is supported by: R01 NR014852. MSO has previously received honoraria, but in the past >60 months has received no support from industry. MSO has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). MSO is an associate editor for New England Journal of Medicine Journal Watch Neurology. MSO has participated in CME and educational activities on movement disorders (in the last 36) months sponsored by PeerView, Prime, QuantiaMD, WebMD, MedNet, Henry Stewart, and by Vanderbilt University. The institution and not MSO receives grants from Medtronic, Abbvie, Allergan, and ANS/St. Jude, and the PI has no financial interest in these grants. MSO has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. PAS: Consulting work for Medtronic Inc., and Boston Scientific; US patent related to closed loop deep brain stimulation in movement disorders. NIH (R01 NR014852 - PIs Butson and Okun; R01 NS096008 - PI Okun). TD: Medtronic employee, Medtronic Shareholder, Intellectual property in these areas. WG: Inventor on licensed patents on temporal patterns of deep brain stimulation and owns equity in Deep Brain Innovations, LLC. WD, PJR, UA, PS, PJR, MR, JS, HC, HB, DR, DD, JJ, and CH: declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

OPINION
published: 23 March 2015
doi: 10.3389/fnint.2015.00022

Neuromodulation and the mind-brain relation

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Keywords: brain-mind interaction, dualism, neuromodulation, non-reductive materialism, psychiatric disorders, reductive materialism

OPEN ACCESS

Edited by:
Markus Christen, University of Zurich, Switzerland

Reviewed by:
Jürg Kesselring, Rehabilitation Centre Valens, Switzerland

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Received: *03 January 2015*
Accepted: *05 March 2015*
Published: *23 March 2015*

Citation:
Glannon W (2015) Neuromodulation and the mind-brain relation. Front. Integr. Neurosci. 9:22. doi: 10.3389/fnint.2015.00022

Many investigators now consider psychiatric disorders to be neural circuit disorders (Lozano and Lipsman, 2013). Cognitive, emotional and volitional symptoms of major depression, generalized anxiety, obsessive-compulsive disorder and other conditions are traceable to dysfunction in critical nodes of circuits in cortical, limbic and subcortical pathways of the brain. Guided by functional imaging, the ability of deep-brain stimulation (DBS) to probe and modulate specific circuits in real-time has elucidated the pathogenesis of these disorders. DBS has validated the neurobiological underpinning of normal and abnormal states of mind. This and other developments in clinical neuroscience discredit a dualist theory of mind and brain that takes psychological properties to be conceptually distinct from and capable of functioning independently of neural properties. Instead, they support a materialist theory of mind that explains mental phenomena in terms of their neural correlates.

A materialist theory of mind suggests that mental illnesses are just diseases of the brain (Fuchs, 2012). This idea is generally consistent with the aim of the Research Domain Criteria (RDoC) initiated by the US National Institutes of Mental Health (NIMH), which is to identify brain mechanisms that can explain the causes of psychiatric disorders and predict treatment responses and outcomes (Insel et al., 2010; Casey et al., 2013). There are, however, reductive and non-reductive versions of materialism (Baker, 2009). According to reductive materialism, phenomena at one level can be completely explained in terms of more basic elements at a different level. On this view, normal and abnormal mental states can be completely explained in terms of brain function and dysfunction. According to non-reductive materialism, the brain necessarily generates and sustains mental states but cannot account for all of their properties. By themselves, probing and modulating neural circuits of people with psychiatric disorders fail to capture how the content and phenomenology of the mind can affect the brain in how these disorders develop and respond to treatment.

Psychiatric disorders are multifactorial disorders resulting from interaction among genes, neurons, immune and endocrine systems and the affected person's psychological response to the natural, social and cultural environment. Describing these disorders at a brain-systems level is necessary but not sufficient for understanding their etiology or how they can be controlled through different types of neuromodulation. It is not dysfunctional neural circuits but people who have these disorders. Persons are constituted by their brains but are not identical to them. The conscious and unconscious mental states that emerge from the brain and define persons are influenced by a dynamic and interacting set of factors both inside and outside of the brain. Mind and brain are shaped by the fact that persons are embodied and embedded in different environments. Our brains alone do not determine everything about who we are and how we experience the world (Churchland, 2013). These considerations suggest that non-reductive materialism is a more plausible theory than reductive materialism for explaining the mind-brain relation in psychiatry and a more helpful model for diagnosing and treating psychiatric disorders.

Neuropsychiatrist Todd Feinberg's conception of the mind as a process emerging from the brain in a nested hierarchy supports non-reductive materialism as a theoretical basis of the mind-brain relation (Feinberg, 2001, pp. 129–131). Higher-level processes associated with conscious and unconscious mental states are compositionally dependent on, or nested within, lower-level processes associated with circuits in the brain. Feinberg's idea of constraint can be used to explain how interacting neural and mental processes promote homeostasis within an organism and its adaptability to the external world. Constraint refers to the control that one level of a system exerts over another level of the same system. The "system" at issue is a human organism, and the relevant "levels" are brain and mind. Constraint operates in both bottom-up and top-down directions as brain and mind mutually influence each other in a series of re-entrant loops. Neural functions constrain mental states to ensure that they accurately interpret information from the environment. Mental states constrain neural circuits to ensure that they are neither underactive nor overactive. Beliefs with heightened emotional content can over-activate the limbic fear system, disable cortical constraint on this system and lead to depression, anxiety or panic disorders. Disabled constraints on belief content from dysfunctional auditory and prefrontal cortices can result in the hallucinations and delusions in the positive subtype of schizophrenia.

Proponents of non-reductive materialism hold that mental properties are part of the material world. They also hold that mental properties can be causally efficacious without being reducible to material properties. Critics of this position argue that if mental events are not reducible to physical events, then they are epiphenomenal (Kim, 1998, p. 81). Mental events are the effects of material or physical causes but cannot cause any material or physical events to occur. If mental processes associated with beliefs, desires and emotions are not reducible to their neural correlates and are epiphenomenal, then presumably they do not influence the etiology of psychiatric disorders or patients' responses to therapies.

But there are many examples in psychiatry where mental states are causally efficacious in disrupting and modulating neural pathways. Persistent psychological stress can cause a cascade of adverse biochemical events in the brain and body, including hyperactivation of the amygdala fear system and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. This can disrupt frontal-limbic connectivity mediating cognitive and affective processing and result in impaired cognition and mood. The contents of a person's beliefs and emotions may play a causal role in the pathophysiology of this disorder. In obsessive-compulsive disorder, excessive conscious reflection on motor tasks ordinarily performed as a matter of course can have a similar disruptive effect on frontal-limbic-striatal pathways and impair sensorimotor and cognitive functions (Melloni et al., 2012; Figee et al., 2013). Yet mental states can be part of a therapeutic process as well. In cognitive behavior therapy (CBT), patients with depression can be trained to reframe their beliefs and emotions in a way that can re-wire some regions of the brain and result in significant improvement in depressive symptoms. Studies have shown that CBT can modulate function in specific sites in limbic and cortical regions mediating mood and cognition (Fuchs, 2004; Goldapple et al., 2004). Disruptive bottom-up effects on mental functions by dysregulated neural functions can be reversed to some degree by top-down modulating effects of this therapy on these functions.

Neurofeedback (NFB) is another example of how mental states can modulate brain activity. With this technique, participants can be trained to down-regulate brain hyperactivity through their cognitive and emotional responses to the sensory feedback of neural function they receive from EEG or fMRI (Linden et al., 2012; Linden, 2014, chapter 3). This type of self-regulation can restore some degree of control of thought and behavior for those who successfully perform the technique and relieve symptoms associated with attention deficit-hyperactivity disorder (ADHD), anxiety, depression, posttraumatic stress disorder (PTSD) and other conditions. It may also be possible for depressed subjects with anhedonia and avolition associated with an underactive nucleus accumbens in the reward system to use NFB to up-regulate activity in this region and improve motivation (Linden, 2014, chapter 3). NFB demonstrates that participants can induce changes in their brains through their own mental states without having to rely on psychoactive drugs or devices implanted and stimulated in specific neural circuits. Moreover, the fact that the cognitive and emotional responses that induce these changes depend on indices of brain activity fed back to the subject shows that mind and brain are not independent but interdependent and interacting processes necessary for flexible and adaptive behavior. It highlights the erroneous assumption that non-reductive materialism implies dualism between mental properties and neural properties and that the first cannot influence the second. It is because of interaction between brain and mind in NFB that this technique can produce its therapeutic effects. Indeed, some investigators describe NFB as "a holistic approach that overcomes bio-psychological dualisms" (Linden et al., 2012, p. 8).

Psychological factors are also significant in brain-computer interfaces (BCIs) used as a form of neurofeedback for neurological disorders. These systems may use scalp-based electrodes to record EEG or a microelectrode array implanted in the motor cortex. More and less invasive forms of BCIs are designed to enable subjects paralyzed from spinal cord or traumatic brain injuries to bypass the site of injury and translate signals from the motor cortex through a computer into actions such as moving a cursor or robotic arm. In addition, BCIs have been studied to determine whether individuals with complete locked-in syndrome can communicate when they are unable to do this verbally or gesturally by activating signals in brain regions mediating semantic processing. Subjects have to be trained to perform these neural and mental acts in manipulating the interface, and there is considerable variation among them in the capacity to be trained. Success in learning how to use the system and activate and translate signals in the motor cortex depends on operant conditioning, which requires sustained motivation, attention and persistence. Not all locked-in subjects have the requisite degree of these psychological capacities to manipulate the interface. One explanation for the failure of researchers and practitioners to train these individuals to communicate with a BCI is that the complete loss of control from paralysis undermines the motivational basis for operant conditioning (Birbaumer et al., 2008, 2014; Linden, 2014, p. 22). They may experience not only physical fatigue but also mental fatigue in repeatedly attempting and failing to activate the cortical regions necessary for communication. Theoretically, though, participants who are sufficiently motivated and have the necessary cognitive capacity could be trained to translate signals in these regions into actions that realized their intentions. Psychological properties of the participant play a causal role in the success or failure in using the technique to induce the desired brain responses. In both NFB and BCIs, the role of the trainer in enabling the participant to exercise the critical mental capacities and induce changes in the brain is one aspect of environmental influence on these capacities and changes.

In treatment-refractory depression and obsessive-compulsive disorder, DBS can modulate dysfunctional circuits enough to make them amenable to CBT. As in NFB, this underscores the complementarity of brain-based and mind-based techniques in controlling symptoms in these disorders. Mind-brain dualism would conceive of these techniques as unrelated or even incompatible. The reductionist view that everything about the mind can be explained by appeal to neural circuits and that mental states are epiphenomenal would also fail to appreciate the causal efficacy of beliefs and other cognitive states on neural function. Dualist and reductive materialist models of the mind and brain both fail to recognize the salutary effects of combined neural and psychological therapies for these disorders. It is thus mistaken to assume that non-reductive materialism in clinical neuroscience implies that mental states have no influence on the brain.

Rather than focusing exclusively on neural mechanisms, a holistic model of psychiatric disorders that explains them in terms of interaction among genes, neurons, mental states, the body and the environment is more helpful in understanding them. The success or failure of different forms of neuromodulation for these disorders demonstrates that interdependent mental and neural processes influence the extent to which they can be controlled. These considerations support a non-reductive materialist model of the mind-brain relation in psychiatry. This rejects the reductionist view that mental illnesses are just diseases of the brain and that how we experience the world is completely determined by neural structure and function. Theoretical models such as the RDoC and techniques such as DBS alone may be too limited to provide an adequate account of mental health and mental illness. They are components of a broader set of factors that shape mind-brain interaction and need to be included in diagnosing and treating psychiatric disorders.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 27 April 2015
doi: 10.3389/fnint.2015.00030

Understanding public (mis)understanding of tDCS for enhancement

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In order to gain insight into the public's perspective on using the minimally invasive technique transcranial direct current stimulation (tDCS) as an enhancement tool, we analyzed and compared online comments in key popular press articles from two different periods (pre-commercialization and post-commercialization). The main conclusion drawn from this exploratory investigation is that public perception regarding tDCS has shifted from misunderstanding to cautionary realism. This change in attitude can be explained as moving from a focus on an emergent technology to a focus on its applications, benefits, and risks as the technology becomes more grounded within the public domain. Future governance of tDCS should include the concerns and enthusiasms of the public.

Keywords: cognitive enhancement, neuroethics, public understanding, transcranial direct current stimulation, brain stimulation, public policy

OPEN ACCESS

Edited by:
Sabine Müller, Charité - Universitätsmedizin Berlin, Germany

Reviewed by:
Markus A. Dahlem, Humboldt University of Berlin, Germany
Gardar Arnason, Universität Tübingen, Germany

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Received: *18 February 2015*
Paper pending published: *27 March 2015*
Accepted: *03 April 2015*
Published: *27 April 2015*

Citation:
Cabrera LY and Reiner PB (2015) Understanding public (mis)understanding of tDCS for enhancement. Front. Integr. Neurosci. 9:30. doi: 10.3389/fnint.2015.00030

Introduction

Brain stimulation techniques are emerging as methods of neuroenhancement. Among these techniques, transcranial direct current stimulation (tDCS) is one that is gaining public attention as a potential neuroenhancer. This portable technology, which involves applying weak direct currents to the scalp via saline-soaked sponge electrodes, appears rather safe with medical supervision, reasonably effective across a range of brain functions, and accessible to an interested public. These features have led to its growing implementation in both research and clinical settings, as well as with home users (Dubljević et al., 2014).

Given the impact that home use of tDCS may have for individuals and society, changes in public perceptions warrant careful attention, as these may be consequential. In order to gain insight into the public's attitudes towards tDCS as an enhancement tool, we used thematic analysis to compare online comments on popular press articles from two different time periods: before and after the introduction of the first widely available commercial product. The main conclusion is that the public's perception regarding tDCS has shifted from misunderstanding to cautionary realism. This change in attitude suggests that as the technology has become more grounded within the public domain, there has been a shift from a focus on an emergent technology to one on its applications and risk-benefit profile.

Trends in Public Attitudes Towards tDCS

Information on tDCS is growing substantially (Dubljević et al., 2014). While acknowledging that public opinion formation, patterns, and trends can be analyzed and understood through different paradigms, our primary focus here is on attitudinal and perceptual trends as revealed through online comments (Capstick et al., 2014).

Methods

We conducted a temporal comparison of online comments addressing the use of tDCS as an enhancement tool. Comments on online articles is not a representative sample of the general population, but are available to large numbers of readers from a range of different backgrounds, who can express their opinions by posting comments online. Thus, online communities "offer a mechanism through which a researcher can gain access to people who share specific interests" (Wright, 2005) and diverse opinions (Faridani et al., 2010). We compared two time periods. For our first time period, the EARLIER PERIOD, we only included articles that were published between August 2007 and May 14, 2013, dates that preceded the first offer of a widely available commercially tDCS product to the general public.[1] We restricted our search to widely read English-language U.S. and U.K. popular media sources that were accessible to readers without a subscription and which had online reader comments. For our second time period, the LATER PERIOD, we included articles from May 15, 2013 to August 2014.

For both time periods, a search was carried out of the Lexis Nexis Academic database and Google using the following terms for newspapers or online magazines: "transcranial stimulation" "tDCS" "neural stimulation" "neurostimulation" "brain stimulation". The initial search yielded 38 articles for the EARLIER PERIOD and 36 for the LATER PERIOD. Each article was read and checked it for relevance according to pre-established exclusion and inclusion criteria: (1) a focus on tDCS as a cognitive enhancer; and (2) 10 or more comments. The 10 comments inclusion criterion was chosen in order to ensure that the popular media article at hand had generated a good level of discussion. For the EARLIER PERIOD, 13 newspapers (N = 8, 61.5%) and magazines (N = 5, 38.5%) articles were included for analysis, while for the LATER PERIOD 14 newspapers (N = 10, 71.42%) and magazines (N = 4, 28.57%) articles were included (see **Figure 1**).

We employed thematic analysis (Chi, 1997; Braun and Clarke, 2006), with comments coded in an interactive manner, in which themes were developed as the coding process progressed. Themes were grouped into categories. Author replies and comments that were duplicated or irrelevant were excluded, leaving a sample of 248 comments for the EARLIER PERIOD and of 465 for the LATER PERIOD. Inter-rater reliability was determined by randomly selecting 10% of the comments and assigning them to a second coder (Lombard et al., 2002); Cohen's Kappa was 0.82 for the EARLIER PERIOD and 0.98 for the LATER PERIOD. Descriptive statistics were used to characterize the composition and properties of the sample.

[1]Invitations to pre-purchase a device from foc.us were sent out on that date.

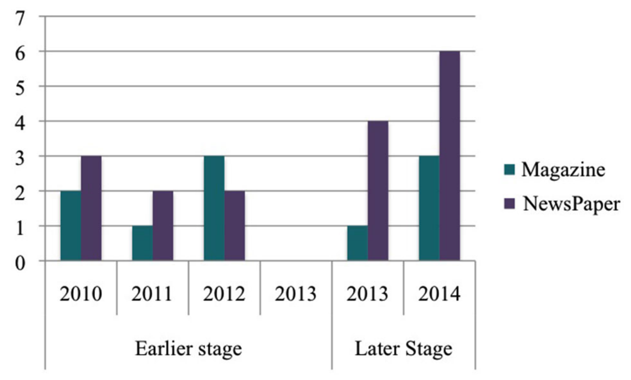

FIGURE 1 | Distribution of articles according to year published.

Limitations

Anonymity of comments can threaten their reliability. Relatively little is known about the demographics of people in online communities (Wright, 2005) which facilitates the posting of polemic, charged and untruthful comments (Lefever et al., 2007). Moreover, we cannot be sure that the posted comment is a result of reading the article or merely responding to the comment thread. Posting of comments is based on volunteer sampling rather than probability sampling (Lefever et al., 2007), and certain websites attract people with like-minded viewpoints, reinforcing biases (Faridani et al., 2010). Finally, our sample composition is limited to English language sources in the United States and United Kingdom, as well as digital natives with access to the Internet. In spite of these limitations, this research provided us with the opportunity to grasp trends and themes regarding the use of tDCS as a cognitive enhancer.

Results

Personal position and Technology issues were the two most frequent categories of codes for both periods of analysis. **Figure 2** displays the comparison between the EARLIER PERIOD and the LATER PERIOD from comments addressing specific categories and themes.

Early Stage on Public Perception Around tDCS: A Misunderstood Technology

The EARLIER PERIOD was a point in time at which the overall level of understanding of tDCS was limited and there was often conflation with other similar technologies. In many instances, comments addressed tDCS either as an extension of other electricity delivering technologies (such as tasers) or as a form of electroconvulsive therapy (ECT). Technical misinterpretation represented another form of misunderstanding. For instance, there were comments implying unsupported assumptions, such as *the more current or voltage used, the better* the results of cognitive enhancement. There were also comments implying that the current administered by tDCS (generally between 1–2 mA) could lead to "fried brains" or even death.

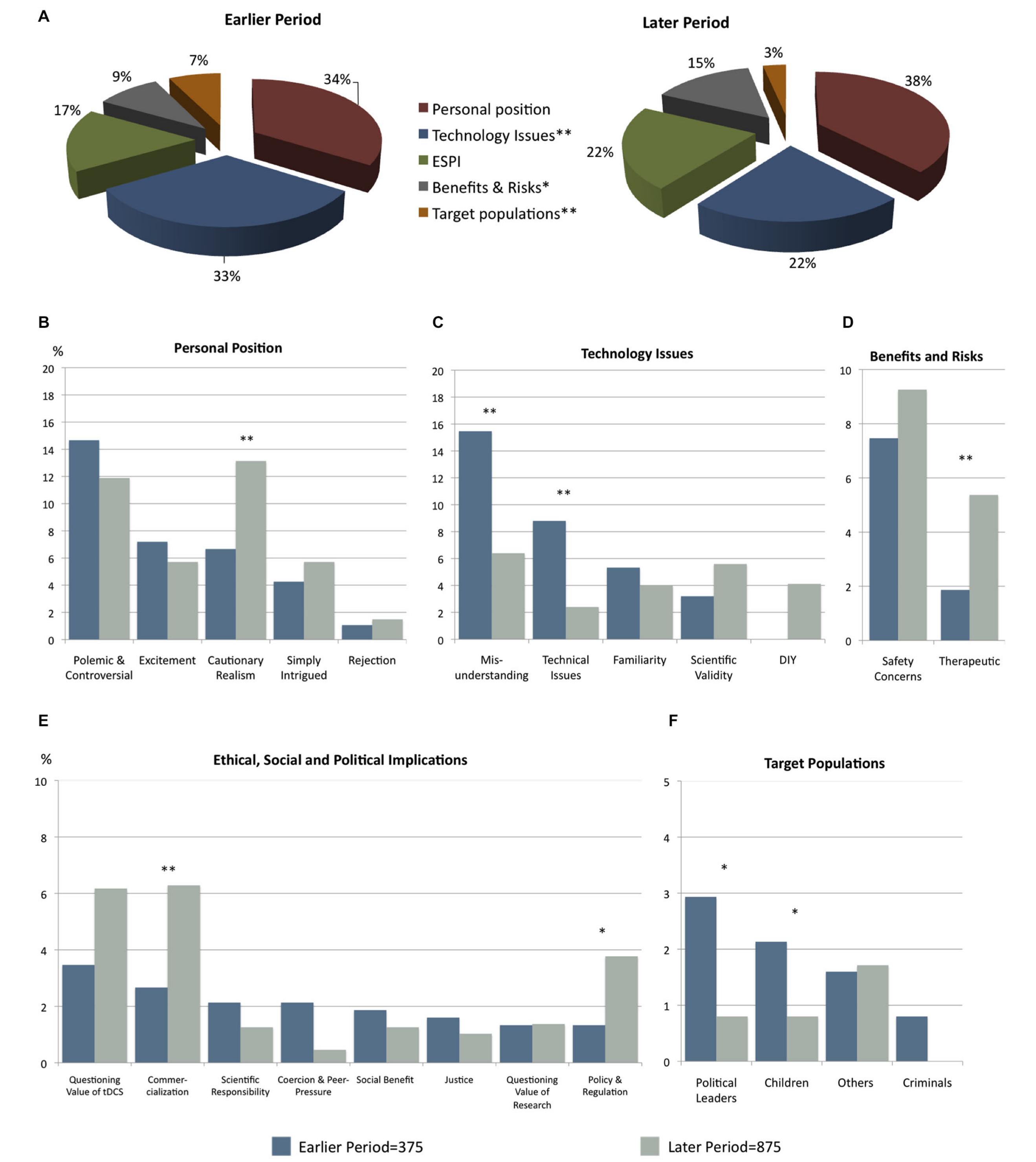

FIGURE 2 | Comparison of Subjects Addressed within tDCS Online Public Comments. χ^2 $^{**}p < 0.001$ and $^{*}p < 0.05$. For bar charts *y* axis represents percentage of the overall coded data points. **(A)** Comparison of **categories** earlier and second period. Comparison of **themes** within Category: **(B)** Personal Position **(C)** Technology Issues **(D)** Benefits and Risks **(E)** Ethical, Social and Political Implications **(F)** Target Population.

The other main theme addressed in the comments during the EARLIER PERIOD was their polemic and controversial tone (14.67%, $N = 55$). That enhancement is controversial may have contributed to the controversial tone of many comments, as well as the fact that online comments enable commentators to remain anonymous, creating a space for polemics (Faridani et al., 2010). In addition people's perceptions are likely to be biased by their hopes, fears, needs and immediate emotional states which can give rise to polarized opinions in pluralistic societies (Pronin et al., 2002).

Even at this early point in time, respondents reported safety concerns in relation to the use of this technology (7.47%, $N = 28$). Ethical issues were not a main category in this sample. For example, even though justice is one of the major concerns regarding cognitive enhancement (Fitz et al., 2014) and tDCS is rather inexpensive compared to other brain stimulation technologies, comments addressing this topic were infrequent. Similarly, comments regarding policy and regulation were also infrequent, despite the fact that a few articles in our sample mentioned the possibility of do-it-yourself (DIY) approaches.

Second Stage on Public Perception Around tDCS: Cautionary Realism

Whereas the EARLIER PERIOD was marked by a growth in basic awareness and misunderstanding about tDCS, the LATER PERIOD entailed a sustained growth of cautionary concerns overall, a steady polemic and controversial stand, and the proliferation of doubts and skepticism regarding tDCS's enhancement potential. Comments in this LATER PERIOD focused on subjects about technological based enhancement not being substitution for effort nor the solution for human improvement, the existence of other of non-technological and less risky methods (such as meditation or exercise) for enhancement, and that people can misuse this technology, all captured under the theme cautionary realism.

The overall growth in cautionary concern ($\chi^2 = 11.07$, $p < 0.001$) mirrors a rise in media attention about the use of tDCS as a cognitive enhancer and in particular as a DIY technology. Whereas no single commenter in the EARLIER PERIOD mentioned DIY, this had risen to almost one in ten comments for the LATER PERIOD. Comments mentioning DIY reflected polarized views, as half of the commenters expressed concerns about this practice and the other half enthusiasm.

Skeptical comments centered most prominently on questioning the value of tDCS as an enhancer ($N = 54$) and its scientific validity ($N = 49$). In this LATER PERIOD, comments portraying misunderstanding diminished ($\chi^2 = 26.03$, $p < 0.001$), as expected in a more mature stage of public awareness of the technology.

Compared to the EARLIER PERIOD, comments mentioning technical issues ($\chi^2 = 26.01$, $p < 0.001$) and use of tDCS for political leaders ($\chi^2 = 8.42$, $p < 0.05$) and children ($\chi^2 = 3.94$, $p < 0.05$) were less frequent, whereas comments mentioning commercialization ($\chi^2 = 6.97$, $p < 0.01$), therapeutic benefit ($\chi^2 = 7.8$, $p < 0.01$) and policy and regulation ($\chi^2 = 5.29$, $p < 0.05$) were more frequent. While most comments on policy and regulation reflected concerns about the lack of regulation ($N = 29$), a minority of these explicitly mentioned being against any regulation of tDCS as an enhancer.

Discussion

A New Phase for Public Perceptions?

Our results are consistent with other temporal analyses of technology and public understanding, such as those on climate change (Capstick et al., 2014). Before 2012, when the technology was still new in the public sphere, we found widespread misunderstanding of tDCS. In both periods but even more so in the LATER PERIOD, we found that in spite of the loaded and often inadequate representation of tDCS in the media, some commenters distinguished sharply between different brain stimulation techniques and openly criticized the inadequate language and analogies used in the media articles, questioning not only the scientific validity of the articles discussed in the popular media but also the domains to be enhanced.

The availability of tDCS as a consumer device, as well as the vivid online exchange of experiences with tDCS as well as instructions for DIY use (cf.: http://www.reddit.com/r/tDCS/; http://www.diytdcs.com) may be explanatory factors shaping the change in public attitudes towards tDCS, The observation that in the LATER PERIOD misunderstanding was reduced can be regarded as evidence that the public was developing a more mature understanding of tDCS. In view of the past trends, it appears important to inform the public accurately on the short- and long-term consequences of tDCS on healthy individuals and on the plausibility of enhancement effects. In addition, detailed knowledge of the current practice and prevalence of DIY tDCS is also needed.

Why Public Understanding Around tDCS Matters

Our findings have several implications. As tDCS becomes assimilated into public's consciousness, beliefs, attitudes, intention and usage of tDCS are likely to change. For example, a flawed understanding of the risk involved could lead to the increased home use. Clear understanding is also of key importance for making informed choices, in this case as a potential consumer of tDCS (Bauer et al., 2006). This becomes a pressing issue if we consider the number of online resources and companies already advertising and promoting a home use of tDCS as a cognitive enhancer. On the other hand, greater familiarity with tDCS and related scientific findings has helped the public to resist pseudo-scientific information, to scrutinize the plausible from the implausible, and to be cautious about using this technology as a cognitive enhancer. Despite the decrease in misunderstanding, the fact that tDCS continues to be confused with ECT may obfuscate the discussion regarding regulation of tDCS. In this view, online comments—ranging from sound counterarguments to the claims made in the article, to personal stories, to seemingly random remarks irrelevant to the article—enable a dynamic construction of meaning and frames in which tDCS can be understood. We invite policy makers to take into account public attitudes and (mis)understanding of tDCS in order to maximize the benefits of innovation while minimizing harms.

Conclusion

Analyses of comments in online discussion forums are a relevant source to study public attitudes towards tDCS. As this technology continues to mature and more applications become available, researchers have the opportunity to explore trends in public understanding as well as to determine the factors shaping these changes. Our results show that while misunderstanding has decreased as the technology matures, the public seems to become more cautionary and at times skeptical of this technology as a cognitive enhancer tool. From a public policy perspective, analysis of public perceptions over time can help to better inform governance and regulatory frameworks for tDCS.

Author Contributions

LYC and PBR conception and design of the work, LYC acquisition, analysis and interpretation of data.

Acknowledgments

We thank Vera Khramova and Megan Mandryck for their time validating the inter-reliability of the data. We also thank Nick S. Fitz for helping develop the coding scheme and for his useful suggestions as the study progressed. Supported by a grant from the Canadian Institutes of Health Research.

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