



Surgical decision making for deep brain stimulation should not be based on aggregated normative data mining

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We read with interest the manuscript by Li et al. “*Toward a unified connectomic target for deep brain stimulation in obsessive-compulsive disorder*”, published on the preprint server bioRxiv (13 april 2019) [18]. We would like to comment on the far-reaching conclusions drawn from the use of aggregated normative and connectomic data for their impact on decision making for surgical targeting in deep brain stimulation (DBS). Furthermore, we would like to discuss the emerging use of publication of unreviewed scientific data in various open formats.

In their work, Li et al. compare two different patient cohorts undergoing DBS for treatment resistant obsessive compulsive disorder (OCD) from two study centers, Grenoble (n = 14) and Cologne (n = 22) with DBS in two different brain targets, the anteromedial subthalamic nucleus (amSTN) in Grenoble and the anterior limb of the internal capsule = ALIC in Cologne. The results of the Cologne cohort have previously been published in a very similar context, somewhat surprisingly with different results [5,18]. Li et al. base their conclusion on the analysis of aggregated normative data (due to a lack of individual tractographic data in both cohorts), assuming by this that these patients have unaltered, identical white matter anatomy. They find a common “tract target” that jointly explains anti OCD effects in both groups, and they conclude that this new pathway might be of further use in DBS. These results are certainly relevant - albeit not new [9,19].

The article implies that the associative/limbic parts of the STN were targeted by DBS for OCD because of image derived circuitry and connectivity. Although the imaging data are highly interesting from a mechanistic viewpoint, the reality is that serendipity was

the driver, after case reports emerged of improvement in concomitant OCD symptoms in patients who had undergone STN DBS for Parkinson's disease [15,20].

Li et al. state: [...] “*This final bundle may indeed represent a “tract-target” to treat OCD with DBS. Given this potential clinical importance, we characterized its anatomical properties using additional views relatively to anatomical landmarks that could be used during stereotactic planning [...]”*. [18] This is probably the most problematic sentence in this paper as it points to the use of normative data for DBS surgical planning. Neurosurgeons have moved away from normative atlases and embraced the evolution of structural MRI in stereotactic surgery (allowing direct targeting); more recently tractographic methods are being investigated for direct targeting [12,23]. Whatever the imaging technology, surgical targeting and planning are based on imaging from the individual who is undergoing surgery. The normative aggregated large cohort data approach recently offered by Horn et al. to the DBS field [16,17] can be very useful when exploring group data, but becomes problematic when it claims to guide DBS surgery in individual patients: the anatomy of large normative cohorts (n) are morphed into a unified space (MNI = Montreal Neurological Institute space) which thereby becomes an atlas, not better and probably even worse than the histological atlases based on the mid-commissural point, “augmented” with normative large cohort connectomic information (e.g. human connectome project [18]). It cannot support conclusions on where an effective electrode should ideally be placed in individual patients considering normal anatomical variations and potentially disease-related alterations of (white matter) anatomy. It is of note that the scientific field perceives this augmentation with normative data and its aggregation as a step towards individualized target definition for DBS in psychiatric diseases [26]. In a stricter and stereotactic sense, it is not. Even papers using high quality patient individual connectome data to analyze lead location as a function of clinical outcome in the better understood neural pathways involved in tremor are more cautious when considering extrapolation of this approach prospectively in patients [1].

Open source systems such as Lead-DBS [16] are not CE or FDA approved and they are not tools intended and cleared for patient treatment (including both surgical planning and neurological programming) but they can be perceived and used as such. These systems characterize as research tools and are used to aggregate data from different sources (and in part from undisclosed, often changing libraries) to analyze and draw conclusions on “optimal”

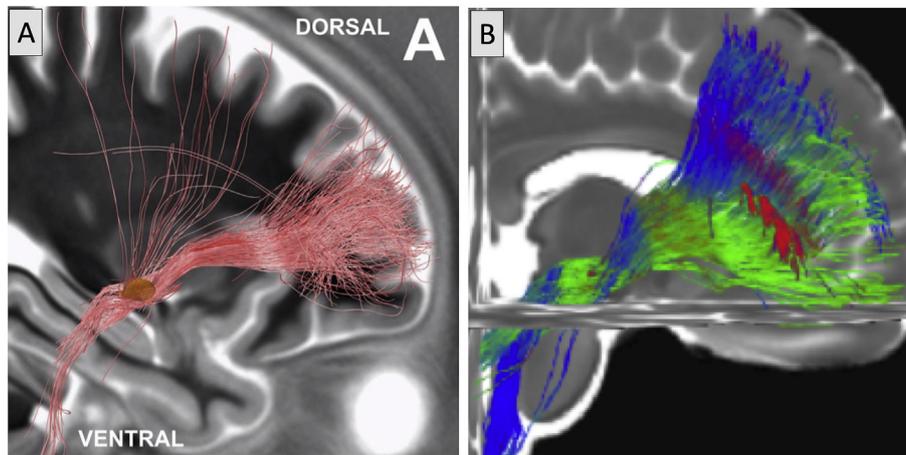


Fig. 1. MFB. A, cropped image from Li et al. showing the “tract target” atlas. B, taken from Ref. [9], showing the sIMFB.

electrode positions, and by this, on targeting. While this is stated in disclaimers, the message is that new generations of DBS clinician-scientists are offered the use of normative information to place electrodes and “test” new targets which they perceive as reality. Although in our opinion it can be useful to work with normative data for pure analysis, it is problematic if normative information is to be used for targeting in a real patient who is not part of the analyzed cohort (*the n + 1 patient*). The use of aggregated patient cohorts is an alternative [1] that can inform targeting that must be based on individual imaging [21]. Until prospectively acquired data have demonstrated the superiority of targeting on the basis of new forms of normative data (beyond the traditional MCP (=midcommissural point) “libraries”) with regards to safety and clinical outcomes, authors should temper conclusions based on retrospective data collection with respect to the complex clinical-surgical decision process. A better example for trial design is the actual comparison of the two target regions (ALIC, amSTN) in a prospective blinded clinical study with a crossover design and analysis of individual connectomic data, published recently [25]. The reality today remains, that targeting decisions are an amalgamation of direct imaging of visualized structures, implicit or explicit use of normative data, possible intraoperative testing in the awake patient, and immediate postoperative imaging for confirmation of lead location and targeting accuracy.

The scientific community should also be alerted to the proliferation of preprint publishing sites. Websites that present unreviewed data include *the bioRxiv service*, the “Lead-DBS” homepage (linked), Research gate and other social media, as well as open digital libraries [16] that in the future might contain normatively derived brain structures.

The bioRxiv homepage states: “Before formal publication in a scholarly journal, scientific and medical articles are traditionally “peer reviewed.” [...] “Readers should therefore be aware that articles on bioRxiv have not been finalized by authors, might contain errors, and report information that has not yet been accepted or endorsed in any way by the scientific or medical community.” [for full statement cf: Anonymous (2019) <https://www.biorxiv.org/content/what-unrefereed-preprint>, assessed 26 april 2019].

It is not always easy to differentiate a self-published and unreviewed preprint from an already reviewed and accepted manuscript preprint. However, this form of unreviewed preprint publishing obviously is in concordance with publication politics of at least some Journals. [Anonymous (2017) Preprints under review. *nature communications*. <https://www.nature.com/articles/s41467-017-00950-5.pdf> (accessed online 26 april 2019)].

Understanding the nature of preprint data publishing is important for the evaluation of scientific data and the above-mentioned disclaimer is helpful. Moreover, in this instance there is a potentially dangerous combination where unreviewed scientific data are made available to the DBS community, open for uncritical use in uncontrolled and unregulated open source planning and visualization environments [16].

Li et al. state: [...] “Finally, we show that most if not all literature-defined DBS targets that were used to treat OCD in the past fall along the tract-target identified in the present study”. [18] This pathway has previously been published as a target for DBS in major depression [23] and OCD [9,19]. It was anatomically characterized [3,7,8,10,11,22,27] (Fig. 1, right) together with a scientific framework, including its relation to other target regions for OCD and major depression (ALIC, NAC= Nucleus Accumbens, amSTN) [9–11,24] (Fig. 2). More than 50 patients have already undergone DBS to this fiber pathway using individual connectomic imaging for targeting across both indications and 30 patients are already published [6,13,23].

For OCD we fear that a potential next step will be: The pathway in question will live in a digital open source library [16] as a “tract target” atlas (in MNI space) and might be used for individual targeting. Recent literature [4,6,12–14,23] is suggestive of a potential (and plausible) superiority of exclusive direct imaging as an individualized targeting rationale. With respect to this literature it is important to remember that the approaches mentioned by Li et al. [18] have never been contrasted in a direct prospective comparison format. While retrospective analysis (including the use of normative data) can inform future research directions, surgical decision making in centers around the world still remains a non-standardized and expertise-driven affair. Until robust data to the contrary becomes available, anatomical information (structural and connectivity data) used for stereotactic surgery should be individual, identified in a scientific and anatomical framework, personalized and of determined accuracy, with full understanding of the pitfalls and limitations of the technique [2,28]. As scientific information can now be widely available in fully un-reviewed formats over preprint servers, social media and free digital libraries, scientists should be cautious with such publication strategies since these may result in inappropriate use of their un-reviewed data. This is especially important in the field of medicine and even more so in surgical decision-making.

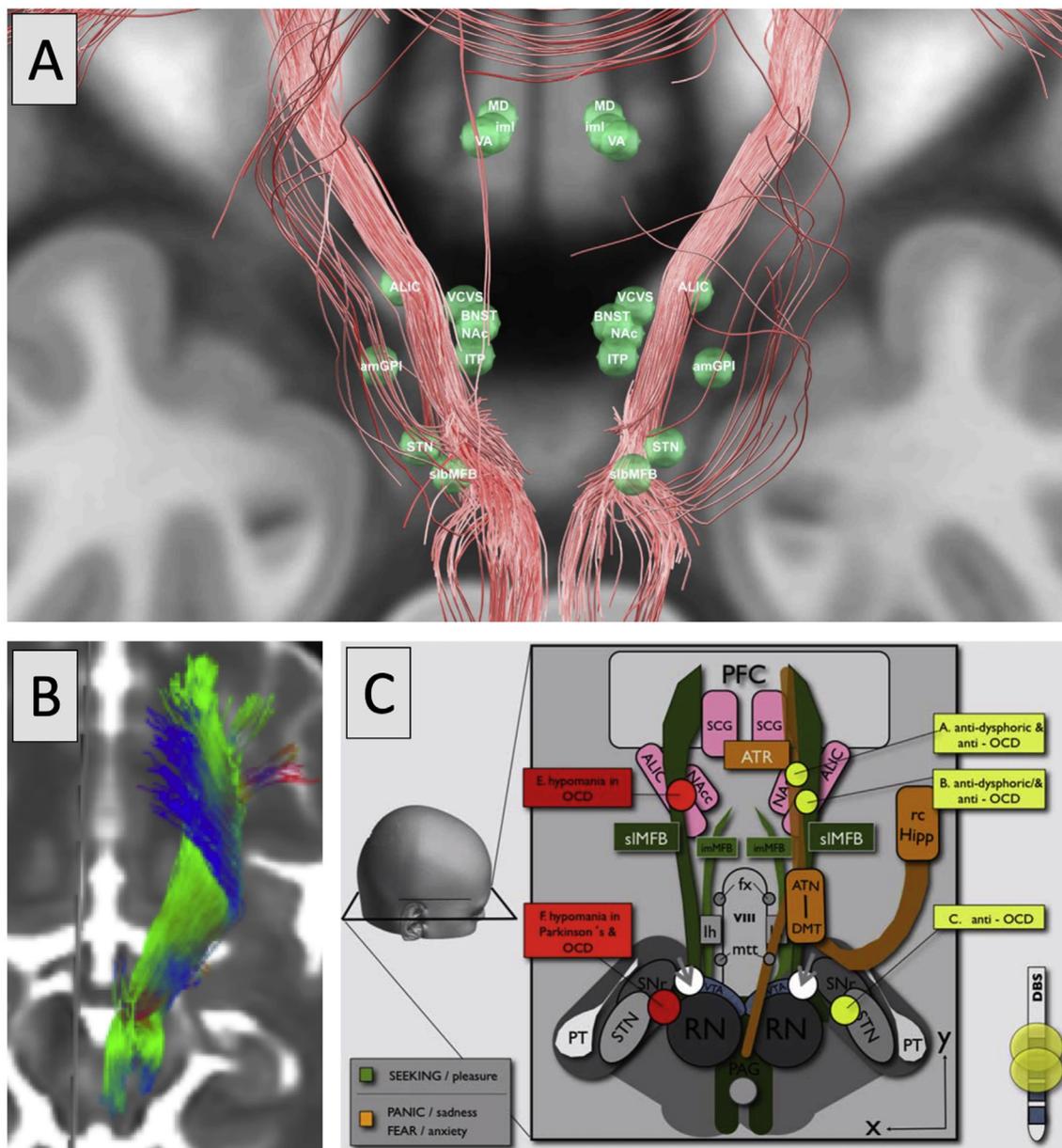


Fig. 2. A, Surgical targets related to the “tract target” taken from Li et al. [18]. B, the sIMFB taken from Ref. [11]. C, surgical targets for OCD (yellow) related to the sIMFB (dark green) taken from Ref. [9]. The anterior thalamic radiation (ATR, orange) which runs parallel to sIMFB in ALIC might in part explain the diverging results from the previous publication [5].

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Center for Basics in Neuromodulation, Freiburg University, Germany

Thomas E. Schlaepfer

Department of Interventional Biological Psychiatry, Freiburg University Medical Center, Medical Faculty of Freiburg University, Germany

Balint Varkuti

Cortics, Munich, Germany

P. Rick Schuurman

Amsterdam UMC, University of Amsterdam, Department of Neurosurgery, Amsterdam Neuroscience, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands

Peter C. Reinacher

Department of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Medical Faculty of Freiburg University, Germany

Juergen Voges

Department of Stereotactic Neurosurgery, Otto von Guericke University, Magdeburg, Germany

Ludvic Zrinzo

Functional Neurosurgery Unit, UCL Queen Square Institute of Neurology, London, UK

Patric Blomstedt

Department of Clinical Neuroscience, University Hospital, 90185, Umeå, Sweden

Albert J. Fenoy

Department of Neurosurgery, McGovern Medical School, University of Texas, Houston, USA

Marwan Hariz

Department of Clinical Neuroscience, University Hospital, 90185, Umeå, Sweden

* Corresponding author.

E-mail address: volker.coenen@uniklinik-freiburg.de (V.A. Coenen).

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Volker A. Coenen*

Department of Stereotactic and Functional Neurosurgery, Freiburg University Medical Center, Medical Faculty of Freiburg University, Germany