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DISSERTATION

Ethical Aspects of Psychiatric Neurosurgery: Evidence, Translation, and Public Attitudes

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Abstract

This dissertation in medical ethics investigates neurosurgical research for intractable psychiatric disorders and for memory impairment and cognitive decline in Alzheimer disease. In particular, it examines the role that scientific evidence for the research rationale plays for the decision-making process in translation research. The dissertation presents an in-depth analysis of ethical aspects of Deep Brain Stimulation for Alzheimer disease from the research initiation based on serendipity to the continuation with prospectively registered randomized clinical trials.

The primary basis for the ethical inquiry are the Principles of Biomedical Ethics, the Declaration of Helsinki and other well-established guidelines that require that a clinical trial “should be initiated and continued only if the anticipated benefits justify the risks” (ICH Guideline for Good Clinical Practice E6(R2)). These general principles need to be interpreted and applied to the specifics of a particular clinical trial. But the same requirements can also be posed for a sequence of clinical trials investigating the same research hypothesis as a whole. Usually, this kind of research justification in terms of risk and benefits happens behind closed doors and the information material (Investigator’s Brochures) on which these decisions are based are not publicly accessible. In turn, the respective decisions are often not evaluated by a broader scientific community. This dissertation examines the research rationale and ethical justification of Deep Brain Stimulation for Alzheimer disease and aims to open the public debate about the most salient of the ethical issues.

An additional aim is the examination of public opinions, expectations, and hopes regarding investigational research in psychiatric neurosurgery. We performed media analyses and conducted focus group interviews with lay-people from the general public from Germany, Spain, Canada, and the USA. The media coverage of psychiatric neurosurgery has re-surged since 2001 with a thematic focus on Deep Brain Stimulation in major depressive disorder and with explicit historical references to psychosurgery. The tone in the majority of newspaper articles was optimistic about contemporary psychiatric neurosurgery and demonstrated an inattention to ethical issues whereas public feedback through reader comments was more pessimistic and mostly targeted to historical psychosurgery.

The public opinion exerts influence on funders, regulators, and other stakeholders for justifying clinical research. Therefore, it is important to evaluate whether research objectives, methods, and rationales are meeting public expectations; especially with regard to the question of scientific evidence and ethical justification.

Kurzzusammenfassung (German Abstract)

Die vorliegende medizinethische Dissertation untersucht die experimentelle Forschung zur psychiatrischen Neurochirurgie, insbesondere zu Morbus Alzheimer und beleuchtet den Zusammenhang zwischen wissenschaftlicher Evidenz und Forschungsbegründung. Insbesondere werden die ethischen Aspekte der Tiefen Hirnstimulation bei Morbus Alzheimer untersucht, vom Zufallsbefund bis hin zu großen randomisierten Studien.

Grundlage für die ethische Untersuchung sind die Prinzipien der „mittleren Ebene“ der Biomedizinischen Ethik, die Deklaration vom Helsinki und andere etablierte Richtlinien, die erfordern, dass klinische Studien "nur begonnen und fortgesetzt werden, wenn die zu erwartenden Vorteile die Risiken rechtfertigen" (ICH Leitlinie zur guten klinischen Praxis E6(R2)). Derartige Normen müssen zunächst interpretiert und dann auf die Besonderheiten einer klinischen Studie angewendet werden. Üblicherweise geschieht diese Rechtfertigung der Forschung ohne direkten Zugang der wissenschaftlichen Öffentlichkeit. Die entsprechenden Entscheidungen werden daher selten im Detail von einer breiteren Wissenschaftsgemeinde unabhängig bewertet. Diese Dissertation untersucht die wissenschaftliche und ethische Begründung der Tiefen Hirnstimulation bei Morbus Alzheimer mit dem Ziel, eine informierte öffentliche Debatte über die wichtigsten ethischen Probleme zu eröffnen.

Ein weiteres Ziel ist die Untersuchung der öffentlichen Meinung, Erwartungen und Hoffnungen zur psychiatrischen Neurochirurgie. Dazu führten wir Medienanalysen durch sowie Fokusgruppeninterviews mit Laien aus der Allgemeinbevölkerung in Deutschland, Spanien, Kanada und den USA. Die Medienberichterstattung war meist optimistisch in Bezug auf die zeitgenössische psychiatrische Neurochirurgie und schenkte möglichen ethischen Problemen wenig Beachtung, während Leserkommentare meist pessimistischer waren und sich vornehmlich auf die historische Psychochirurgie fokussierten. Der thematische Schwerpunkt der Medienberichterstattung in Deutschland lag auf der Tiefen Hirnstimulation, insbesondere bei Depression, aber enthielt auch explizite Bezügen zur historischen Psychochirurgie.

Die öffentliche Meinung beeinflusst, wie Wissenschaftsförderer, Aufsichts-behörden und andere Interessengruppen die Rechtfertigung riskanter klinischer Forschung bewerten. Daher ist es wichtig zu untersuchen, ob die Ziele und Methoden der Forschung den Erwartungen der Öffentlichkeit entsprechen, insbesondere mit Blick auf die Evidenzgrundlage und die ethische Rechtfertigung.

List of Abbreviations

AD	Alzheimer disease (ICD-10 G.30)
DBS	Deep Brain Stimulation
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
NBM	Nucleus Basalis of Meynert
PICO	Population Intervention Comparison Outcome
PNS	Psychiatric Neurosurgery
UNESCO	United Nations Educational, Scientific and Cultural Organization
UK	United Kingdom
US	United States (of America)
WHO	World Health Organization
WMA	World Medical Association

1 Introduction

When examining the rise and fall of psychosurgery, the eminent neuroscientist Elliot Valenstein coined the term of the "great and desperate cures" (Valenstein, 1986). Such cures raise high therapeutic promises in desperately ill patients that would otherwise be considered "treatment-refractory". To this day, psychiatric clinics are confronted with patient suffering, which is intractable with available treatment options. In such patients, neurosurgical interventions remain a “last resort”. Neurosurgical research is being performed for diverse psychiatric indications ranging from schizophrenia (Kuhn et al., 2011a), major depressive disorder (Mayberg, 2009, Coenen et al., 2019), eating disorders, (Diaz et al., 2016, Lutter, 2017), alcohol use disorder (Kuhn et al., 2011b), to obsessive-compulsive disorder (Raymaekers et al., 2017) but also memory impairment in Alzheimer disease (Laxton et al., 2010, Kuhn et al., 2015a).

Not only is there a great number and variety of medical conditions being explored in psychiatric neurosurgery (PNS) research and closely related fields; also the neurosurgical approaches vary greatly and include markedly different approaches such as Gamma Knife radiosurgery, Deep Brain Stimulation (DBS), and even ablative procedures such as stereotactic cingulotomy. Each of these neurosurgical approaches comes with a specific risk-benefit ratio (Müller et al., 2015).

In addition, there is a great variety of brain targets being investigated. In 2013, the neurosurgeon Marwan Hariz counted at least 27 different brain targets for PNS and pointed out that the “rationale for choosing this or that target in psychiatric DBS has relied on serendipity, theoretical models [..], data from brain imaging, either functional or tractography, historical lesioning procedures, surgeons’ and/or psychiatrists’ preferences, and on various combinations of the above” (Hariz et al., 2013).

However, the limited number of eligible “treatment-refractory” patients to enroll into PNS research poses practical and methodological limits for clinical research questioning the chances of success of multiple competing “research programmes” (Lakatos, 1976) being pursued simultaneously. The limited number of patients to enroll becomes an even more important factor if many “free parameters”, such as distinct brain targets, are explored in non-coordinated ways. If research is plainly exploratory but involves serious intervention-related risks such as PNS, the state of evidence underlying the benefit-risk assessment for the research rationale becomes a topic of high interest in research ethics.

Meta-research (Ioannidis, 2018) may reveal how research on a given hypothesis is overall organized and whether it supports the accumulation of conclusive evidence over time or whether research efforts are stuck in a state of uncertainty leading to so-called “clinical agnosticism” (Carlisle et al., 2018).

Already in 1986, Valenstein noted that offering therapeutic promise to the desperate ill comes with greater responsibility for those who know more (Valenstein, 1986). The concept of the "great and desperate cures" adequately describes the medically, and morally vexed situation where unbearable suffering coincides with a state of “therapeutic nihilism”, where little is left what a physician can responsibly offer the patient for relief. “Treatment-resistance” of a medical condition or the lack of effective and proven treatment options may compel doctors and patients alike to fathom a risky “innovative” investigational treatment out of sheer despair, and sometimes to place hopes on “off-label” applications (Muskens et al., 2019). This is understandable in the individual case, but it does not exempt the scientific community of the respective medical specialties to develop new therapeutic options in evidence-based ways. Even in early stages and in patients with high “risk tolerance”, clinical research needs to be based on a sound ethical rationale that maximizes the likelihood of direct medical benefits and safety in form of a favorable risk-benefit ratio (Chiodin et al., 2019).

Taken together, there are various factors that determine the complexity of research ethics of the “great and desperate cures”. This includes:

(a) the severity of patient suffering,

(b) the burden on caregivers or family members,

(c) the little prospects provided by the established standard of care,

(d) the lack of alternative research options being offered,

(e) the promising allure of innovative research, and

(f) the scientific uncertainty of the evidence state for a given research hypothesis.

In order to protect the long-term public trust in biomedical research and to maintain a rational basis for research volunteers to participate in clinical research, the scientific community as a whole has the responsibility to critically appraise the design, outcomes, and rationale of individual clinical research activities but also the rational organization of the large-scale research efforts as a whole. This expresses a basic expectation of the general public and constitutes a hallmark of science, which “is one of the very few human activities – perhaps the only one – in which errors are systematically criticized and fairly often, in time, corrected” (Popper, 1963).

However, increasing evidence indicates that such high aspirations may not always be realized by-default in current biomedical research practices. Recent findings show that frequent methodological flaws in Translational Research need much broader scientific attention and ethical responses (Ioannidis, 2005, Ioannidis et al., 2014, Macleod et al., 2014, Wieschowski et al., 2018, Carlisle et al., 2018).

> "For example, vertebroplasty – the injection of polymethylmethacrylate cement into fractured bone [of the spine] – gained popularity in the early 2000s for the treatment of osteoporotic fractures […]. Claims of benefit were strongly contradicted in 2 randomized trials that included a sham procedure, which alone might have been responsible for pain relief. Trials without sham control might continue to show benefit, but it is difficult to justify performing invasive, expensive operations simply to obtain placebo effects. Despite the evidence, many specialists will not abandon the procedure." (Prasad et al., 2012)

However, PNS is even riskier than spinal surgery. There are an abundance and diversity of medical indications, brain targets, and neurosurgical approaches, which are part of the exploratory investigation of PNS in "treatment-refractory" patients. In consequence, there is a high potential for it becoming yet another case in point of "medical reversal" (Prasad et al., 2012). "Off-label" PNS for treatment-refractory psychiatric patients could practically become part of the clinical practice as a rare "last resort" treatment attempt. If PNS is adopted as clinical practice for otherwise "treatment-refractory" patients before robust data is obtained, the phenomenon of "medical reversal" could occur if later studies with more rigorous designs, higher statistical power, or more relevant, specific, and sensitive outcome measures revealed that PNS is *de facto* equivalent or inferior to a preexisting, less invasive treatment options (Prasad et al., 2012).

Moreover, the phenomenon of "clinical agnosticism" (Carlisle et al., 2018) could occur if such later high-quality confirmatory studies are never performed at all and, thus, scientific uncertainty about the credibility of the observed treatment effects remained. To reduce the risk of "medical reversals" and "clinical agnosticism" in PNS applications, it is crucial to critically appraise the strength of available evidence before translating a research idea from one study phase into another and to reflect on the ethical implications of potential evidence gaps.

For instance, no PNS application achieved so far the self-imposed standards of the World Society for Stereotactic and Functional Neurosurgery that set a benchmark for granting approval of the application as a therapeutic option in clinical practice (Nuttin et al., 2014). These standards state that "[a]t least two blinded (if possible) randomised controlled clinical trials from two different groups of researchers need to be published, both showing an acceptable risk–benefit ratio, at least comparable with other existing therapies." (Nuttin et al., 2014). However, only a Humanitarian Device Exemption from the United States Food and Drug Administration has been granted so far for obsessive-compulsive disorder (OCD), whereas the "official" route to market approval has not been successful in the U.S. (Fins et al., 2012). In the E.U. there is a similar label for DBS for OCD. All PNS applications other than "compassionate use" of DBS in OCD remain experimental and "off-label". In particular, this is true for the many other psychiatric indications for which small investigational clinical studies are underway.

Research ethics (Emanuel et al., 2000) has the important responsibility to critically appraise researchers' decision-making before initiating a new clinical trial, e.g., before exploring a new DBS target. Critical appraisal may happen on the individual level of assessing the eligibility criteria for safely enrolling human subjects into research (Galpern et al., 2012). It may also happen on the design-level of particular clinical studies in order to guarantee overall the ethical validity and a favorable risk-benefit ratio as well as "clinical equipoise" (Freedman, 1987) between experimental arms. Finally, research ethics may also examine the ethical justification of research trajectories by assessing the evidential support for a hypothesis and by evaluating the decision to proceed from one phase of clinical translation to the next (Hey, 2011, Hey et al., 2013).

In the context of this broader theoretical background, the current dissertation project examined the ethical aspects of the scientific rationale of PNS research and some of its ethically most salient boundary cases.

Attitudes of diverse stakeholder groups play an important role in setting research priorities. Additionally, public opinion exerts influence on funders, regulators, and other stakeholders for justifying state-funded but also privately funded research. Therefore, it is important to evaluate whether research objectives, methods, and rationales are meeting public expectations; especially with regard to the question of scientific and ethical validity and with regard to the social value of research outputs. This is an important task of the ERA-NET NEURON project funding scheme "Ethical, Legal, and Societal Aspects" of the European Union.

This dissertation project was part of an international ERA-NET NEURON consortium "Psychiatric Neurosurgery: Ethical, Legal, and Social Aspects" (01GP1621A), which was led by Sabine Müller. The dissertation was written in the ethics subproject, which examined specific ethical aspects of particular research programmes. The dissertation project contributed to media analyses of international newspaper articles and reader comments on contemporary PNS and contributed to focus group interviews (Morgan, 1997) with lay-people of the general public. Moreover, the enrollment of patients with compromised capacity for informed consent poses a particularly vexing problem, and the translation of investigational neurosurgical interventions to such populations warrants special attention in the field of psychiatry and neurology alike. Therefore, we also performed an in-depth ethical analysis of DBS for Alzheimer disease (AD).

The aim of the first publication was to open the public debate about the ethical justification of clinical research on DBS as an investigational intervention for symptomatic relief from AD (Bittlinger and Müller, 2018). It was motivated by the above-outlined merits of meta-research to examine the underlying scientific rationale of a particular research programme and to disclose potential methodological pitfalls. It also analyzes the transition from one research phase to another, e.g., from preclinical to clinical research, in light of established scientific requirements (Cayen, 2011) and ethical standards (Emanuel et al., 2000).

The aim of the second publication was to ethically examine the specific eligibility criteria of ongoing clinical research on DBS for AD in light of the putative disease mechanisms (Viaña et al., 2017). This aim was set after the scoping of the literature had revealed two distinct paradigms of DBS for AD trials that were ongoing in parallel but using inherently different approaches in terms of brain targets (fornix versus nucleus basalis of Meynert) and DBS parameter settings. Both research paradigms were recruiting AD patients of 65 years of age and younger, who thus suffer from early-onset AD. An important portion of patients with early-onset AD may possess a genetic susceptibility, i.e., autosomal-dominant mutations, that is associated with an atypical and more rapid symptom progression (Campion et al., 1999) and marked differences in the onset and symptomatology of the cognitive impairment (Viaña et al., 2017). This raises the question of how the grouping together of patients with dissimilar characteristics is reflected in the justification of the research rationale of DBS for AD. This question motivated the ethical analysis of the rationale with regard to the eligibility criteria for the enrollment of AD patients into clinical trials investigating DBS (Viaña et al., 2017).

The aim of the third publication was theoretical in nature (Bittlinger, 2018). Conceptual analysis was used for assurance about key concepts from epistemology and philosophy of science that serve as background assumptions of this dissertation project. Most importantly, one assumption holds that biomedical research is justified only if it enables patients or health care providers to rely on previous findings by-and-large without having to worry whether the *reliance* is warranted and whether it is reasonably based on *reliable evidence* (externalist epistemic justification (Feldman, 1985)). In turn, the widespread expectation that scientific research is reliable gives rise to *normative* implications (Goldberg, 2018). The legitimacy with which patients generally expect that biomedical research is based on sound and reliable science leads to collective responsibility for evidence-based drug and medical device research. This responsibility is a strong reason to endorse rigorous measures such as Open Science, which promote and strengthen the reliability of research (Nosek et al., 2015) and, therefore, justify the trust of patients into research (Bittlinger, 2018).

The aim of the fourth and fifth publication was to empirically examine the expectations of the general public and the public attitudes toward PNS research (Cabrera et al., 2018b, Cabrera et al., 2018a, Cabrera et al., submitted). Since news media play an essential role in exposing the public to trends in health care, we examined a large international sample of newspaper articles (Cabrera et al., 2018a) and reader comments to articles in newspapers and magazines on PNS (Cabrera et al., 2018b). We examined news media articles from Canada, the USA, Germany, and Spain. This was achieved in collaboration with the Canadian team members of the Social Science subproject of the ERA-NET NEURON consortium “Psychiatric Neurosurgery: Ethical, Legal, and Social Aspects” (01GP1621A). In addition, we aimed to directly examine public opinions, expectations, hopes, and concerns regarding advances in PNS by performing focus group interviews with lay-people from the general public form Germany, Spain, Canada, and the USA. This pending publication is not part of the dissertation, but it’s findings are discussed to the extent they are relevant for the dissertation (Cabrera et al., submitted). In this pending publication, we conducted group interviews (focus groups) with interested laypeople of the general public between 2017 and 2018 in four cities (Vancouver and Montreal, Berlin, and Madrid) and used content analysis to analyze common themes in the international public attitudes (Cabrera et al., submitted). The overall research objective of this dissertation project was to perform an in-depth ethical analysis of the research rationale of DBS for AD and to investigate the public attitudes towards PNS.

2 Methods

Medical ethics and related fields evaluate a state of affairs in the world based on normative evaluation and moral deliberation. In practice, such evaluations are frequently based on ethical principles that aim to reconstruct a broad consensus about the basic core of the common morality (Birnbacher, 2013). This holds also for research ethics and Neuroethics, of which the latter is the "deliberate reflection of ethical problems arising from the neurosciences and their predominantly neurotechnological application" (Müller et al., 2018).

As such, there are two requirements to be met: First, the relevant facts determining the subject matter need to be described accurately with regard to all relevant details. For the ethical evaluation in the field of clinical research, this is done in the form of an empirical assessment. Second, the subject matter needs to be evaluated using ethical principles or value judgments that require a separate justification using normative reasons, ethical principles or moral values.

In the following, the basic approach for this dissertation project is briefly outlined, while any methodological details are described in the methods sections of the respective publication that are part of this dissertation project.

2.1 Empirical Assessment

For the collection of empirical data in medical ethics, the same methodological quality criteria apply as for any empirical discipline such as social science, public health, meta-research, or clinical epidemiology. As Kalichman (2009) has put it succinctly, "[t]he practice of evidence-based research ethics means integrating individual expertise with the best available external evidence from systematic research".

Of particular importance for the empirical assessment in research ethics is the comprehensive and systematic collection of published evidence which makes it useful to adopt methodologies typically applied in Systematic Reviews or in cross-sectional bibliometric cohort studies. This comprises the use of principled eligibility criteria (PICO schemes (Huang et al., 2006)) and a systematic search strategy on independent medical databases such as MEDLINE and EMBASE as well as provisions to reduce the risk of bias during abstract screening, information extraction, and any further steps involved in obtaining the data required to perform an ethical analysis that is adequately informed by all available published evidence.

For the media analysis (Publication 4 & 5), additional quality criteria guided the methodological approach, which are specific for qualitative data analysis as described in more detail in the methods sections of the respective publications. On reflection of the qualitative methods used in many interview studies with DBS patients, two additional publications resulted from the project which raise awareness for important aspects of interpreting qualitative data and patient reports in the field of *neuroethics* (Bittlinger, 2017, Müller et al., 2017).

2.2 Normative Assessment

The ethical analysis plays a central role in all publications of this dissertation project. For performing an ethical analysis, it is necessary but not sufficient to describe empirical facts. In addition, the relevant matters of fact need to be evaluated on the basis of moral values or ethical principles. This can be achieved by developing genuinely new ethical arguments or by the application of established evaluative criteria. In the following, I will describe the major sources that I used for deriving evaluative criteria to conduct the normative assessments performed in this dissertation project.

Medical ethics and research ethics are often normatively guided by established practical guidelines or by authoritative theoretical frameworks, such as the Principles of Biomedical Ethics (Beauchamp and Childress, 2013). This particular framework is ubiquitously used and outlines general principles that can serve as a shared common ground. These principles are the (1) Respect for Autonomy, (2) Beneficence, (3) Non-maleficence, and (4) Justice; in particular, the fair allocation of medical resources and the prevention of unfairly distributed research burdens (Beauchamp and Childress, 2013).

Although forming a well-established common ground, the Principles of Biomedical Ethics can only serve as a starting point for an in-depth ethical analysis. The reasons for this are first and foremost that the internal logic of these principles is not ordered by precedence and that the principles can easily come into conflict, which makes conceptual argumentation and the prudent weighing of value judgments necessary. Second, these principles are abstract ideals. Such ideals do not apply in a simple and unambiguous way to the respective decision-making of different stakeholders involved in a particular biomedical research practice.

Since biomedical research is highly structured by means of regulatory oversight (Cayen, 2011), international ethics guidance documents are additional sources for normative assessments. For instance, the Declaration of Helsinki (World Medical Association, 2013) encapsulates fundamental ethical principles for clinical research. The Declaration of Helsinki specifies moral responsibilities that are the basis for many national legislations and therefore plays a prominent role in normative assessments of clinical research. In addition, the World Health Organization (WHO) jointly with the United Nations Educational, Scientific and Cultural Organization (UNESCO) outlines very similar ethical principles (CIOMS, 2017)

Compliance with such guidelines is an important moral obligation for authors when publishing clinical research. Moreover, publications of clinical research should also be consistent with reporting standards such as the CONSORT statement (Schulz et al., 2010), because only methodological sound research has the potential to be ethical (Emanuel et al., 2000).

Finally, individual scientific articles from medical ethics, bioethics, and related fields may provide compelling arguments of ethical relevance that can be used as additional criteria for the deliberative processes required for normative assessments.

Ethics committees or Institutional Research Boards (IRB) are responsible for the prospective assessment of ethical aspects and for human subject protection, including methodological aspects (German Medical Devices Act (MPG) § 22). However, it is neither sufficient nor effective to simply impress all normative assessments on such regulatory bodies. Their normative assessment is severely limited by time constraints and increased workloads (Abbott and Grady, 2011).

Furthermore, the assessment of ethics committees depends on the selection of information provided by Principal Investigators in the submitted proposals (Hahn et al., 2002). Thus, ethical aspects beyond plain regulatory requirements as well as aspects on a meta-research level such as the consistency between clinical trial protocols and the reported methods are not likely to be part of the prospective ethical oversight performed by ethics committees or IRBs. This is not to question the work of ethics committees but to illustrate the need for and legitimacy of additional in-depth ethical analyses of clinical research and its organization.

In addition, detailed methodological aspects can critically affect the credibility of translational research decision-making about whether to abandon a research paradigm or to initiate further clinical investigations. For instance, meta-research on the practice of statistical subgroup analysis in randomized controlled trials examined a large sample of registered protocols and corresponding scientific articles (Kasenda et al., 2014). The findings suggest a high prevalence of inconsistencies (54%, n=132), which question the by-and-large credibility of the reported subgroup effects (Kasenda et al., 2014). However, subgroup effects were the key driver of clinical translation of DBS for AD as shown in publication 1 of this dissertation project (Bittlinger and Müller, 2018)

Time and again, methodologists have emphasized that in the case of exploratory subgroup effects “extreme caution” is required when “interpreting striking results that are data derived even for the generation of hypotheses.” (Yusuf et al., 1991). Finally, in 2019 the European Medicines Agency (EMA) issued a norm (EMA/CHMP/539146/2013) specifying strict criteria for the credibility of subgroup analyses. This norm requires that a credible subgroup analysis needs to be replicated by independent studies and provides a compelling explanation based on clinical, pharmacological, and mechanistic considerations (EMA/CHMP/539146/2013, 2019)

Nonetheless, exploratory subgroup effects may be used pervasively to postulate new hypotheses for future research and it is unclear how extensively their credibility has been critically appraised by ethics committees in the past. Launching research on spurious post hoc subgroup effects may contribute to the inefficiencies in clinical research (Sun et al., 2014). Even worse, if potential spurious findings are not flagged as such, future clinical trial design risks to be misinformed; in the worst case causing unnecessarily high numbers of subjects to be exposed to potentially unsafe and ineffective clinical research on investigational interventions.

Such risks are typically hidden from the prospective assessment of ethics committees and require new and additional methodologies in research ethics. One method is to use empirical approaches such as the independent, retrospective, and systematic assessment of diverse types of scientific publications to unravel evidence gaps of normative relevance in a broader research field such as PNS. This meta-research approach can provide valuable insights to inform scientific discussion of important normative aspects in research ethics and can help to protect public trust in the long run. After all, public trust is the bedrock of biomedical research.

2.3 Application of the Methodology

For publication 1, we performed a systematic search on MEDLINE and EMBASE. After screening of 811 abstracts, we included 166 publications about DBS for AD into the full-text analysis of research rationales as well as risks and ethical aspects and provide a flow diagram displaying the inclusion and exclusion of the searched literature (Bittlinger and Müller, 2018).

For publication 2, we collaborated with Australian researchers from the University of Tasmania who were working on the state of preclinical evidence of DBS for AD. The cooperation was used for the evidence-based critical appraisal of the scientific rationale behind the eligibility criteria for enrollment of early-onset AD patients into DBS clinical trials (Viaña et al., 2017).

Publication 3 is theoretical in nature and used conceptual analysis of normative and epistemological arguments as methodology (Bittlinger, 2018).

The method of publication 4 involved an analysis of media articles covering all types of psychiatric neurosurgery published in Canada, USA, Germany, and Spain between the years 1960 and 2015 (Cabrera et al., 2018a). We applied both quantitative and qualitative methods to elucidate patterns of reporting for medical conditions, themes and tone, across different countries, time, and for the type of intervention (Cabrera et al., 2018a).

In publication 5, we continued the thematic analysis of these media articles by including reader comments to the magazine articles (N = 662 coded units of data) posted in response to 115 newspaper and magazine articles from four countries (Canada, USA, Germany, and Spain) between 2006 and 2017 (Cabrera et al., 2018b). We used established qualitative research methods to iteratively code and refine the coding scheme that was structured around pre-defined categories based on results from the media analysis of publication 4 (Cabrera et al., 2018b).

3 Results

The following five peer-reviewed publications present the most important results of this dissertation project. Publications 1, 2 and 3 report the outcomes of the in-depth ethical analysis of DBS as investigational intervention for patients with AD.

Publications 4 and 5 present the results of an international media analysis to capture the spectrum of international public attitudes towards psychiatric neurosurgery.

3.1 Publication 1: In-depth ethical analysis of DBS for AD patients

Bittlinger, M & Müller, S. Opening the Debate on Deep Brain Stimulation for Dementia - A Critical Evaluation of Rationale, Shortcomings, and Ethical Justification. BMC Medical Ethics. DOI: 10.1186/s12910-018-0275-4

Rank in category “MEDICAL ETHICS”: 2/16 (Q1)*

Journal Impact Factor 2018 of *BMC Medical Ethics*: 2.507*

Eigenfactor score 2018: 0.00417*

3.2 Publication 2: Ethical issues of DBS in early-onset AD patients

Viaña, J. N. M., Bittlinger, M., & Gilbert, F. (2017). Ethical considerations for deep brain stimulation trials in patients with early-onset Alzheimer’s disease. *Journal of Alzheimer's Disease*, 58(2):289-301. DOI: 10.3233/JAD-161073.

Rank in category “NEUROSCIENCES”: 99/267 (Q2)*

Journal Impact Factor 2018 of *Journal of Alzheimer's Disease*: 3.517*

Eigenfactor score 2018: 0.04147*

3.3 Publication 3: Epistemic justification of exploratory DBS research

Bittlinger, M. (2018). Call of duty at the frontier of research: normative epistemology for high-risk/high-gain studies of deep brain stimulation. *Cambridge Quarterly of Healthcare Ethics, Clinical Neuroethics issue*, 27(4), 647-659 DOI: 10.1017/S0963180118000142

Rank in category “HEALTH POLICY and SERVICES”: 71/81 (Q4)*

Journal Impact Factor 2018 of *Cambridge Quarterly of Healthcare Ethics*: 0.941*

Eigenfactor score 2018: 0.00074*

3.4 Publication 4: Media analysis of public discourse on psychiatric neurosurgery

Cabrera, L., Bittlinger, M., Lou, H., Müller, S., Illes, J. The Re-emergence of Psychiatric Neurosurgery: Insights from a Cross-national Study of Media Coverage. *Acta Neurochirurgica*. DOI: 10.1007/s00701-017-3428-1.

Rank in category "SURGERY": 106/203 (Q3)*
Journal Impact Factor 2018 of *Acta Neurochirurgica*: 1.834*
Eigenfactor score 2018: 0.00916*

3.5 Publication 5: Analysis of public attitudes towards psychiatric neurosurgery

Cabrera, L. Y., Bittlinger, M., Lou, H., Müller, S., & Illes, J. (2018). Reader comments to media reports on psychiatric neurosurgery: past history casts shadows on the future. *Acta Neurochirurgica*, *160*(12), 2501-2507. DOI: 10.1007/s00701-018-3696-4

Rank in category "SURGERY": 106/203 (Q3)*
Journal Impact Factor 2018 of *Acta Neurochirurgica*: 1.834*
Eigenfactor score 2018: 0.00916*

4 Discussion

The in-depth analysis of the ethical rationale of DBS for AD patients revealed serious ethically relevant methodological shortcomings in the translational research process. Research enrolling human subjects was performed before decisive preclinical research had been published (Bittlinger and Müller, 2018).

The decision of researchers to translate from preclinical into early clinical research is critical for examining the potential safety and efficacy of an intervention. Such decision require robust evidence from preclinical studies with valid study designs (Landis et al., 2012). Moreover, they require confirmatory replication of promising findings if based solely on exploratory studies (Kimmelman et al., 2014).

Even very recent preclinical studies on DBS for AD do not meet these standards and only report beneficial effects of fornical DBS in an AD mouse model that are merely “transient” and “heavily mediated by sex” (Gallino et al., 2019). In consequence, for preclinical scientists, “DBS's mechanism of action, delivery regimen, optimal brain target, and timeline of behavioural and neuroanatomical outcomes are all open fields of investigation” (Gallino et al., 2019). While in mice it is still an open question whether DBS of the fornix is a safe procedure of sufficiently large and sustained benefits, clinical research already advanced into a pivotal phase (“ADvance II” study with clinical trial registry number: NCT03622905).

In addition to the fornix, DBS for AD has been investigated in the nucleus basalis of Meynert (NBM) and “ventral striatum, nucleus accumbens, and internal capsule“ (NCT01559220) as competing research programmes using different brain targets. After publications of overall inconclusive results of DBS of the NBM by German researchers (Kuhn et al., 2015a, Kuhn et al., 2015b, Hardenacke et al., 2016), the research paradigm was not continued by the German researchers.

However, clinical research on this brain target is continued in Asia with no published results so far (NCT02253043, NCT03352739 NCT03115814, NCT03959124). One of these studies explicitly stated to enroll demented patients with severe cognitive impairments (NCT03115814), who by definition have compromised capacity to consent to invasive neurosurgical procedures. This is in conflict with Article 28 of the Declaration of Helsinki because there is no evidence for a likely direct benefit and the procedure poses significantly more than just minimal harms (Bittlinger and Müller, 2018).

In the European Union, the enrollment of study participants suffering from a medical condition, and especially demented patients, into research not likely to yield direct benefit would also violate medical device law (e.g. German MPG §21 Abs.2), in particular Article 64 (g) of Regulation (EU) 2017/745 (2017).

Another registered clinical study even advanced to research that aims to simultaneously examine "comparative" efficacy and safety of competing experimental brain targets (NBM versus fornix), which further illustrates the exploratory research approach pursued in the field (NCT03352739).

Our analysis shows that this quick translation from serendipity to competing clinical research programmes is not based on empirically informed mechanistic reasoning or predictive evidence from well-designed and independently replicated preclinical studies (Bittlinger and Müller, 2018). This is a marked difference compared to the history of DBS in Parkinson's Disease (Moutaud and Desmoulin-Canselier, 2019). Instead, multiple distinct hypotheses of beneficial effects of DBS for AD were postulated rather *ad hoc* (Mirzadeh et al., 2016), i.e., only after the initiation of early clinical investigations ("ADvance I" study: NCT01608061, NCT00658125).

Noteworthy, the rationale was explained (Laxton et al., 2012, Mirzadeh et al., 2016) after having seen first provisional but inconclusive results (Laxton et al., 2010, Lozano et al., 2016). This can be considered as a methodologically questionable variant of *Hypothesizing After the Results Are Known* (Kerr, 1998). It occurs on a meta-level of the justification of translational research and turns the logical order and chronological sequence of clinical research upside-down. In addition, it obscures the inherent explorative character of the research rationale as if the rationale were based on pre-specified mechanistic and theory-derived considerations.

Moreover, the clinical translation from pilot studies to pivotal research phases was based on observations of unspecific surrogate markers (i.e. blood glucose metabolism) that are not established AD biomarkers and on small sample (N=6) *post hoc* analyses that were not publicly pre-specified (see "Secondary Outcomes" at NCT00658125, NCT01608061, NCT03622905). These post hoc analyses referred to patients' disease stage which correlates with patients' age, i.e., patients in earlier disease stages tend to be younger and had slower disease progression (Laxton et al., 2010). In a subsequent trial, younger patients were targeted for patient enrollment including patients with Early-Onset AD (Viaña et al., 2017). However, the rationale of including younger patients was then contradicted by the findings from this later trial (Lozano et al., 2016).

In addition, the later trial did not yield significant main effects on the primary clinical outcome (Lozano et al., 2016). Nonetheless, these results were used to warrant further clinical translation into a pivotal phase based on surrogate marker findings, i.e., blood glucose metabolism (Lozano et al., 2019). The pivotal phase is the last step before market approval (US Food Drug Administration, 2013). This pattern of research decision-making raises questions about the ethical justification of the research translation process and warrants further evidence-based investigation of the benefit-risk assessment underlying the enrollment of AD patients in the currently ongoing pivotal phase (NCT03622905).

Additional serious ethical issues are questionable informed consent processes, conflicts of interests, and a tendency to spin the small sample findings in the abstracts of the respective publications (Bittlinger and Müller, 2018). The severity and number of ethical issues were surprising and imply, in part, even direct violations of the Declaration of Helsinki (Bittlinger and Müller, 2018).

This methodological criticism and ethical issues were presented at two scientific conferences in personal communication to the Principal Investigator of the clinical trials of DBS for AD using the fornix, i.e., at an informal but concise conversation at one conference poster (Bittlinger and Müller, 2017). Additionally, the results of the ethical analysis (Bittlinger and Müller, 2018) were directly discussed with reassuring and well-received remarks in the closing lecture “Ethics of DBS for disorders of mood and mind” of Marwan Hariz on the XXIII. congress of the European Society for Stereotactic and Functional Neurosurgery in Edinburgh in 2018.

The impact of the opening of this debate (Bittlinger and Müller, 2018) was, however, not as effective as would seem appropriate for the high importance of the subject matter. This is particularly disappointing as our published recommendations for future DBS for AD trials (Viaña et al., 2017, Bittlinger and Müller, 2018) anticipated that patients with early-onset AD need special protection to mitigate potential harms from being enrolled in these experimental studies (Viaña et al., 2017).

Therefore, the field of DBS urgently needs more serious and more vigorous implementation of “open science, transparent exhaustive data reporting, preregistration, and continued constant critical appraisal via pre- and post-publication peer review” (Bittlinger, 2018).

Recently it has been independently argued by Fuller (2018) that such "research on research" would provide additional evidence, i.e., "meta-evidence" (Fuller, 2018). The continuation of these efforts to systematically map all PNS research trajectories in detail based on scientific merits and the strength of evidence is an important desiderate. It could be achieved by future work using a variant of graphical causal models (Pearl, 2009) called *Accumulating Evidence and Research Organization* (AERO) models (Hey, 2011, Hey et al., 2013).

In contrast to the high standards of research ethics, actual research decision-making seems often to deviate from rigorous evidence-based frameworks and to operate with more "pragmatic" criteria. In particular, it seems that research on severely medically burdened patient populations, such as AD patients, is sometimes based on serendipity combined with a medical impetus to help ("*beneficence"*).

Instead invasive neurosurgical research would be better advised to focus on the rigorous scientific demonstration that the research rationale is robust and reliably informed by pre-existing evidence (Bittlinger, 2018, Bittlinger and Müller, 2018, Viaña et al., 2017). This also requires empirical demonstration that the application of the neurosurgical intervention in this particular disease population is sufficiently safe and potentially effective by means of well-designed, high-quality preclinical evidence (*non-maleficence*).

This is important because a heroic medical impetus to help still requires the empirically sound demonstration of a favorable risk-benefit ratio. In general, the rationale for "compassionate use" cannot figure as a rational basis of clinical translation more broadly because it would presuppose expectable clinical benefits in a circular way before clinical benefits have been empirically demonstrated. In contrast, a lack of proven treatments in some therapeutic areas gives rise to the responsibility of the scientific community to perform intensive basic, preclinical, and clinical research in a well-designed and organized way to efficiently provide definite evidence on what works and what may not work. However, in the absence of robust and reliable evidence, there is no responsibility to transform unproven investigational interventions into an exploratory research program.

This would be an inverse variant of a "therapeutic misconception" (Appelbaum et al., 1987), where researchers falsely assume that the obligation to provide clinical care (Miller and Brody, 2003) implies some "sham" obligation to perform clinical research even if only based on speculative benefits and despite well-known risks.

In contrast, clinical research on risky investigational interventions should only be initiated if the overall risk-benefit ratio is expected to be favorable in light of preclinical and other relevant evidence but genuine uncertainty of the adequately informed scientific community exists whether or not it is superior to a well-defined “standard of care” or to alternative research options (Freedman, 1987, Djulbegovic, 2011). This does not result from the mere absence of suggestive evidence but requires high-quality positive evidence suggesting the possibility of a favorable risk-benefit ratio.

To endorse and defend such high standards for clinical translation is additionally motivated by the expectations of the general public as indicated by our media analysis, the examination of reader comments, and group interviews. Overall our findings are consistent with the thesis that risky and innovative clinical research in biomedical sciences is expected to be externally justified by means of reliable pre-existing evidence on the safety and provisional efficacy and is not performed as an exploratory research agenda.

The media coverage of PNS has re-surged since 2001 (Cabrera et al., 2018a). Thematic focuses of the media coverage are DBS in depression and explicit historical references to psychosurgery (Cabrera et al., 2018a). The tone in the majority of newspaper articles was optimistic about contemporary PNS, but also demonstrated an inattention to ethical issues (Cabrera et al., 2018a). This key finding is well-known for biotechnology research and related fields (Caulfield, 2004) and has been associated with the increased commercialization of science (Caulfield and Ogbogu, 2008). However, our media analysis identified also some reports of critical appraisal of the evidence state such as: “Last year, the therapy [vagal nerve stimulation] was approved as a treatment for depression in European Union countries, ‘despite the limited evidence’ [that] it helps” (SFGate (2002) as cited in Cabrera et al. (2018a)).

In sum, the public feedback to media reports was dominated by reference to historical psychosurgery and by mostly negative and pessimistic comments about ablative neurosurgical interventions (Cabrera et al., 2018b). We also found many expressions of distrust towards medical professionals in the context of brain interventions and concerns about social and individual control (Cabrera et al., 2018b).

Moreover, our results from 8 Focus Groups comprising 48 members of the general public revealed the importance of the concepts “authentic self” and “last resort” as overarching themes in all groups” (Cabrera et al., submitted). Noteworthy, ethical issues related to patient desperation, decision-making, and the social response to mental illness were at the center of discussions about PNS (Cabrera et al., submitted). These findings about the public attitudes towards contemporary PNS can promote informed health policy, and foster further ethical analysis about the validity and justification of translational research on PNS (Cabrera et al., submitted).

5 Conclusion

Developing new, safe, and effective therapeutic options is an important task of clinical research for many patient populations including patient volunteers with “treatment-resistant” psychiatric conditions or AD.

The results of this dissertation project argue for the continued adherence to international standards that “encourage researchers to design independent, randomized and blinded (where possible) controlled trials, with the least possible conflict of interest and bias, to strive towards the generation of level I (U.S. Preventive Services Task Force) or level A (U.K. National Institute of Clinical Excellence […]) clinical evidence with regard to neurosurgical procedures for psychiatric disorders.” (Nuttin et al., 2014)

This is an ambitious, resource-intensive, and methodological challenging task but remains of high societal priority. Advances in meta-research methodologies are promising to disclose important ethical loopholes that emerge in translational research decision-making. Ethical analysis can benefit from such approaches when examining the justification of clinical translation from one research phase to another. The comprehensive mapping of evidence accumulation for all the different PNS approaches across the phases of research translation remains a key desiderate for future evidence-based research ethics.

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Eidesstattliche Versicherung (statutory declaration)

Ich, Timon Merlin Miguel Bittlinger, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Titel *“Ethical Aspects of Psychiatric Neurosurgery: Evidence, Translation, and Public Attitudes“* selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE www.icmje.org*)* kenntlich gemacht. Die Abschnitte zu Methodik und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM und werden von mir verantwortet.

Meine Anteile an den Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit der Betreuerin, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des StGB) sind mir bekannt und bewusst.

Datum Unterschrift

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Anteilserklärung (authorship contributions)

The following explanation of the scientific contributions for authorship is based on the CASRAI Contributor Roles Taxonomy (CRediT), which is endorsed by many scientific publishers including Elsevier, Oxford University Press, Springer Publishing Company, and others. In all publications Timon Merlin Miguel Bittlinger contributed to Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing.

PUBLICATION 1 (Bittlinger and Müller, 2018): Timon Merlin Miguel Bittlinger was the primary and corresponding author, and his contribution comprised approximately 85% of the work for this manuscript. He was mainly responsible for conceptualizing the main ideas for this project, organizing the structure and flow of the paper, and writing the majority of the text. He designed the search strategy, screened titles and abstracts and performed the systematic full text analysis of the included scientific, medical, and ethical literature for information presented in this manuscript, especially regarding DBS and AD. He also filled in the data for, constructed, and formatted the tables and figures. He facilitated the revision of the manuscript, responded to the comments of the editor and reviewers, and carefully proofread it prior to final publication.

PUBLICATION 2 (Viaña et al., 2017): Timon Merlin Miguel Bittlinger contributed to conceptualization of the ideas and ethical considerations posited in this manuscript, especially in the “Considerations for patient selection” and “Interpretation and communication of study results” sections to which he also provided written text. He also provided critical feedback to other sections of the paper and helped ensure the accuracy of the information presented in the text and in the tables and the normative evaluations. He also helped fill in data for Table 1, where criteria for patient volunteer recruitment in studies on DBS for AD were presented. He also assisted in the critical revision of the manuscript text. The contribution as co-author to this manuscript is approximately 25%.

PUBLICATION 3 (Bittlinger, 2018): The contribution of Timon Merlin Miguel Bittlinger comprised 100%.

PUBLICATION 4 (Cabrera et al., 2018a): Timon Merlin Miguel Bittlinger contributed approximately 25% to the work for this manuscript. He curated the list of German newspapers to be included in the search strategy and performed the search and the qualitative analysis of German newspaper articles on psychiatric neurosurgery. He also contributed text paragraphs for writing the results and discussion section. He provided feedback and comments to the first draft and to any revisions of the paper.

PUBLICATION 5 (Cabrera et al., 2018b): Timon Merlin Miguel Bittlinger contributed approximately 20%. His contribution consisted in collecting the sample of newspaper comments and he performed the qualitative assessment of the German comment texts. He contributed to the interpretation of the findings and added some content for writing the results and discussion section. He also read and commented on the first and on the final draft of the manuscript before submission.

Signature, date, and stamp of the first supervisor

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Signature, Timon Merlin Miguel Bittlinger

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Druckexemplare der ausgewählten Publikationen (publications)

Publication 1: In-depth ethical analysis of DBS for AD patients

Bittlinger, M & Müller, S. Opening the Debate on Deep Brain Stimulation for Dementia - A Critical Evaluation of Rationale, Shortcomings, and Ethical Justification. BMC Medical Ethics. DOI: 10.1186/s12910-018-0275-4

Rank in category “MEDICAL ETHICS”: 2/16 (Q1)*

Journal Impact Factor 2018 of *BMC Medical Ethics*: 2.507*

Eigenfactor score 2018: 0.00417*

*All statements in academic field-specific category ranks, Journal Impact Factors, and Eigenfactor scores are based on information from ISI Web of Knowledge, *Clarivate Analytics*, 2018.

Publication 2: Ethical issues of DBS in early-onset AD patients

Viaña, J. N. M., Bittlinger, M., & Gilbert, F. (2017). Ethical considerations for deep brain stimulation trials in patients with early-onset Alzheimer's disease. *Journal of Alzheimer's Disease*, 58(2):289-301. DOI: 10.3233/JAD-161073.

Rank in category "NEUROSCIENCES": 99/267 (Q2)*

Journal Impact Factor 2018 of *Journal of Alzheimer's Disease*: 3.517*

Eigenfactor score 2018: 0.041470*

*All statements in academic field-specific category ranks, Journal Impact Factors, and Eigenfactor scores are based on information from ISI Web of Knowledge, *Clarivate Analytics*, 2018.

Publication 3: Epistemic justification of exploratory DBS research

Bittlinger, M. (2018). Call of duty at the frontier of research: normative epistemology for high-risk/high-gain studies of deep brain stimulation. *Cambridge Quarterly of Healthcare Ethics, Clinical Neuroethics issue*, 27(4), 647-659 DOI: 10.1017/S0963180118000142

Rank in category “HEALTH POLICY and SERVICES”: 71/81 (Q4)*

Journal Impact Factor 2018 of *Cambridge Quarterly of Healthcare Ethics*: 0.941*

Eigenfactor score 2018: 0.000740*

*All statements in academic field-specific category ranks, Journal Impact Factors, and Eigenfactor scores are based on information from ISI Web of Knowledge, *Clarivate Analytics*, 2018.

Publication 4: Media analysis of public discourse on psychiatric neurosurgery

Cabrera, L., Bittlinger, M., Lou, H., Müller, S., Illes, J. The Re-emergence of Psychiatric Neurosurgery: Insights from a Cross-national Study of Media Coverage. *Acta Neurochirurgica*. DOI: 10.1007/s00701-017-3428-1.

Rank in category “SURGERY”: 106/203 (Q3)*

Journal Impact Factor 2018 of *Acta Neurochirurgica*: 1.834*

Eigenfactor score 2018: 0.009160*

*All statements in academic field-specific category ranks, Journal Impact Factors, and Eigenfactor scores are based on information from ISI Web of Knowledge, *Clarivate Analytics*, 2018.

Publication 5: Analysis of public attitudes towards psychiatric neurosurgery

Cabrera, L. Y., Bittlinger, M., Lou, H., Müller, S., & Illes, J. (2018). Reader comments to media reports on psychiatric neurosurgery: past history casts shadows on the future. *Acta Neurochirurgica*, *160*(12), 2501-2507. DOI: 10.1007/s00701-018-3696-4

Rank in category “SURGERY”: 106/203 (Q3)*

Journal Impact Factor 2018 of *Acta Neurochirurgica*: 1.834*

Eigenfactor score 2018: 0.009160*

*All statements in academic field-specific category ranks, Journal Impact Factors, and Eigenfactor scores are based on information from ISI Web of Knowledge, *Clarivate Analytics*, 2018.

Lebenslauf (academic curriculum vitae)

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste (complete list of peer-reviewed publications)

2020 Cabrera LY, Courchesne C, Bittlinger M, et al. Authentic Self and Last Resort: International Perceptions of Psychiatric Neurosurgery [ahead of print]. *Cult Med Psychiatry*. 2020;10.1007/s11013-020-09679-1. DOI: 10.1007/s11013-020-09679-1. Journal Impact Factor 2019: 1.217

2019 Guillen Gonzalez, D., Bittlinger, M., Erk, S., & Müller, S. (2019). Neuroscientific and Genetic Evidence in Criminal Cases: A Double-Edged Sword in Germany but not in the USA?. *Frontiers in Psychology*, *10*, 2343. DOI: 10.3389/fpsyg.2019.02343. Journal Impact Factor 2018: 2.129.

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Abstract Schwietering, J., Bittlinger, M., & Strech, D. (2019). 42 Investigator's brochures: do they adhere to basic principles of evidence synthesis methods? *BMJ Evidence-Based Medicine,* (Suppl. 1) 24:A26-A27. Journal Impact Factor 2018: *Not available*.

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