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DISSERTATION

**Vergleich individueller und normativer Konnektivitätsprofile im  
Rahmen der Tiefen Hirnstimulation**

**Comparison of patient-specific and normative connectivity  
profiles in deep brain stimulation**

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**Abstract:**

**Objective:** Brain connectivity profiles seeding from deep brain stimulation (DBS) electrodes have emerged as informative tools to estimate outcome variability across DBS patients. Given the limitations of acquiring and processing patient-specific diffusion-weighted imaging data, a number of studies have employed normative atlases of the human connectome. To date, it remains unclear whether patient-specific connectivity information would strengthen the accuracy of such analyses. Here, we compared similarities and differences between patient-specific, disease-matched and normative structural connectivity data and estimated the clinical improvement that they may generate.

**Methods:** Data from 33 patients suffering from Parkinson's disease who underwent surgery at three different centers were retrospectively collected. Stimulation-dependent connectivity profiles seeding from active contacts were estimated using three modalities, namely, either patient-specific diffusion-MRI data, disease-matched or normative group connectome data (acquired in healthy young subjects). Based on these profiles, models of optimal connectivity were constructed and used to estimate the clinical improvement in out-of-sample data.

**Results:** All three modalities resulted in highly similar optimal connectivity profiles that could largely reproduce findings from prior research based on a novel multicenter cohort. In a data-driven approach that estimated optimal whole-brain connectivity profiles, out-of-sample predictions of clinical improvements were calculated. Using either patient-specific connectivity ( $R = 0.43$  at  $p = 0.001$ ), an age- and disease-matched group connectome ( $R = 0.25$ ,  $p = 0.048$ ) or a normative connectome based on healthy/young subjects ( $R = 0.31$  at  $p = 0.028$ ), significant predictions could be made, and the underlying optimal connectivity profiles were highly similar.

**Conclusion:** Our results of patient-specific connectivity and normative connectomes lead to similar main conclusions about which brain areas are associated with clinical improvement. Nevertheless, although the results were not significantly different, they hint at the fact that patient-specific connectivity has potential for estimating slightly more variance when compared to group connectomes. Furthermore, the use of

normative connectomes involves datasets with high signal-to-noise acquired on specialized MRI hardware, while clinical datasets such as the ones used here may not exactly match their quality. Our findings support the role of DBS electrode connectivity profiles as a promising method to investigate DBS effects and to potentially guide DBS programming.



## Zusammenfassung

**Zielsetzung:** Konnektivitätsprofile des Gehirns, die von Elektroden zur Tiefenhirnstimulation (THS) ausgehen, haben sich als informativ für die Schätzung von Variabilität im Behandlungserfolg bei THS-PatientInnen erwiesen. Angesichts von Einschränkungen bei der Erhebung und Verarbeitung patientenspezifischer, diffusionsgewichteter Bilddaten wurden in einer Reihe von Studien normative Atlanten des menschlichen Konnektivitätsprofils verwendet. Bis heute ist unklar, ob patientenspezifische Konnektivitätsinformation die Genauigkeit solcher Analysen verbessern würde. Ziel dieser Studie war der Vergleich zwischen Ähnlichkeiten und Unterschieden patientenspezifischer, krankheits-gematchter und normativer, struktureller Konnektivitätsdaten, sowie der Fähigkeit dieser Methoden zur Vorhersage eines etwaigen klinischen Behandlungserfolges.

**Methoden:** Die Analysen basierten auf retrospektiven Daten von 33 Parkinson-PatientInnen, welche an drei verschiedenen Zentren operiert worden waren. Stimulationsabhängige Konnektivitätsprofile mit Ursprung in aktiven DBS-Kontakten wurden mittels der drei Modalitäten geschätzt, also entweder basierend auf patientenspezifischen, diffusionsgewichteten MRT-Daten, oder auf krankheits-gematchten sowie auf normativen Gruppenkonnektivitätsdaten (erhoben an gesunden, jungen ProbandInnen). Auf Grundlage dieser Profile wurden Modelle optimaler Konnektivität konstruiert und zur Schätzung des klinischen Behandlungserfolges in unabhängigen Daten herangezogen.

**Ergebnisse:** Alle drei Modalitäten führten zu sehr ähnlichen optimalen Konnektivitätsprofilen, mit Hilfe derer sich auf Grundlage einer neuartigen multizentrischen Kohorte vorherige Forschungsbefunde weitgehend reproduzieren ließen. In einem datengesteuerten Ansatz, bei dem optimale Konnektivitätsprofile über das gesamte Gehirn hinweg geschätzt wurden, wurden Vorhersagen über den klinischen Behandlungserfolg in unabhängigen Daten berechnet. Unter Verwendung entweder der patientenspezifischen Konnektivität ( $R = 0,43$  bei  $p = 0,001$ ), eines alters- und krankheits-gematchten Gruppenkonnektivitätsprofils ( $R = 0,25$ ,  $p = 0,048$ ) oder eines normativen Konnektivitätsprofils basierend auf Daten gesunder/junger ProbandInnen ( $R = 0,31$  bei  $p = 0,028$ ) konnten signifikante Vorhersagen getroffen

werden, wobei die zugrunde liegenden optimalen Konnektivitätsprofile große Ähnlichkeit aufwiesen.

**Schlussfolgerung:** Unsere Ergebnisse, welche patientenspezifische sowie normative Konnektivitätsprofile einbeziehen, führen zu ähnlichen Hauptschlussfolgerungen darüber, welche Hirnareale mit klinischem Behandlungserfolg assoziiert sind. Obwohl sich die Ergebnisse nicht signifikant unterscheiden, deuten sie dennoch darauf hin, dass patientenspezifische Konnektivität über Potenzial zur Schätzung geringfügig höherer Varianz im Vergleich zu gruppenbasierten Konnektivitätsprofilen verfügt. Darüber hinaus stützen sich Analysen, welche auf normativen Konnektivitätsprofile basieren, auf Datensätze mit hohem Signal-Rausch-Verhältnis, welche durch spezialisierte MRT-Technologie erfasst wurden, während klinische Datensätze, wie sie auch in dieser Studie herangezogen wurden, diesen an Qualität möglicherweise nicht gleichkommen. Unsere Befunde stützen die Rolle von Konnektivitätsprofilen, welche von THS-Elektroden ausgehen, als eine vielversprechende Methode zur Untersuchung von THS-Effekten und möglicherweise zur Verbesserung der THS-Programmierung.

## List of Abbreviations

DBS	Deep brain stimulation
PD	Parkinson's disease
STN	Subthalamic Nucleus;
MRI	Magnetic Resonance Imaging.
dMRI	diffusion-weighted Magnetic Resonance Imaging
SMA	Supplementary motor area
pre-SMA	pre-Supplementary Motor Area
M1	Primary motor cortex
PFC	Prefrontal cortex
LEDD	L-dopa equivalent dose
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III
TR	Repetition time
TE	Echo time
ANTs	Advanced Normalization Tools
CT	Computed tomography
VTA	Volumes of tissue activated
HCP	Human Connectome Project
PPMI	Parkinson's Progression Markers Initiative
DWI	Diffusion weighted imaging

## **1 Introduction:**

### **1.1 Deep brain stimulation in Parkinson's disease**

Parkinson's disease is the second most common neurodegenerative disorder and it involves multiple motor and nonmotor neural circuits in the basal ganglia<sup>1,2,3</sup>. Normally, patients have a good response to medications at an early stage. However, medication-related complications develop in a majority of patients, usually 5 years later<sup>4</sup>. Deep brain stimulation (DBS) is one of the most effective treatments for advanced Parkinson's disease, alleviating motor symptoms and improving quality of life<sup>5,6</sup>. DBS does not only exert focal stimulation of specific brain nuclei (i.e., at the subthalamic nucleus; STN) but also modulates distributed basal-ganglia cortical cerebellar networks<sup>7,8,9,10,11,12,13</sup>. The impact of DBS on pathological networks has been highlighted in PD<sup>7,10,11</sup> as well as other diseases such as essential tremor<sup>14</sup>, dystonia<sup>15</sup> and obsessive-compulsive disorder<sup>16,17</sup>.

### **1.2 Patient-specific connectivity in deep brain stimulation**

Preoperative diffusion-weighted imaging (dMRI) has been used to explore the structural connectivity of DBS in previous studies<sup>18,19</sup>. Structural connectivity patterns of clinically beneficial DBS electrodes were assessed in PD patients. Specifically, modulation of white matter tracts directed to the superior frontal gyrus and the thalamus was associated with effective DBS outcomes<sup>18</sup>. Similarly, Akram and colleagues investigated the cortical connectivity patterns associated with treatment efficacy based on individual dMRI acquisition<sup>19</sup>. Different cortical connectivity patterns were associated with maximum clinical improvements: tremor control with connectivity to the primary motor cortex (M1), bradykinesia with the supplementary motor area (SMA) and rigidity to both the prefrontal cortex (PFC) and SMA. However, a practical limitation of using individual dMRI is small cohort sizes, high cost and nonstraightforward pooling across centers due to inconsistencies in MR acquisition protocols, which leads to the use of individual brain connectivity measures not being feasible. Considering the limited numbers of patients who undergo surgery worldwide, the limitation of dMRI is particularly obvious in dystonia

that is treated with nontraditional targets (for example, the STN)<sup>20,21</sup> and in new indications such as Alzheimer's disease<sup>22,23</sup> or psychiatric indications<sup>24,25</sup>.

### **1.3 Normative connectome**

A novel development to overcome this limitation is to use normative connectomes –, i.e., atlases of average brain connectivity developed from large cohorts of subjects<sup>26,27,28,29,30,31</sup>. The advantages of normative connectomes are a high N, the acquisition with specialized MRI hardware and, as a result, a better definition of the wiring diagram of the brain<sup>32</sup>. A previous article demonstrated the feasibility in the field of DBS by estimating functional and structural connectivity profiles of the ventral intermediate nucleus of the thalamus<sup>33</sup>. A second study estimated the optimal structural and functional connectivity profiles for STN-DBS<sup>9</sup>. Specifically, a connectivity fingerprint of effective DBS electrodes was estimated by the correlation between the structural and functional connectivity after DBS and UPDRS-III changes across patients. Next, the connectivity profiles from another independent cohort were calculated and then used to obtain the similarity between this connectivity and the optimal fingerprint. The degree of similarity was used to estimate the variability in clinical improvement. This concept has since been widely applied to explore connectivity associated with clinical or behavioral changes in multiple diseases<sup>14,16,34,17,35,36,37,38</sup>. However, one main limitation of the approach is that connectivity data taken from connectome atlases can never represent individual differences in connectivity profiles from the actual DBS patients of the study. With the increasing use of the normative connectome, it is necessary to directly compare the connectivity profiles achieved by patient-specific dMRI with those obtained when using normative connectivity data.

### **1.4 The aim of this study**

The main goal of this study was to explore the specific similarities and differences between patient-specific connectivity and normative connectome information when seeding from DBS electrodes to the rest of the brain. To achieve this aim, three main steps were performed. First, based on individual diffusion imaging acquisition scanned from each individual patient undergoing STN-DBS, individual structural connectivity was estimated. Second, we substituted these data with either a disease-

and age-matched group connectome or a normative connectome acquired from young healthy subjects. Third, we compared the amount of variance in clinical improvements that could be estimated by using individualized DTI data versus either of the two group connectome atlases that were based on either healthy subjects or PD patients.

## **2 Materials and methods**

### **2.1 Patient cohorts and imaging**

Thirty-three DBS patients from 3 different DBS centers (Center 1 (London): N = 17, Center 2 (Mainz): N = 12, Center 3 (New York): N = 4) were included in this retrospective study. The patient demographics are summarized in Table 1.

All patients underwent stereotactic DBS surgery for the treatment of PD and received bilateral DBS electrodes (Table 1). Clinical variables, including age, sex, disease duration before surgery, and L-dopa equivalent dose (LEDD) at baseline, were recorded. Clinical improvement was measured by comparing Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) scores OFF medication preoperatively (baseline) and postoperatively ON DBS OFF medication. This study was approved by the local ethics committee of the Charité, University Medicine Berlin (master vote EA2/186/18). The study in London received ethical approval from the West London NHS Research Ethics Committee (10/H0706/68). At Columbia and Mainz University, all procedures were also approved by the local Institutional Review Board.

### **2.2 Preoperative diffusion MRI acquisition and tractography**

Preoperative diffusion MRI acquisition came from the above 3 centers. For the London and New York cohorts, the diffusion data were preprocessed, including topup and Eddy (FSL v5.0), as implemented in FSL<sup>39,40</sup>. In the Mainz cohort, only Eddy was applied. Tractography was performed using the generalized Q-sampling imaging method<sup>41</sup> as implemented in DSI studio (<http://dsi-studio.labsolver.org>) using the default parameter sets implemented in Lead-Connectome<sup>27</sup>.

### **2.3 Localization of DBS electrodes and VTA estimation**

DBS electrodes were localized using the Lead-DBS toolbox (<https://www.lead-dbs.org/>; <sup>42</sup>) in the current form (version 2.2.3,<sup>10</sup>) using PaCER<sup>43</sup> or the TRAC/CORE approach <sup>42</sup> for either postoperative CT or MRI, respectively. Based on the long-term DBS settings, volumes of tissue activated (VTA) were estimated using a finite element method (FEM)-based model as implemented in Lead-DBS (Horn et al., 2019). This model estimates the E-field on a tetrahedral four-compartment mesh including gray & white matter, electrode contacts, and insulating parts.

### **2.4 Structural connectivity and optimal model estimation**

Whole-brain structural connectivity profiles seeding from the bilateral VTA for each patient were calculated using patient-specific dMRI data, a disease- and age-matched connectome estimated based on a cohort of 85 Parkinson's disease patients acquired within the Parkinson's Progression Markers Initiative ([www.ppmi-info.org](http://www.ppmi-info.org),<sup>29</sup>), and a state-of-the-art multishell dMRI dataset based on 32 healthy young subjects within the Human Connectome Project at Massachusetts General Hospital (<https://ida.loni.usc.edu/login.jsp>,<sup>44</sup>). Then, structural connectivity maps (based on either patient specific, age- and disease-matched or young/healthy data) seeded from the bilateral VTA were Spearman rank-correlated with %-UPDRS-III change across patients in a voxelwise fashion, which led to a map that showed positive or negative associations with UPDRS-III improvements (henceforth referred to as *R-maps*).

### **2.5 Estimating improvement in out-of-sample patients**

To estimate the DBS outcome in out-of-sample data, spatial correlations between the optimal structural connectivity model (defined by data-driven *R-maps* or a previously published optimal model from<sup>9</sup>) and the VTA-derived structural connectivity profile in each patient were calculated. The resulting similarity indices – again expressed as (spatial) Spearman's rank correlation coefficients – estimate 'how optimal' each connectivity profile was and were used to explain the variability of clinical improvement (%UPDRS-III improvement) in a linear regression model. An overview of the methodology applied is shown in Figure 1 in<sup>45</sup>.

**Table 1:** Patient demographics of the cohorts analyzed

Cohort	No. (female)	Age, [yrs]	Disease Duration, [yrs]	UPDRS-III baseline, OFF medication	LEDD Reduction [%]	Clinical Assessment	UPDRS-III postop, OFF medication	Preop Imaging	dMRI resolution	Postop Imaging	Registration Modalities	Electrode type
Center 1	17(4)	59.9±2.3	11±1.1	50.5±4.3	60±4.1	On vs. OFF one year postop	27±3	T1, T2, PD*, R1, R2*, MT	1.5×1.5×1.5	MRI	T1, T2, PD*, R1, R2*, MT,	3389 Medtronic
Center 2	12(3)	66.7±2.4	15.7±1.1	34.1±2.2	64.7±6.2	On vs. OFF 6 months postop	14.9±1.8	T1, T2	2×2×2	MRI	T1, T2,	3389 Medtronic
Center 3	4 (0)	59±3.7	12.3±1.3	31±1.9	58±18.2	On vs. OFF 2.5-7 months postop	13.8±3.2	T1, T2	1.88×1.88×2.5	MRI, CT	T1, T2,	3387, 6179, Boston Sci Vercise 8 contact linear

PD\*, effective proton density; R1, 1 mm high-resolution maps of the longitudinal relaxation rate ( $R1 = 1/T1$ ); R2\*, effective transverse relaxation rate ( $R2^* = 1/T2^*$ ); MT, magnetization transfer saturation

### 3 Results

In the current study, 33 patients were from 3 independent centers (7 women, mean age  $62.5 \pm 1.6$  years). The disease duration in the entire sample was  $12.9 \pm 0.8$  years. The reduction in LEDD from baseline to post-DBS on average was  $61.5 \pm 3.6\%$ . The preoperative UPDRS-III score was  $42.0 \pm 2.8$  compared to a postoperative score of  $28.1 \pm 2.1$  points. LEDD reduction and UPDRS-III improvements were not significantly different across the three datasets ( $p > 0.05$  for both variables). Patient demographics of the cohorts analyzed are shown in Table 1<sup>45</sup>.

Electrode localization confirmed accurate placement across the three cohorts (Fig. 2 and Fig. S1 in<sup>45</sup>). The special relationships of active electrode contacts and STN are shown in S4 in<sup>45</sup>. A total of 57 contacts were inside, 8 at the border region and 4 outside the STN. Structural connectivity profiles based on three connectomes from two patient cases are shown in Figure 5. For most patients, the fibers were predominantly connected to the sensorimotor strip (M1, SMA or pre-SMA). However, in a few patients, the patient-individual structural connectivity estimates differed (Fig. 3 in<sup>45</sup>).



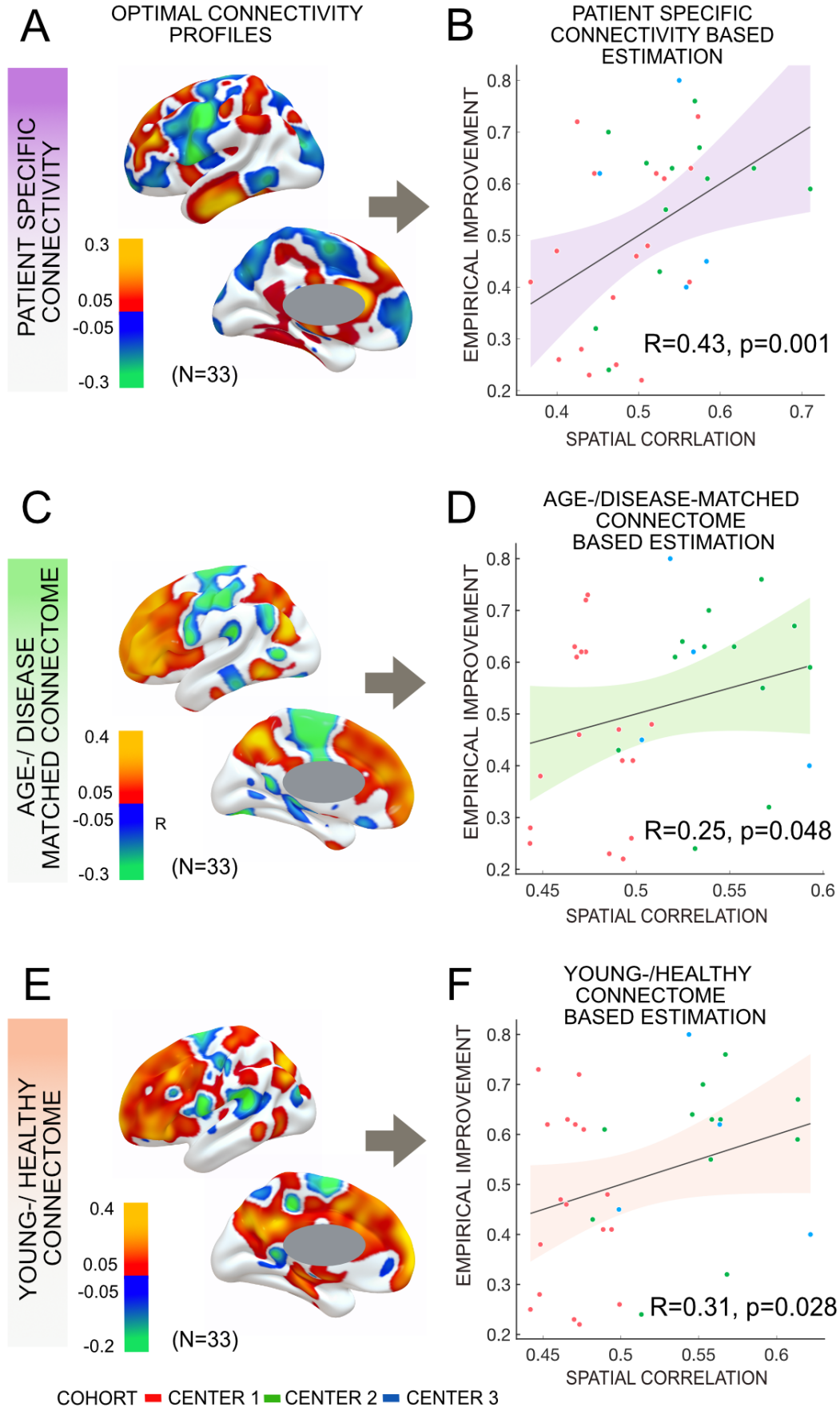
Correlations between connectivity metrics across the group of patients were high for apical cortical regions but lower for more frontal regions (see Fig. S4 and Fig. S5 in <sup>45</sup>). The specific correlations between patient-specific and age-/disease-matched connectivity and young-/healthy and age-/disease-matched connectivity are shown in Table 2 in <sup>45</sup>.

One previous optimal connectivity model (defined by 95 patients) in Horn et al. 2017 was used to predict clinical outcome based on patient-specific connectivity (Fig. 4 in <sup>45</sup>;  $R = 0.28$ ,  $p = 0.045$ ), the age- and disease-matched connectome ( $R = 0.30$ ,  $p = 0.031$ ) or the young/healthy connectome ( $R = 0.33$ ,  $p = 0.021$ ). Furthermore, data-driven optimal connectivity maps (R-maps) were estimated using individual dMRI, the age-/disease-matched connectome or the young-/healthy connectome.

Using either metric, connectivity to the primary motor cortex (M1) and primary somatosensory cortex (S1) was associated with worsening of motor symptoms, whereas connectivity to the pre-SMA, anterior cingulate and medial frontal cortices was associated with symptom improvement (Fig. 1). All three metrics, i.e., patient-specific connectivity ( $R = 0.43$ ; 95% CI = 0.1, 0.68;  $p = 0.001$ ), age-/disease-matched connectome ( $R = 0.25$ ; 95% CI = -0.09, 0.55;  $p = 0.048$ ) and healthy-/young connectome ( $R = 0.31$ ; 95% CI = -0.03, 0.59;  $p = 0.028$ ) could account for a significant part of the variance in clinical outcome in a leave-one-out design (Fig. 1). Based on the above results, 6-18% of the variance in clinical outcomes could be explained by out-of-sample data.

Correlations derived from either metric were not significantly different from each other in head-to-head comparisons based on a Fisher r-to-z transformation ( $p > 0.4$  for all comparisons). Furthermore, cross-estimates between metrics were worse and not significant, i.e., when the R-map was based on a group connectome, structural connectivity maps were based on patient-specific structural connectivity or vice versa (Fig. 6 in <sup>45</sup>). This may underline the importance of consistency in the choice of metric when performing such dMRI-based connectivity analyses.

## LEAVE-ONE-PATIENT-OUT CROSS VALIDATION



**Figure 1:** Structural connectivity (patient-specific connectome, age-/disease-matched and healthy-/young) estimated change in UPDRS-III score using a leave-one-patient-out model ( $N = 33$ )<sup>45</sup>. The optimal structural connectivity model generated with the patient-specific connectome (A), age-/disease-matched connectome (C) and young-/healthy connectome (E) effectively estimated patient improvement based on the respective connectome (B, D, F). Slightly more variance was estimated from the patient-specific connectivity model than from the other two metrics. Please note that the values shown on the R-maps are not necessarily significant since mass-univariate tests were applied. Rather, the spatial profile of these maps was used to make predictions for out-of-sample data, which were then tested for significance.

## **4 Discussion:**

### **4.1 Normative group connectomes vs. patient-specific connectivity**

Recent studies have introduced and validated the normative connectome for motor improvement<sup>9,37</sup>, change in depression<sup>36</sup>, behavioral effects including movement speed<sup>35</sup> and motor learning<sup>34</sup> within the DBS context, as well as side effects such as DBS-induced seizures<sup>46</sup>, weight-changes<sup>47</sup> and panic attacks<sup>48</sup>. This method was also used in DBS for essential tremor<sup>14</sup>, obsessive-compulsive disorder<sup>16,17</sup> and epilepsy<sup>49</sup>. However, there is a lack of research directly comparing the use of the normative connectome and patient-specific connectivity.

In the current study, we directly compared the similarity and difference of patient-specific connectivity estimates to those derived from group connectomes (which were either age-/disease-matched or were even acquired in a young-/healthy cohort). Our optimal connectivity profiles, which followed the same overall distribution irrespective of the applied connectivity metric, show that structural connectivity with M1 was negatively associated with optimal improvement, while more frontal regions (such as SMA, pre-SMA and dorsomedial PFC) were positively associated. Using either method, connectivity profiles were able to estimate the variability in clinical improvement in a leave-one-out design. Furthermore, a previous optimal model could estimate the outcome using either method, which suggests that optimal profiles could potentially be learned based on large cohorts (and even using normative connectomes) and still be applied to patient-specific data. This is crucial since it is complicated to obtain diffusion-weighted imaging data from large cohorts of DBS patients, particularly some DBS cohorts from patients suffering from Alzheimer's disease stimulated with fornicals within the ADvance trials<sup>50</sup> or rare diseases such as Tourette's syndrome<sup>38</sup> or STN-DBS datasets for the treatment of cervical dystonia<sup>20</sup>.

### **4.2 The case for using brain connectivity to investigate STN-DBS**

Previous studies have found significant relationships between electrode placements and clinical outcomes, without the need to add connectivity information. Specifically, there are significant correlations between coordinate proximity to the dorsolateral

STN and clinical improvements<sup>19,51,52</sup>. While the variance in clinical outcomes is explained by such coordinate-based approaches, investigating connectomic mapping could add more information within the DBS context.

First, brain connectivity may provide insights into the potential mechanism of DBS. The concept that strong connectivity to M1 is counterproductive for optimal outcomes but more frontal connections seem favorable qualitatively goes beyond knowledge of an optimal sweet spot in the STN. Second, individual patient-specific connectivity may differ from the norm and could help identify patient-specific DBS targets<sup>53</sup>. In essential tremor, where clear associations between clinical outcomes and specific structural bundles (the dentatothalamic tract) have been established, this concept has already become clinical practice<sup>54</sup> and has been methodically explored using functional MRI<sup>55</sup>. Third, modulation networks of side effects by DBS could be identified as well. In essential tremor, Al-Fatly and colleagues similarly defined networks that were associated with the occurrence of side effects such as ataxia and dysarthria<sup>14</sup>. Finally, considering that the same networks across 14 diseases seem to be modulated by both invasive and noninvasive neuromodulation, connectivity profiles could be the bridge between the two modulation approaches<sup>56</sup>.

#### **4.3 Pros and Cons of normative vs. patient-specific connectivity data**

In previous studies, network targets based on the normative connectome have been widely investigated<sup>19,14,16,57,58,9,59,60</sup>. It has the advantage of large subject numbers, excellent signal-to-noise ratios, and acquisition using unique high-power MRI scanners specifically designed for connectivity imaging. For instance, a 200  $\mu\text{m}$  isotropic postmortem scan of the brainstem acquired at 7T was applied to resolve the Wernekinck decussation of the dentatothalamic tract<sup>57</sup>. Weigand et al. applied functional imaging data averaged across 1000 subjects, leading to a high signal-to-noise ratio<sup>61</sup>. The structural connectome used in Horn et al. was acquired on a customized Siemens 3T Connectome scanner with multishell diffusion-encoding gradients and b-values reaching up to 10,000<sup>44</sup>. Clinically approved 7T systems may offer novel opportunities for preoperative imaging in the near future.

Acquiring connectivity data from each patient provides the best sensitivity for individual differences but has poor signal-to-noise and test-retest reliability. This was

demonstrated in a study by Petersen and colleagues in which the same subject was scanned ten times. In each, the peak of connectivity to motor/premotor cortices was identified within the STN. Distances across peaks were 0.5–1 mm on average<sup>60</sup>. In addition, Jakab et al.<sup>62</sup> used connectivity data to create thalamic subparcellations that are relevant for DBS surgery (such as the ventral intermediate nucleus). The variability of these targets introduced by the choice of MRI hardware was similar to or higher than the intersubject variability.

Given that patient-specific connectivity provides the best sensitivity for individual differences, it is necessary to reach the ultimate goal of deriving personalized deep brain stimulation. One answer would be to scan patients repeatedly and to quantify test-retest reliability. Currently, openly available datasets could be used to investigate the test-retest reliability of individualized subjects. For example, 45 of the 1200 human connectome project participants were scanned twice to allow for quantification of retest error<sup>63</sup>. Similar data would be needed in patients who will undergo DBS in the near future, particularly image data scanned using state-of-the-art methods or 7T systems. In the future, as new methods for direct dMRI registrations, the quality and speed of patient-specific dMRI sequences will improve, and the indication or need for group average templates may be challenged.

## **5 Conclusions**

Our study analyzed optimal connectivity profiles seeding from STN-DBS electrodes based on patient-specific vs. group-level structural connectivity profiles. We demonstrated that on a group level, the results from individualized, age- and disease-matched connectomes and healthy/young connectomes are comparable but not completely interchangeable. Although the differences were not significant, the results suggest that individualized structural connectivity has the potential to estimate clinical outcomes following STN-DBS slightly more accurately. Nevertheless, the use of normative connectomes seems sensible in cases where individualized connectivity data are lacking.

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## Statutory Declaration

“I, Qiang Wang, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Comparison of patient-specific and normative connectivity profiles in deep brain stimulation”, ” Vergleich individueller und normativer Konnektivitätsprofile im Rahmen der Tiefen Hirnstimulation” independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; [www.icmje.org](http://www.icmje.org)) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date

Signature

## **Declaration of personal contributions to co-authored publications**

Qiang Wang had the following share in the following publication:

**Publication I:** Wang, Qiang, Harith Akram, Muthuraman Muthuraman, Gabriel Gonzalez-Escamilla, Sameer A. Sheth, Simón Oxenford, Fang-Cheng Yeh, Sergiu Groppa, Nora Vanegas-Arroyave, Ludvic Zrinzo, Ningfei Li, Andrea Kühn, and Andreas Horn. 2020. "Normative vs. Patient-Specific Brain Connectivity in Deep Brain Stimulation." *NeuroImage*, August, 117307. (IF=5.902)  
<https://doi.org/10.1016/j.neuroimage.2020.117307>.

Contribution in detail:

The main focus of this publication was the comparison of the similarity and difference of patient-specific and normative connectivity profiles in deep brain stimulation. I participated the development of the concept and conducted all the data analysis including DWI data preprocessing and tractography, the electrode localization, linear /non-linear co-registration, normalization, the estimation of connectivity profiles and optimal model, as well as the prediction of outcome.

I manually created the workflow figure (Fig.1), electrode localization figure (Fig.2) and two example of connectivity visualization figure (Fig.3). Based on of my statistical evaluation, I create validation of optimal connectivity profile figure (Fig.4), the optimal models and prediction results figure (Fig.5) and cross-perdition results figure (Fig.6). In addition, I designed the table 1 to analyze the demographic of cohort and table 2 showed correlations between connectivity metrics. Furthermore, I conducted all supplementary information, including Table S1, Table S2 and Figure S1 to S7 in publication.

Finally, I wrote the original draft, and did all the new analysis based on reviewer comments and suggestions, including nonlinear co-registration, head motion correction, outliner analysis and edit the published manuscript.



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Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

## Publication 1:

### Normative vs. Patient-Specific Brain Connectivity in Deep Brain Stimulation

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12	STEREOTACTIC AND FUNCTIONAL NEUROSURGERY	1,807	1.905	0.002220
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14	KLINISCHE NEUROPHYSIOLOGIE	40	0.325	0.000030

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## Normative vs. patient-specific brain connectivity in deep brain stimulation



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### ABSTRACT

Brain connectivity profiles seeding from deep brain stimulation (DBS) electrodes have emerged as informative tools to estimate outcome variability across DBS patients. Given the limitations of acquiring and processing patient-specific diffusion-weighted imaging data, a number of studies have employed normative atlases of the human connectome. To date, it remains unclear whether patient-specific connectivity information would strengthen the accuracy of such analyses. Here, we compared similarities and differences between patient-specific, disease-matched and normative structural connectivity data and their ability to predict clinical improvement.

Data from 33 patients suffering from Parkinson's Disease who underwent surgery at three different centers were retrospectively collected. Stimulation-dependent connectivity profiles seeding from active contacts were estimated using three modalities, namely patient-specific diffusion-MRI data, age- and disease-matched or normative group connectome data (acquired in healthy young subjects). Based on these profiles, models of optimal connectivity were calculated and used to estimate clinical improvement in out of sample data.

All three modalities resulted in highly similar optimal connectivity profiles that could largely reproduce findings from prior research based on this present novel multi-center cohort. In a data-driven approach that estimated optimal whole-brain connectivity profiles, out-of-sample predictions of clinical improvements were calculated. Using either patient-specific connectivity ( $R = 0.43$  at  $p = 0.001$ ), an age- and disease-matched group connectome ( $R = 0.25$ ,  $p = 0.048$ ) and a normative connectome based on healthy/young subjects ( $R = 0.31$  at  $p = 0.028$ ), significant predictions could be made.

Our results of patient-specific connectivity and normative connectomes lead to similar main conclusions about which brain areas are associated with clinical improvement. Still, although results were not significantly different, they hint at the fact that patient-specific connectivity may bear the potential of explaining slightly more variance than group connectomes. Furthermore, use of normative connectomes involves datasets with high signal-to-noise acquired on specialized MRI hardware, while clinical datasets as the ones used here may not exactly match their quality. Our findings support the role of DBS electrode connectivity profiles as a promising method to investigate DBS effects and to potentially guide DBS programming.

### 1. Introduction

Deep brain stimulation (DBS) is a well-established treatment for Parkinson's disease (PD), leading to alleviation of motor symptoms and improvement in quality of life (Deuschl et al., 2006; Schuepbach et al.,

2013). DBS does not only exert focal effects (i.e. on the subthalamic nucleus; STN) but also affects distributed basal-ganglia-cortico-cerebellar networks (Accolla et al., 2016; Helmich et al., 2012; Horn, 2019; Horn et al., 2017b; Kahan et al., 2019; Lozano and Lipsman, 2013; Muthuraman et al., 2018). While the notion that DBS modulates distributed brain networks is certainly not new, we can now apply advanced MRI methods to study this relationship more deliberately, as has been done in PD (Accolla et al., 2016; Horn, 2019; Kahan et al., 2019;

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Treu et al., 2020), Essential Tremor (Al-Fatly et al., 2019), dystonia (Corp et al., 2019) or obsessive-compulsive disorder (Baldermann et al., 2019; Li et al., 2020).

Using preoperative diffusion-weighted imaging (dMRI), Vanegas-Arroyave and colleagues assessed the connectivity patterns of clinically beneficial DBS electrodes in PD patients. Their results suggested that modulation of white matter tracts connecting electrodes to superior frontal gyrus and thalamus were associated with positive clinical improvement (Vanegas-Arroyave et al., 2016). Similarly, Akram and colleagues used preoperatively acquired dMRI to investigate the cortical connectivity patterns associated with treatment efficacy (Akram et al., 2017). Maximal improvement in cardinal motor symptoms was associated with connectivity of DBS electrodes to different cortical regions: tremor control with connectivity to primary motor cortex (M1), bradykinesia with the supplementary motor area (SMA) and rigidity to both prefrontal cortex (PFC) and SMA. These two studies acquired dMRI in each patient preoperatively. While this approach represents the gold-standard of practice, and variability in fibertracts has been shown in the DBS context (Makris et al., 2016), a practical limitation is that resulting cohort sizes will often be small, studies costly and pooling across centers non-straightforward due to data-heterogeneity. Furthermore, preoperative dMRI data is not routinely acquired preoperatively in a large fraction of DBS patients and cannot be acquired postoperatively (without substantial constraints). This is especially relevant in novel indications such as Alzheimer's Disease (Baldermann et al., 2018; Ponce et al., 2016) or psychiatric indications (Hamani et al., 2011; Huys et al., 2019) where limited numbers of patients undergo surgery, even on a world-wide scale. The same applies to "classical diseases" (such as dystonia) that are treated with unconventional targets (such as the STN), again resulting in a low number of available patients, world-wide (Ostrem et al., 2011; Yao et al., 2019).

A potential approach to overcome this limitation is to substitute individualized dMRI data with normative connectomes – i.e. atlases of average brain connectivity calculated from large cohorts of subjects (Ewert et al., 2018; Horn et al., 2014a, 2019; Horn and Blankenburg, 2016; Marek et al., 2011; Thomas Yeo et al., 2011; Yeh et al., 2018; Yeh and Tseng, 2011). A first study that explored this concept investigated functional and structural connectivity profiles of the ventral intermediate nucleus of the thalamus (Horn et al., 2017a). A second study then investigated optimal connectivity profiles for STN-DBS (Horn et al., 2017b). In this study, the optimal connectivity profiles were estimated on one cohort from a first DBS center and used to predict the motor outcome in patients operated at a different DBS center (Horn et al., 2017b). Specifically, structural and functional connectivity between DBS electrodes and other brain regions were correlated with UPDRS-III changes across patients. This resulted in an optimal connectivity 'fingerprint' of effective DBS electrodes. To validate these maps of optimal connectivity, similarity indices between each electrode's connectivity profile from an independent cohort and the 'optimal' fingerprint were calculated. These were then correlated with empirical clinical improvement.

The concept has since been applied to explore connectivity associated with clinical or behavioral changes in multiple diseases (Al-Fatly et al., 2019; Johnson, et al., 2020 Baldermann et al., 2019; de Almeida Marcelino et al., 2019; Li et al., 2020; Neumann et al., 2018; Irmen et al., 2020; Treu et al., 2020). With the increasing popularity of this approach, it is timely to compare results achieved by examining patient-specific connectivity with those obtained using normative connectivity data. One main limitation of the normative connectome approach is that connectivity data taken from atlases will never represent individual differences in connectivity profiles from the actual DBS patients of study. Thus, the use of connectome atlases has clear similarities to the use of other atlases. For instance, histological atlas information was applied to inform DBS for decades (Schaltenbrand G, 1977; Talairach and Tournoux, 1988). Similarly, subcortical atlases – for instance of the STN – have been widely applied to study DBS electrode placement (for an overview see Ewert et al., 2018). However, despite

conceptual similarities to other atlases, some aspects of connectome atlases are novel and require further study.

Here, we have retrospectively analyzed individual connectivity estimates that were based on diffusion imaging data (dMRI) scanned from each individual patient before undergoing STN-DBS surgery. In a second step, we substituted these data with either a disease- and age-matched group connectome acquired in different PD patients or a normative connectome acquired in young/healthy subjects. It should be emphasized that the latter was of superior quality and acquired on specialized MRI hardware (Setsompop et al., 2013) while the age-/disease-matched connectome was of largely comparable quality as patient-specific data. The analysis reproduced workflows that were previously published using normative datasets. Finally, we compared the amount of variance in clinical improvements that could be estimated using individualized dMRI data versus either of the two group connectome atlases. By doing so, we explored the specific similarities and differences between these types of connectivity information when seeding from DBS electrodes to the rest of the brain.

## 2. Materials and methods

### 2.1. Patient cohorts and imaging

Thirty-three DBS patients from 3 different DBS centers (Center 1 (London):  $N = 17$ , Center 2 (Mainz):  $N = 12$ , Center 3 (New York):  $N = 4$ ) were included in this retrospective study. Patient demographics are summarized in Table 1.

All patients underwent stereotactic DBS surgery for treatment of PD and received bilateral DBS electrodes (Table 1). Patients had been enrolled following the standard procedure to screen for eligibility of DBS which excluded structural brain abnormalities or severe psychiatric contraindications. Surgical planning was performed based on MRI imaging and DBS lead localizations were verified by microelectrode recording during surgery and intraoperative macrostimulation for the New York and Mainz centers. Specifically, STN-cells were observed by a team of neurologists while slowly advancing the microelectrodes from 10 mm distance toward the target. Cell activity were manually classified into either no cell activity, cell activity of unknown origin or cell activity clearly attributable to either STN or SNr by one or two expert raters. This information was used to verify the lead or to move to a different trajectory. Postoperative imaging was carried out to verify accurate electrode placement in all cohorts (see below). Specifically, the postoperative imaging parameters were as follow. Center 1: postoperative MRI  $0.39 \times 0.39 \times 2.00$  mm; Center 2: postoperative MRI  $0.83 \times 0.83 \times 0.80$  mm; Center 3: patient #1 postoperative MRI  $0.51 \times 0.51 \times 1.40$  mm, patient #2 postoperative CT  $0.47 \times 0.47 \times 1.25$  mm, patient #3 postoperative CT  $0.46 \times 0.46 \times 1.0$  mm, patient #4 postoperative CT  $0.55 \times 0.55 \times 1.25$  mm. Clinical variables including age, sex, disease duration before surgery, L-DOPA equivalent dose (LEDD) at baseline were recorded. Clinical improvement was measured by comparing Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) scores OFF medication preoperatively (baseline) and postoperatively ON DBS OFF medication. Improvement was expressed as percentage improvement between the two scores. This study was approved by the local ethics committee of the Charité, University Medicine Berlin (master vote EA2/186/18). The study in London received ethical approval from the West London NHS Research Ethics Committee (10/H0706/68). At Columbia and Mainz University, all procedures were also approved by the local Institutional Review Board.

### 2.2. Preoperative diffusion MRI acquisition

Center 1: For details on the London dataset, please see (Akram et al., 2017). Briefly, imaging data were acquired on a 3T Siemens Magnetom Trio TIM Syngo MR B17 using a padded 32-channel receive head

**Table 1**  
Patient demographics of cohorts analyzed.

Cohort	No. (female)	Age, [years]	Disease Duration, [years]	UPDRS-III baseline, OFF medication	LEDD Reduction [%]	Clinical Assessment	UPDRS-III postop, OFF medication	Preop Imaging	dMRI resolution	Postop Imaging	Registration Modalities	Electrode type
Center 1	17(4)	59.9±2.3	11±1.1	50.5±4.3	60±4.1	On vs OFF one year postop	27±3	T1, T2, PD*, R1, R2*, MT	1.5 × 1.5 × 1.5	MRI	T1, T2, PD*, R1, R2*, MT	3389 Medtronic
Center 2	12(3)	66.7±2.4	15.7±1.1	34.1±2.2	64.7±6.2	On vs OFF 6 months postop	14.9±1.8	T1, T2	2 × 2 × 2	MRI	T1, T2	3389 Medtronic
Center 3	4(0)	59±3.7	12.3±1.3	31±1.9	58±18.2	On vs OFF 2.5-7 months postop	13.8±3.2	T1, T2	1.88 × 1.88 × 2.6T	MRI	T1, T2	3387, 6179, BostonSci Vercise 8 contact linear

PD\*, effective proton density; R1, 1 mm high-resolution maps of the longitudinal relaxation rate ( $R1 = 1/T1$ ); R2\*, effective transverse relaxation rate ( $R2^* = 1/T2^*$ ); MT, magnetization transfer saturation.

coil to reduce discomfort and head motion. Siemens' 511E-Advanced Echo Planar Imaging Diffusion WIP was used. In-plane acceleration was used (GRAPPA factor of 2) with partial Fourier 6/8. In-plane resolution was  $1.5 \times 1.5 \text{ mm}^2$  (Field of view  $219 \times 219 \text{ mm}^2$ , TR = 12,200 ms, TE = 99.6 ms) and 85 slices were acquired with a 1.5 mm thickness. Diffusion-weighting with  $b = 1500 \text{ s/mm}^2$  was applied along 128-directions uniformly distributed on the sphere and seven  $b = 0 \text{ s/mm}^2$  volumes were acquired. To correct for distortions all acquisitions were repeated with reversed phase encoding direction (left to right and right to left phase encode) giving a total of 270 volumes acquired ( $[128 + 7] \times 2$ ). The total acquisition time for the dMRI sequences was 62 min.

Center 2: Diffusion-weighted imaging from Mainz were acquired with 32-directions at  $b = 1000 \text{ s/mm}^2$  and one  $b = 0 \text{ s}$  volume images for each acquisition (TR=11855 ms, TE=59 ms, fat saturation "on", 60 contiguous slices). dMRI of the whole brain at 2 mm isometric voxel resolution covering a field of view of  $224 \times 224 \text{ mm}$  was obtained. The total acquisition time for the whole protocol was 35 min which included 24 min ( $3 \times 8 \text{ min}$ ) for dMRI sequences.

Center 3: The diffusion weighted image sequences from New York cohort were acquired with 64-directions at  $b=1000 \text{ s/mm}^2$  and  $b = 0 \text{ s/mm}^2$  volumes were also acquired. In-plane resolution was  $1.88 \times 1.88 \text{ mm}^2$  (TR=8500 ms, TE=108 ms, slice thickness=2.50 mm). To correct for distortions, three acquisitions ( $2 \text{ } b = 0 \text{ s/mm}^2$  and  $1 \text{ } b = 1000 \text{ s/mm}^2$  volumes) were repeated with a reversed phase encoding direction (left to right and right to left phase encode) giving a total of 73 components ( $[64 + 6] + 3$ ). The total acquisition time for the dMRI sequences was 10 min.

### 2.3. Diffusion pre-processing and tractography

For all but the Mainz cohort (where only one  $b_0$  volume was acquired), the diffusion data were acquired with reversed phase-encode blips (left-to-right and right-to-left), resulting in pairs of images with distortion going in opposite directions. From these pairs, the susceptibility induced off-resonance field was estimated using a method described by Andersson et al. (2003) as implemented in FSL (Smith et al., 2004) and the two images were combined into a single corrected one using Topup as implemented in FSL v5.0. The output from Topup was then fed into Eddy (FSL v5.0) for correction of eddy current distortions and subject movement (Andersson and Sotiropoulos, 2016). In the Mainz cohort, only Eddy was applied.

Tractography was performed using the generalized Q-sampling imaging method (Yeh et al., 2010) as implemented in DSI studio (<http://dsi-studio.labsolver.org>) using the default parameter sets implemented in Lead-Connectome ([www.lead-connectome.org](http://www.lead-connectome.org); Horn et al., 2014b), which performed whole-brain fiber tracking in patient space and transformed of the tractogram into ICBM 2009b Nonlinear Asymmetric ('MNI') space (Fonov et al., 2011). Whole-brain tractograms were estimated by random-sampling of seedpoints within a white-matter mask defined by (i) segmenting structural (T1 and T2) imaging data using the New Segment approach as implemented in SPM12 (Ashburner and Friston, 2005) and (ii) linearly co-registering the mask to  $b_0$ -space. In total, 200,000 fiber streamlines were estimated in each patient. Tractograms were then nonlinearly warped into standard space using Advanced Normalization Tools (ANTs; [stnava.github.io/ANTs/](http://stnava.github.io/ANTs/); Avants et al., 2008) and the "Effective: Low Variance + subcortical refinement" preset implemented in Lead Connectome (Ewert et al., 2019a). Naturally, the same warp was used as in the process of transferring DBS electrodes into standard space (see below). To investigate the role of diffusion-artifacts (especially in the cohort from center 3, where diffusion-correction was not available), we repeated the analysis but instead nonlinearly co-registered between diffusion and anatomical space using a linear stage followed by a SyN stage with default parameters.



#### 2.4. Localization of DBS electrodes and VTA estimation

DBS electrodes were localized using Lead-DBS (<https://www.lead-dbs.org/>; Horn and Kühn, 2015) in its current (version 2.2.3; Horn et al., 2019) using PaCER (Husch et al., 2018) or the TRAC/CORE approach (Horn and Kühn, 2015) for either postoperative CT or MRI, respectively. Briefly, postoperative CT or MRI were linearly co-registered to preoperative MRI using ANTs. Subcortical refinement was applied as implemented in Lead-DBS to correct for brain shift that may have occurred during surgery. All preoperative volumes were then normalized into MNI space applying the same deformation fields calculated in previous steps mentioned above.

Based on the long-term DBS settings, volumes of tissue activated (VTA) were estimated using a Finite Element Method (FEM)-based model as implemented in Lead-DBS (Horn et al., 2019). This model estimates the E-field (i.e. the gradient distribution of the electrical charge in space measured in Volts per millimeter) on a tetrahedral four-compartment mesh that accounts for grey and white matter, electrode contacts and insulating parts. Grey matter was defined by components of the DISTAL atlas (Ewert et al., 2018) (STN, internal and external pallidum, red nucleus). The electric field (E-field) distribution was then simulated using an adaptation of the FieldTrip-SimBio pipeline (Vorwerk et al., 2018) that has been integrated into Lead-DBS (<https://www.mrt.uni-jena.de/simbio/>; <http://www.fieldtriptoolbox.org/>). The E-Field gradient was thresholded for magnitudes above a commonly used value of 0.2 V/mm to define the extent and shape of the VTA (Astrom et al., 2015). VTAs were warped into template space (2009b NLIN ASYM “MNI” Space, Fonov et al., 2011) by applying the same warp of the ANTs registration to VTA files. This is the space in which both group connectomes were available and hence, VTAs were used as seeds in this space. Fig. 1 provides an overview of the methodology applied.

#### 2.5. Structural connectivity estimation

Whole-brain structural connectivity profiles seeding from bilateral VTA in each patient were calculated using three different approaches: First, patient-specific dMRI data were processed for each patient, individually. Second, a disease- and age-matched connectome was estimated based on a cohort of 85 Parkinson’s Disease patients acquired within the Parkinson’s Progression Markers Initiative (PPMI). Third, connectivity profiles were estimated based on a state-of-the-art multi-shell dMRI dataset based on 32 healthy young subjects that were scanned on specialized MRI hardware within the Human Connectome Project (HCP). The latter two group connectomes were created by performing whole-brain tractography in each individual patient/subject, normalization of tracts (using the same methods as in the present study) and aggregation of tracts across patients/subjects. This led to whole-brain tract-density images seeding from VTAs for each patient based on patient-specific, age-/disease-matched and healthy-/young connectivity data.

**Patient-specific dMRI data:** Each patient’s specific connectome was based on dMRI data acquired pre-operatively. Using the generalized q-sampling imaging approach (which was applied in all three modalities) as implemented in DSI Studio (<http://dsi-studio.labsolver.org/>, Yeh et al., 2010), a whole-brain set of 200,000 fiber tracts was estimated using the default processing stream of Lead Connectome. This led to one set of (whole-brain) tract-density volumes for each patient.

**Age-/disease-matched connectome:** dMRI data from 85 patients were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (Marek et al., 2011) and processed using DSI Studio/Lead-Connectome in the same fashion as described above. This PPMI connectome of PD patients that is approximately age- and sex-matched to our full cohort was previously computed (Ewert et al., 2018) and has been used in DBS studies, before (Horn et al., 2017b; Immen et al., 2019; Neumann et al., 2018). The underlying dMRI data had been acquired in 64 gradient-directions at  $b = 1000$  s/mm<sup>2</sup>. In-plane resolution

was  $1.98 \times 1.98$  mm and 72 slices with a 2 mm thickness were acquired. Detailed scanning parameters can be found on the project website ([www.ppmi-info.org](http://www.ppmi-info.org)), processing details are reported in Ewert et al. (2018).

**Young/healthy connectome:** dMRI data from 32 healthy young subjects of the Human Connectome Project at Massachusetts General Hospital (<https://ida.loni.usc.edu/login.jsp>, Setsompop et al., 2013) were obtained and processed using DSI Studio/Lead-Connectome in the same fashion as described above. This ‘MGH Adult Diffusion’ dataset of the HCP was acquired using state-of-the-art scanning sequences on specialized hardware and from a quality perspective may be considered as one of the best openly available, in-vivo dMRI datasets. Diffusion-weighting with  $b = 1000$  s/mm<sup>2</sup> and 3000 s/mm<sup>2</sup> was applied along 64 directions. Furthermore, additional shells at b-values of 5000 and 10,000 s/mm<sup>2</sup> were applied along 128-directions. In-plane resolution was  $1.5 \times 1.5$  mm and 96 slices with a 1.5 mm thickness were acquired.

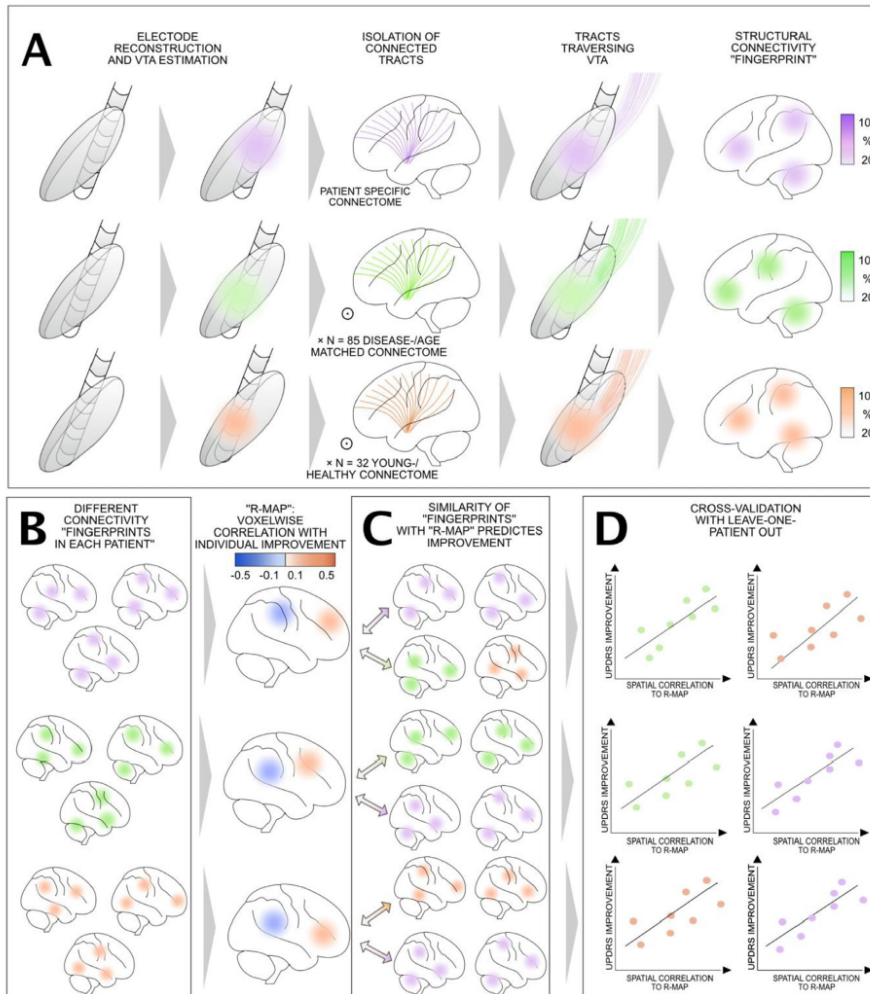
Structural connectivity between each VTA and voxels in the rest of the brain was estimated using the above connectome datasets and led to whole-brain fiber-density maps as produced by the Lead Connectome Mapper software (Horn et al., 2019). To do so, fibers traversing through VTA were selected from the group connectome and projected to volumetric space of the brain in template space of 2 mm isotropic resolution, denoting the number of fibers (connected to the VTA) that traversed through each voxel. To ensure this didn’t affect results, the step was repeated by exporting density-maps in 1 mm resolution. In addition, to explore the similarity and differences between patient-specific and young-/healthy, age-/disease-matched connectivity in specific cortical regions we added a region-of-interest (ROI) analysis. Here, structural connectivity to primary motor cortex (M1), supplementary motor area (SMA), pre-supplementary motor area (pre-SMA) and dorsomedial PFC as defined by the HMAT (Mayka et al., 2006) and Brainnetome atlases (Fan et al., 2016) were calculated. ROIs were chosen from prior literature-informed hypotheses (Akram et al., 2017; Vanegas-Arroyave et al., 2016), indicating that effective DBS was associated with connectivity to these brain structures.

#### 2.6. Estimating a model of optimal connectivity profiles

To estimate a model of optimal connectivity, structural connectivity (tract-density) maps (based on either patient-specific, age- and disease-matched or young/healthy data), seeding from bilateral VTA were Spearman rank-correlated with %-UPDRS-III change across patients in a voxel-wise fashion. This led to a map that showed positive or negative associations with UPDRS-III improvements (henceforth referred to as R-maps). Spearman’s correlation was used because structural connectivity results are generally non-Gaussian distributed (Horn et al., 2014b). R-maps denote to which areas connectivity is associated with beneficial or detrimental outcomes. By doing so, their spatial distribution is a direct estimate of the optimal connectivity profile of STN-DBS electrodes for PD. In case of patient-specific connectivity, for methodological considerations, two pathways were chosen to derive at group-level R-maps. The first (which is equivalent to the pathway used in case of normative connectomes) involved warping fibertracts to template space and aggregating tract-density maps there (from which R-maps were calculated). The second created tract-density maps in native space (from unnormalized fibertracts) and ported these maps into template space to create R-maps. This was done to rule out effects introduced by the order of processing steps.

#### 2.7. Estimating improvement in out-of-sample patients

To estimate DBS outcome in out-of-sample data, spatial correlations between the optimal structural connectivity model (defined by data-driven R-maps or a previously published optimal model from 2017b) and the VTA-derived structural connectivity profile in each patient were



**Fig. 1.** Applied methodological pipeline of data analysis: (A) For each patient, DBS leads were localized in MNI space using Lead-DBS software, and volumes of tissue activated (VTA) were estimated based on the actual DBS stimulation parameters. Streamlines representing traversing through each patient's VTA to the rest of the brain were selected from either patient-specific dMRI data, an age- and disease-matched group connectome or a young-/health group connectome, resulting in DBS stimulation-dependent connectivity "fingerprints". (B) Connectivity "fingerprints" were obtained for each patient using each of the three sources of connectivity data. Across each group of patients, an optimal connectivity profile (R-Map) was generated by correlating connectivity fingerprints with UPDRS-III improvement. (C) R-maps represent models for "optimal" connectivity fingerprints. Comparing similarities between each new (out-of-sample) patient's connectivity fingerprint with these models (by means of spatial correlation), clinical improvements can be estimated (shown in D for a leave-one-out design).

calculated. For instance, in some analyses, this was done in a leave-one-out fashion (i.e. data from patients #1-32 were used to create an R-map, which was then compared to the connectivity map of patient #33 to estimate improvement in this patient. The same was iteratively done for all patients.). The resulting similarity indices – again expressed as a (spatial) Spearman's rank correlation coefficients – estimate 'how optimal' each connectivity profile was and used to explain the variance in clinical improvement (%UPDRS-III improvement) in a linear regression model.

Throughout the paper, we used randomized permutation tests (5000 permutations) to test for significance (at a 0.05 significance

level) and all analyses were carried out in MATLAB (The Mathworks, Natick, MA).

### 3. Results

Our DBS cohort included 33 patients enrolled at 3 independent centers (7 females, mean age  $62.5 \pm 1.6$  years). The average disease duration in the entire sample was  $12.9 \pm 0.8$  years. Reduction in LEDD comparing baseline to post-DBS on average was  $61.5 \pm 3.6\%$ . Baseline UPDRS-III score was  $42.0 \pm 2.8$ , postoperative score  $28.1 \pm 2.1$  points (leading to a  $51.0 \pm 3.0\%$  improvement). LEDD reduction and UPDRS-III

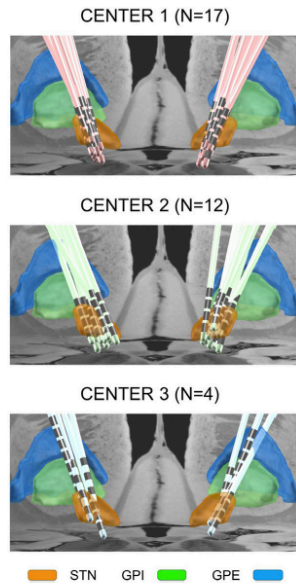


Fig. 2. DBS electrode reconstructions in the three cohorts from the three centers. Subcortical structures are defined by the DISTAL Atlas (Ewert et al., 2018), axial and coronal planes of the 7T MRI *ex vivo* human brain template shown (Edlow et al., 2019).

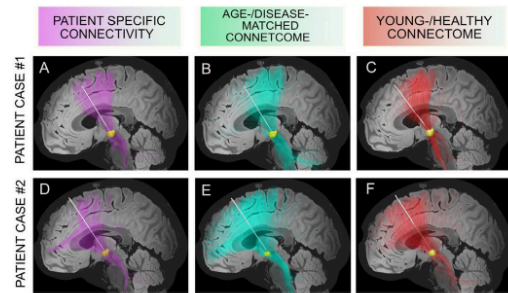


Fig. 3. Two representative examples of structural connectivity between individual DBS sites (left hemisphere) and the rest of the brain based on patient-specific connectivity, the disease- and age-matched connectome and young-/healthy connectome. A sagittal plane of the 7T MRI *ex vivo* human brain template (Edlow et al., 2019) is shown at  $x = 3$  mm. The yellow sphere represents the VTA. While in most patients, connectivity profiles were largely similar using either method (as in case #1), few patients had differing results across methods (as in case #2).

improvements were not significantly different across the three datasets ( $p > 0.05$  for both variables). Of all patients, 4 were tremor-dominant, 21 were akinetic rigid and 8 were mixed following criteria defined in Eggers et al. (2011).

DBS electrode placement was comparable across the three cohorts (Fig. 2, see also Fig. S1) and structural connectivity profiles from two typical patient cases are shown in Fig. 3. Distances between active electrode centers and the closest voxel center in the STN were calculated and this was used to estimate how many electrode contacts were inside ( $< 1$  mm), at the border (1–2 mm) or outside ( $> 2$  mm) of the STN (given

Table 2

Correlations between connectivity metrics.  $R$ -values show agreement between connectivity estimates connecting VTAs to M1, SMA, pre-SMA, and PFC across the group of patients. For instance, the first entry denotes that connectivity strength between VTAs and M1 estimated using patient-specific connectivity (i) and an age-/disease-matched connectome (ii) correlated by a Spearman's rho of 0.73. Note that similarities between patient-specific and group-level data become lower when advancing in frontal direction while it remains high between normative connectomes. (iii) stands for the young-/healthy connectome.

	M1	SMA	pre-SMA	PFC
i vs ii	$R=0.73$ , $p=0.004$	$R=0.43$ , $p=0.009$	$R=0.33$ , $p=0.062$	$R=0.18$ , $p=0.17$
i vs iii	$R=0.57$ , $p=0.004$	$R=0.40$ , $p=0.015$	$R=0.33$ , $p=0.044$	$R=0.21$ , $p=0.17$
ii vs iii	$R=0.85$ , $p=0.001$	$R=0.85$ , $p=0.001$	$R=0.70$ , $p=0.002$	$R=0.96$ , $p=0.001$

(i) patient-specific connectivity, (ii) age-/disease-matched connectivity and (iii) young-/health connectivity.

a diameter of the electrodes of  $\sim 1.24$  mm and a voxel-size of 0.22 mm in the STN atlas). 57 contacts were inside, 8 at the border region and 4 outside the STN (also see Figs. S2 and S3).

Average volumes of VTAs were  $149 \pm 68$  mm<sup>3</sup> (left) and  $175 \pm 118$  mm<sup>3</sup> (right). This led to connections of  $2999 \pm 1363$  of streamlines per VTA in patient-specific data,  $27,548 \pm 8951$  in the age-/disease-matched connectome data and  $21,875 \pm 17,791$  in the healthy/young connectome. On average, spatial correlations amounted to  $R = 0.39 \pm 0.05$  between patient-specific and age-/disease-matched connectivity (across the whole brain), to  $R = 0.38 \pm 0.05$  between patient-specific data and the young/healthy connectome and to  $R = 0.58 \pm 0.05$  between the healthy/young and age-/disease-matched connectomes. This was the case for most patients, and fibers predominantly connected to the sensorimotor strip (M1, SMA or pre-SMA). Only in a few patients did patient-individual structural connectivity estimates differ largely (for an example see bottom row of Fig. 3).

Correlations between patient-specific and young-/healthy connectivity estimates across the group of patients were high for apical cortical regions but lower for more frontal regions (see Fig. S5). Specifically, connectivity estimates between electrodes and these regions as estimated from patient-specific versus the healthy-/young connectome correlated across patients: primary motor cortex:  $R = 0.57$ ,  $p = 0.004$ , supplementary motor area:  $R = 0.40$ ,  $p = 0.015$ , pre-supplementary motor area pre-SMA:  $R = 0.33$ ,  $p = 0.044$  and dorsomedial prefrontal cortex:  $R = 0.21$ ,  $p = 0.17$ . Furthermore, an outlier analysis using skipped correlations as implemented in the robust correlation toolbox (Pemet et al., 2013) was performed to further confirm these results (Table S1). Further correlations between patient-specific and age-/disease-matched connectivity, young-/healthy and age-/disease-matched connectivity are shown in Table 2.  $P$ -values were corrected for multiple comparisons using the Bonferroni–Holm method.

In Horn et al., 2017b, an R-map that defined optimal connectivity values was estimated based on a two-center cohort of  $N = 95$  patients. Here, this R-map was used to account for a certain percentage of outcome in the presnet independent three-center cohort based on individualized diffusion data (Fig. 4;  $R = 0.28$ ,  $p = 0.045$ ). When instead using the age- and disease-matched connectome ( $R = 0.30$ ,  $p = 0.031$ ) or the young-/healthy connectome ( $R = 0.33$ ,  $p = 0.021$ ), correlations remained significant. These estimates were not significantly different from each other in head-to-head comparisons based on a Fisher  $r$ -to- $z$  transformation ( $p > 0.8$  for all comparisons).

In a next step, we calculated data-driven optimal connectivity maps (R-maps) from scratch based on the presnet three-center cohort using patient-specific dMRI, the age-/disease-matched connectome or the young-/healthy connectome, respectively. Using either metric, connectivity to primary motor cortex (M1) and primary somatosensory cortex



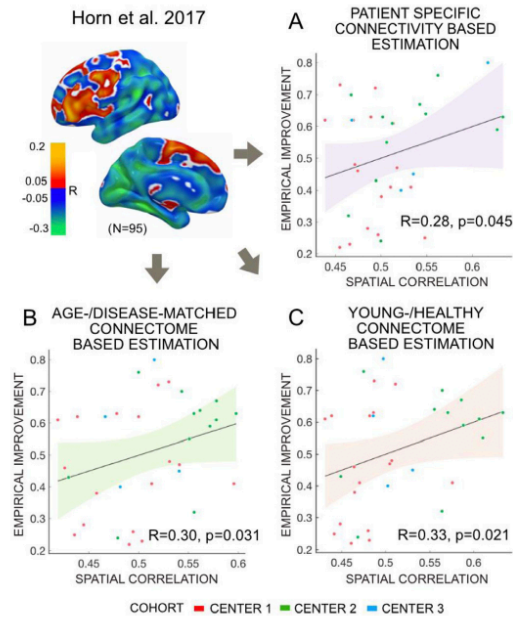


Fig. 4. Validation of optimal connectivity profiles estimated in, [Hom et al., 2017b](#)) on the present three-center cohort ( $N = 33$ ), in which individual dMRI data was available. Clinical improvements could be significantly estimated using patient-specific connectivity (A), a disease-/age-matched connectome (B) and a young-/healthy connectome (C).

(S1) was negatively correlated with DBS outcome. In contrast, connectivity to pre-SMA, anterior cingulate and medial frontal cortices was associated with beneficial DBS outcome ([Fig. 5](#)).

All three metrics, i.e. patient-specific connectivity ( $R = 0.43$ ;  $p = 0.001$ ), age-/disease-matched connectome ( $R = 0.25$ ;  $p = 0.048$ ) and healthy-/young connectome ( $R = 0.31$ ;  $p = 0.028$ ) could account for a significant part of the variance in clinical outcome in a leave-one-out design ([Fig. 5](#)). In case of patient-specific connectivity, a second analysis pathway (see methods) was tested, that led to inferior results ( $R = 0.35$ ,  $p = 0.017$ , see [Fig. S6](#)). Based on these values, we conclude that  $\sim 6$ – $18\%$  of the variance in clinical outcomes could be explained in out-of-sample data. Furthermore, to investigate effects of distortion artifacts in diffusion imaging, the analysis (following the first pathway) was repeated but applying a non-linear registration strategy between diffusion and anatomical space. This reduced correlations from  $R = 0.43$  to  $R = 0.37$  at  $p = 0.011$ . Finally, to rule out effects introduced by downsampling of spatial similarity steps, the main analysis was repeated after exporting tract-density maps in 1 mm resolution (as opposed to 2 mm as above). Results remained highly similar ( $R = 0.42$  at  $p = 0.002$  for patient-specific connectivity;  $R = 0.27$ ,  $p = 0.041$  for the age- and disease-matched group connectome;  $R = 0.31$  at  $p = 0.032$  for the healthy-/young connectome).

Frame-to-frame displacements within individual dMRI volumes were  $0.31 \pm 1.64$  mm on average, rotation  $0.003^\circ \pm 0.001^\circ$ , respectively. Specific head motion information (rotation/translation) of individual patients is reported in [Table S2](#). Head motion, including the displacement and rotation across each dataset did not explain prediction errors in our main analysis ( $R^2 = 0.03$  at  $p = 0.63$ ). To further assess whether head motion played a significant role, we repeated the aforementioned analysis using patient-specific connectivity data after excluding dMRI volumes that were affected by the top 2% of head motion/rotation. Con-

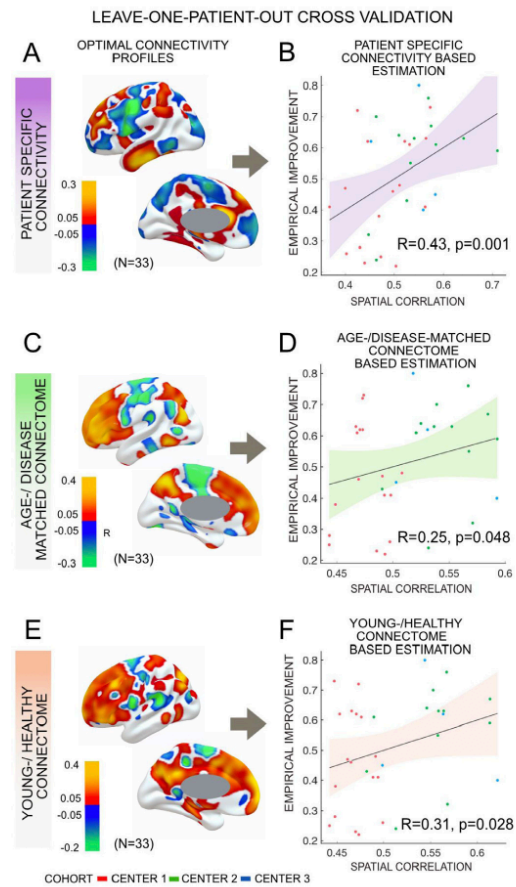


Fig. 5. Structural connectivity (patient-specific connectome, age-/disease-matched and healthy-/young) estimated change in UPDRS-III score using a leave-one-patient-out model ( $N = 33$ ). Optimal structural connectivity model generated with patient-specific connectome (A), age-/disease-matched connectome (C) and young-/healthy connectome (E) effectively estimated patient's improvement based on respective connectome (B, D, F). Slightly more variance was estimated from the patient-specific connectivity model than the other two metrics. Please note that values shown on the R-maps are not necessarily significant since mass-univariate tests were applied. Rather, the spatial profile of these maps was used to make predictions in out-of-sample data which are then tested for significance.

nectomes were then calculated again, and the analysis was repeated. Results remained identical ( $R = 0.41$  at  $p = 0.009$ ; [Fig. S7](#)).

Finally, this main analysis was repeated when thresholding R-maps to account for positive values, only. Again, this led to similar correlations while amounts predicted by the patient-specific analysis decreased most ( $R = 0.35$  at  $p = 0.012$  for patient-specific connectivity,  $R = 0.27$ ,  $p = 0.046$  for the age- and disease-matched group connectome and  $R = 0.43$  at  $p = 0.002$  for healthy-/young connectome).

Correlations derived from either metric were not significantly different from each other in head-to-head comparisons based on a Fisher  $r$ -to- $z$  transformation ( $p > 0.4$  for all comparisons). Furthermore, cross-estimates between metrics were poorer and not significant, i.e. when the R-map was based on a group connectome, but structural connectiv-

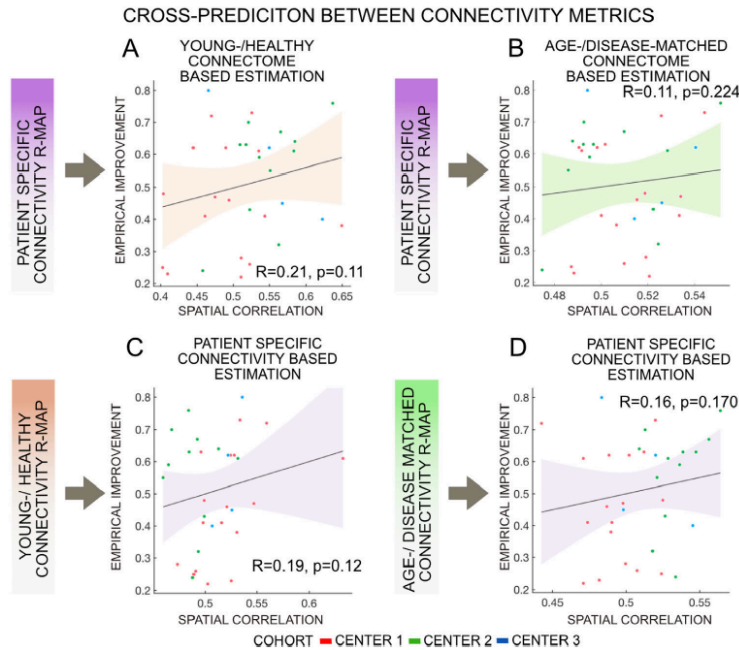


Fig. 6. Structural connectivity (patient-specific, age-/disease-matched, healthy-/young connectome) cross-prediction change in UPDRS-III scores under STN-DBS. Patient-specific connectivity couldn't explain patient's change following DBS based on healthy-/young connectome (A) and age-/disease-matched connectome (B). Similarly, R-Map generated with young-/healthy connectome (C) and age-/disease-matched connectome (D) could not estimate patient's improvement based on patient-specific connectome.

ity maps were based on patient-specific structural connectivity or vice versa (Fig. 6). This is not-surprising since normative and patient-specific connectivity estimates are not completely interchangeable. Still, it may underline the importance of consistency in the choice of metric when performing such dMRI based connectivity analyses.

#### 4. Discussion

Three main conclusions may be drawn from the present study. First, findings confirm a previously published model of optimal STN-DBS electrode connectivity based on a novel independent sample of patients operated in three different centers (Horn et al., 2017b). Crucially, while the original model had been derived from normative connectivity estimates, patient-specific dMRI data was successfully used to account for DBS outcome in the present cohort. Second, we show that optimal connectivity maps defined using individualized data are highly similar to the ones defined using group connectomes. Irrespective of using patient-specific, age-/disease-matched or healthy-/young connectome data, structural connectivity to pre-SMA, anterior cingulate and medial frontal cortices was associated with beneficial DBS outcome. However, third, the amount of variance in clinical improvement explained by either method was not exactly the same. While none of the metrics resulted in significantly higher predictions than the other two, the use of patient-specific connectome data resulted in the highest  $R$ -value between estimated and empirical improvements ( $R = 0.43$  vs.  $0.31$  or  $0.25$ ). This was true although the quality of the patient specific diffusion datasets differed between the three centers resulting in an 'overall' poorer data quality than found in normative connectomes.

##### 4.1. Normative group connectomes vs. patient-specific connectivity

Recently, normative structural connectomes were introduced to account for motor improvements (Horn et al., 2017b; Treu et al., 2020) and changes in depressive symptoms (Irmén et al., 2020) in Parkin-

son's disease patients following STN-DBS. The concept was also applied to DBS in Essential Tremor syndrome (Al-Fady et al., 2019), Obsessive-Compulsive disorder (Baldermann et al., 2019; Li et al., 2020) and Epilepsy (Middlebrooks et al., 2018). Furthermore, normative connectomes were used to explain behavioral effects following STN-DBS such as movement speed (Neumann et al., 2018) and motor learning (de Almeida Marcelino et al., 2019) or stopping of ongoing movements (Lofredi et al. 2020). Finally, the concept was applied to investigate side-effects such as DBS induced seizures (Boutet et al., 2019), weight-changes (Baldermann et al., 2019) or panic attacks (Elias et al., 2019). While the approach was successful to explain variance in clinical improvement in out-of-sample data (i.e. models were learned on one cohort to predict improvements in the other), it was so far not directly compared to the use of patient-specific connectivity.

So far, the only study that combined both normative and patient-specific connectivity data in the context of DBS was carried out by Baldermann and colleagues (Baldermann et al., 2019) in 22 patients suffering from Obsessive Compulsive Disorder. Here, patient-specific data in 10 patients were available but lacked in the remaining 12. When optimal connectivity profiles associated with high clinical improvement were estimated based on these 12 patients using a normative connectome, the outcome in the remaining 10 could be predicted by use of their patient-specific connectivity data ( $R = 0.7$ ,  $p = 0.01$ ). The same was true for the opposite case ( $R = 0.6$ ,  $p = 0.02$ ). Indirectly, this finding suggested that normative connectomes could be used to define models of optimal connectivity that would remain predictive when applying patient-specific connectivity datasets.

Here, we directly compared patient-specific connectivity estimates to the ones derived from group connectomes (which were either age-/disease-matched or even acquired in a young-/healthy cohort). We show that optimal connectivity profiles that were associated with good clinical improvement in our sample followed the same overall distribution irrespective of the applied connectivity metric. Namely, functional connectivity with M1 was negatively associated with optimal improve-

ment while more frontal regions (such as SMA, pre-SMA and dorsomedial PFC) were positively associated. Using either method, connectivity profiles were able to account for part of the variance in clinical improvement in out-of-sample patients (leave-one-out design). Moreover, a previously published model of optimal connectivity was associated with clinical outcome using either method. This finding is crucial since it shows that optimal profiles could potentially be estimated based on large cohorts (and even using normative connectomes) and still applied to patient-specific data. Especially when aggregating large cohorts of DBS patients, it may be complicated if not impossible to obtain diffusion-weighted imaging data from all patients, as well. For instance, large clinical endeavors such as the Early-Stim study cohort (Schuepbach et al., 2013) or the nonmotor study cohort of the International Parkinson and Movement Disorder Society (Dafsari et al., 2018) were acquired without diffusion-weighted imaging data but could still be used to inform optimal symptom-specific connectivity profiles. Similarly, some DBS cohorts are rare or unique world-wide and individualized connectivity data was not acquired for them. Examples include patients suffering from Alzheimer's Disease stimulated with fornical DBS within the ADVANCE trials (Laxton et al., 2010), DBS cohorts suffering from rare diseases such as Tourette's Syndrome (Johnson et al., 2020) or STN-DBS datasets for treatment of cervical dystonia (Ostrem et al., 2011).

#### 4.2. The case for using brain connectivity to investigate STN-DBS

Several studies have found significant relationships between electrode placements and clinical outcome, without the need to add connectivity information. Specifically, the same optimal target coordinate within the dorsolateral STN was defined by four independent studies, and three of them showed significant correlations between proximity to this coordinate and resulting clinical improvements (Akram et al., 2017; Bot et al., 2018; Horn et al., 2019; Nguyen et al., 2019). If such a clear relationship between the local stimulation sites and clinical improvements exist, why should we investigate connectomic mapping at all? The variance in clinical outcomes explained by such coordinate-based approaches is in the same ballpark of the one explained by brain connectivity in the present study. So, what is the added value?

First, brain connectivity may bear insights into the mechanism of action of DBS. The concept that strong connectivity to M1 is counterproductive for optimal outcomes but more frontal connections seem favorable qualitatively goes beyond knowledge of an optimal sweet-spot in the STN. From such knowledge, we may derive pathophysiological models and translate findings between systems neuroscience and animal models.

Second, brain connectivity could at some point be applied to explore variance in clinical outcome of novel patients, potentially even before surgery. For instance, work by Muthuraman and colleagues showed that atrophy in the SMA before surgery was associated with poor clinical outcome following DBS, matching present connectivity findings (Muthuraman et al., 2017).

Third, individual patient specific connectivity may differ from the norm and could one day help identify patient-specific DBS targets. In Essential Tremor, where clear associations between clinical outcome and a specific structural bundle (the dentatohalamic tract) have been established, this concept has already become clinical practice (Coenen et al., 2014). Similar concepts have been methodically explored using functional MRI (Andersen and Buneo, 2002). So far, to the best of our knowledge, whole-brain connectivity profiles as the ones explored here have not been used in clinical practice, although the general concept has been introduced in 2015 (Fernandes et al., 2015).

Fourth, networks that lead to side-effects when stimulated could be identified. For instance, Irmen and colleagues recently reported a connectivity profile that was associated with depressive symptoms following STN-DBS in PD (Irmen et al., 2019). Crucially, this network, centered on the left dorsolateral prefrontal cortex, could be reproduced in three international cohorts and was successfully used to cross-predict

depressive symptom changes across all cohorts. Such a robust map of a circuit that leads to depressive symptoms could be useful to inform stimulation sites that should be avoided. In Essential Tremor, Al-Fatly and colleagues similarly defined networks that were associated with the occurrence of side-effects such as ataxia and dysarthria (Al-Fatly et al., 2019).

Finally, connectivity profiles could be used to bridge fields of invasive and noninvasive brain stimulation. In 2014, Fox and colleagues demonstrated that across 14 diseases, the same networks seem to be modulated by both invasive and noninvasive neuromodulation (Fox et al., 2014). In PD, excitatory TMS to M1 and inhibitory TMS to SMA had beneficial effects (the opposite cases did not). If DBS is seen congruent to a functional lesion (i.e. to disrupt information flow within a specific network), this finding is in agreement with optimal connectivity profiles defined here.

Thus, it seems sensible to investigate brain connectivity measures in the DBS field for reasons that go beyond finding an optimal target coordinate. The question is which connectivity metric should best be used. We discuss the advantages of normative vs. patient-specific connectivity data in the following.

#### 4.3. Pros and Cons of normative vs. patient-specific connectivity data

In a number of studies, network targets were identified by using connectivity data that was *not* derived from each individual patient (Al-Fatly et al., 2019; Baldermann et al., 2019; Calabrese et al., 2015; Cash et al., 2019; Horn et al., 2017b; Petersen et al., 2019; Weigand et al., 2018). One reason for this is data quality. For instance, Calabrese et al. applied a 200  $\mu\text{m}$  isotropic postmortem scan of the brainstem acquired at 7T to be able to resolve the Wemekinkc decussation of the dentatohalamic tract. Weigand et al. applied functional imaging data which was averaged across 1000 subjects, leading to a high signal-to-noise ratio (Yeo et al., 2011). The structural connectome used in Horn et al. was acquired on a customized Siemens 3T Connectom scanner with multi-shell diffusion-encoding gradients and b-values reaching up to 10,000  $\text{s}/\text{mm}^2$  (Setsompop et al., 2013). Given the strong limitations of diffusion-MRI in general, Petersen and colleagues abandoned MRI-based connectivity altogether and instead created a realistic tract-atlas based on prior anatomical knowledge (Petersen et al., 2019). Hence, normative connectome datasets are of highest quality which may not be straightforward to match during routine preoperative clinical scans in every DBS center. Quality obtained from postmortem connectomes (where scanning times over >24 h are typical) may never be achieved in the living brain of individual patients. Introduction of clinically approved 7T systems may offer novel opportunities for preoperative imaging in the near future.

Along the same lines, investigating each patient's individualized connectivity data is challenging due to poor signal-to-noise and test-retest reliability. This was demonstrated in a study by Petersen and colleagues in which the same subject was scanned ten times. In each, the peak of connectivity to motor-/premotor cortices was identified within the STN (Petersen et al., 2017). Distances across peaks were 0.5–1 mm on average. While this subject was scanned using state-of-the-art methods, test-retest reliability will likely be poorer in clinical datasets acquired in movement disorder patients. A variability of ~1 mm may seem low at first glance but represents half the distance between two DBS contacts and is in the order of distances between responding and non-responding DBS patients (Horn et al., 2019). Moreover, the displacement between some runs was found to be of several millimeters, transposing the peak of M1-connectivity from the sensorimotor to the associative functional zone of the STN. In a similar study with even more pessimistic outcome, Jakab and colleagues repeated scans of the same subjects on different MRI scanners (Jakab et al., 2016). Authors used connectivity data to create thalamic subparcellations relevant for DBS surgery (such as the ventral intermediate nucleus). Variability of these targets introduced by the choice of MRI hardware was similar or higher to inter-subject vari-



ability (!). Moreover, the variability introduced by the MRI hardware made it obvious that single-subject tractography may not be an optimal choice to define surgical targets (see Fig. 6 in the publication by Jakab and colleagues).

Despite the practical and theoretical advantages of normative connectomes and the shortcomings of individual diffusion MRI data, the latter still is needed to reach an ultimate goal of realizing personalized deep brain stimulation. How could the gains of individualized connectivity be combined with the robustness of normative connectomes? One answer would be to scan patients repeatedly and to quantify test-retest reliability. For instance, the midnight scan club endeavor acquired MRI based (but functional) connectivity data of the same subjects in 12 imaging sessions (Gordon et al., 2017). Doing so in each patient that undergoes DBS surgery is impractical and would be very demanding for patients. However, the dataset was recently used to investigate individualized vs. group-level connectivity-based DBS targets (Greene et al., 2019). Similarly, 45 of the 1200 human connectome project participants were scanned twice to allow for quantification of retest error (Van Essen et al., 2013). Such openly available datasets may be used to investigate the test-retest reliability of individualized subjects, while similar data would be needed in patients that will actually undergo DBS afterwards.

An additional strategy could be to *integrate* patient-specific and normative connectomes and yield hybrid estimates. Patient-specific connectivity-profiles could be matched to variants that are robustly found within large normative cohorts and thus used to reshape normative connectomes. This concept could be used to reduce the amount of noise in individualized patient acquisitions, but such an approach would require further methodological work and validation studies.

This being said, we should not ignore the fact that all group studies will require co-registrations from the group connectome to the patient or vice-versa. This process will introduce registration bias. New methods for direct dMRI registrations are being developed and will hopefully become broadly available. Meanwhile, image acquisitions in single patients and MRI technology are also improving. Thus, while group connectomes are currently useful to investigate general relationships between clinical improvement and electrode connectivity, in the future, as the quality and speed of patient specific dMRI sequences improve, the indication or need for group average templates may be challenged.

#### 4.4. Limitations

There are several limitations that apply to the current study. First, heterogeneity, such as the differences in the MRI acquisition protocol and assessments of UPDRS-III between the three cohorts should be considered. Slight differences between raters of symptom scores cannot be ruled out, although the UPDRS-III has a comparably high inter-rater reliability (e.g. intra-class correlation of 0.95 reported in de Deus Fonticoba et al., 2019). Aggregation of datasets was necessary to obtain a large enough sample size and should bias our out-of-sample prediction results toward non-significance. Also, it may match the heterogeneity of clinical DBS cohorts that are usually aggregated across centers in clinical (e.g. Schuepbach et al., 2013). Second, inaccuracies in lead localization result from the approach of mapping electrodes into MNI space. To minimize the amount of error introduced by this step, we applied a modern neuroimaging pipeline that was specifically designed for the task at hand. Processing approaches that were designed to reduce error included brain shift correction, multispectral normalization with sub-cortical refinement steps (Horn et al., 2019) and a phantom-validated electrode localization approach (Husch et al., 2018). The normalization strategy applied here was recently evaluated by two international teams and led to automatic segmentations of the STN that were nearly as precise as manual expert segmentations (Ewert et al., 2019b; Vogel et al., 2020). Each step of the pipeline was carefully assessed and corrected if needed. Still, the processing steps include errors that could be further reduced by acquiring data of higher resolution as well as test-retest datasets (see above).

Movement artifacts are another limitation that are especially relevant in a cohort suffering from movement disorders. This favors shorter acquisition protocols and the one used in our sample – albeit representative for clinical datasets – may not have been optimal in this regard. Similar dataset quality could potentially have been acquired in less time by applying multiband sequences or similar methods (Harms et al., 2018). We report frame-to-frame movement parameters for the present sample and the average values did not correlate with prediction errors of our model. Still, movement errors do constitute a problem and are likely even more substantial when studying patients suffering from hyperkinetic symptoms such as in tremor dominant PD, Tourette's syndrome or dystonia.

A large limitation that applies to both individualized and normative connectivity mapping can be seen in diffusion MRI in general. Tractography using typical methods on diffusion MRI datasets was recently found to include four times the amount of false-positive tracts as true-positive tracts (Maier-Hein et al., 2017). This fundamental problem has led other groups that investigate similar topics to abandon dMRI based tractography altogether and to instead use detailed literature- and expert-based anatomical knowledge (Gunalan et al., 2017; Petersen et al., 2019). Together with poor test-retest reliability outlined above, these issues challenge the overall concept of connectomic DBS. It remains to be seen whether dMRI based tractography may indeed hold up to some of the promises outlined here, in the future (or not). While our results indicate that significant relationships between connectivity profiles and clinical improvements may be observed, this does not mean that these correlations are significant to clinical practice. Currently, these models are not suitable to predict outcomes in individual patients. Further improvements in diffusion imaging, with higher spatial and angular resolution and improved MRI gradients could add to the value of this modality (Jbabdi and Johansen-Berg, 2011; Sotiropoulos et al., 2013). The choice of whole-brain tractography as well as deterministic tractography on average likely lead to less streamlines to be connected to each VTA (Maier-Hein et al., 2017).

Furthermore, the use of high-resolution postmortem connectome data that is available in submillimeter resolution could be advantageous to employ, as well (Calabrese et al., 2015); again with the same inherent problem of lacking patient-specificity).

Finally, the optimal connectivity model in the current study was based on full UPDRS-III scores which included multiple symptoms in PD patients, such as tremor, bradykinesia, and rigidity. While the current study was not powered to investigate symptom-specific network fingerprints and addressed a different question, future studies could investigate symptom-specific network effects.

#### 5. Conclusions

Our study analyzed optimal connectivity profiles seeding from STN-DBS electrodes based on patient-specific vs. group-level structural connectivity profiles. We demonstrate that on a group level, results from individualized, age- and disease-matched connectomes and healthy/young connectomes are comparable but not completely interchangeable. Although differences were not significant, results suggest that individualized structural connectivity has the potential to estimate clinical outcomes following STN-DBS slightly better. Still, the use of normative connectomes seems sensible in cases where individualized connectivity data is lacking.

#### Credit author statement

QW and AH conceptualized the study, wrote the manuscript and acquired funding for the project. QW created figures and conducted analyses. HA, MM, GG-E, SAS, SG, NV-A and LZ collected data, provided critical methodological and conceptual advice and edited the manuscript. SO, NL and AH conducted additional analyses and wrote code used for in analyses. F-CY conducted analyses, created figures and wrote code

used for in analyses. AAK provided resources, critical methodological and conceptual advise and edited the manuscript.

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#### Supplementary materials

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## **Curriculum Vitae**

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.



## Complete List of Publications

1. Wang, Qiang, Harith Akram, Muthuraman Muthuraman, Gabriel Gonzalez-Escamilla, Sameer A. Sheth, Simón Oxenford, Fang-Cheng Yeh, Sergiu Groppa, Nora Vanegas-Arroyave, Ludvic Zrinzo, Ningfei Li, Andrea Kühn, and Andreas Horn. 2020. "Normative vs. Patient-Specific Brain Connectivity in Deep Brain Stimulation." *NeuroImage*, August, 117307. <https://doi.org/10.1016/j.neuroimage.2020.117307>. (IF=5.902)

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