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Connectivity Profile for Subthalamic Nucleus Deep Brain Stimulation in Early-Stage Parkinson's Disease

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Abstract

Objective: To describe relationships between electrode localization and motor outcomes from the subthalamic nucleus (STN) deep brain stimulation (DBS) in early-stage Parkinson's disease (PD) pilot trial.

Methods: To determine anatomical and network correlates associated with motor outcomes for subjects randomized to early DBS (n=14), voxel-wise sweet spot mapping and structural connectivity analysis were carried out using outcomes of motor progression [Unified Parkinson

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AUTHOR CONTRIBUTIONS

1) conception and design of the study: MH, AH, DC

2) acquisition and analysis of data: MH, NR, SO, NL, AL, TD, PK, AH, DC

3) drafting a significant portion of the manuscript or figures: MH, CN, BH

POTENTIAL CONFLICTS OF INTEREST

Authors MH and DC are shareholders of Arena Therapeutics, a company focused on advancing DBS for the treatment of patients recently diagnosed with PD. Author PK has equity ownership in Neurotargeting LLC, which has developed a system that facilitates the operative phases of DBS procedures. Author AH received lecturing fees from Boston Scientific, which manufactures DBS systems. Authors NR, CN, BH, SO, NL, AS, and TD have nothing to report.

Disease Rating Scale Part-III (UPDRS-III) 7-day OFF scores (Δbaseline ▫ 24 months, MedOFF/StimOFF)] and symptomatic motor improvement [UPDRS-III ON scores (%Δbaseline ▫ 24 months, MedON/StimON)].

Results: Sweet spot mapping revealed a location associated with slower motor progression in the dorsolateral STN (AC/PC coordinates: 11.07±0.82mm lateral, 1.83±0.61mm posterior, 3.53±0.38mm inferior to the midcommissural point; MNI coordinates: +11.25, −13.56, −7.44mm). Modulating fiber tracts originating from supplementary motor area (SMA) and primary motor cortex (M1) to the STN correlated with slower motor progression across STN-DBS subjects, whereas fiber tracts originating from pre-SMA and cerebellum were negatively associated with motor progression. Robustness of the fiber tract model was demonstrated in leave-one-patient-out (R=0.56, P=0.02), 5-fold (R=0.50, P=0.03), and 10-fold (R=0.53, P=0.03) cross-validation paradigms. The sweet spot and fiber tracts associated with motor progression revealed strong similarities to symptomatic motor improvement sweet spot and connectivity in this early-stage PD cohort.

Interpretation: These results suggest that stimulating the dorsolateral region of the STN receiving input from M1 and SMA (but not pre-SMA) is associated with slower motor progression across subjects receiving STN-DBS in early-stage PD. This finding is hypothesis-generating and must be prospectively tested in a larger prospective study.

INTRODUCTION

Subthalamic nucleus (STN) deep brain stimulation (DBS) is an established adjunctive therapy for mid- and advanced-stage Parkinson's disease (PD) that improves motor symptoms and quality of life while also reducing medication burden and dyskinesia[1,2]. While many PD patients receive notable clinical benefit, individual motor response to DBS can be highly variable [ex: 3% to 63% improvement[3]]. Numerous studies have investigated this heterogeneity, and patient factors such as younger age, shorter disease duration, and strong pre-operative levodopa response predict good STN-DBS response in advanced-stage PD[4,5].

Outside of patient characteristics, precise delivery of DBS intervention (i.e., electrode placement; stimulation programming) is also strongly associated with clinical outcome[6–8]. Although there is no consensus on the STN "sweet spot"[9], recently, there is general agreement on optimal symptomatic motor improvement with active contacts within the dorsolateral/sensorimotor region[6,7,10]. The STN receives input from numerous functional areas in the frontal cortex, and therefore, stimulation site will also determine the exact network modulated by DBS. While PD has been considered a network disease since its discovery and neuromodulation has targeted networks since the first days of electric brain stimulation, advanced neuroimaging sequences are increasingly used to conceptualize DBS as a network treatment in individual patients, defining networks as three-dimensional structures in stereotactic space[10–13]. Moreover, from a bioelectrical perspective considering tissue surrounding the electrode, effects arise from stimulating axons, not cell bodies, which may underline the increasing focus on determining white matter targets[14]. Associations between PD motor improvement and the hyperdirect, pallidofugal, and nigrofugal/striatofugal pathways suggest that precisely stimulating specific

fiber tracts connecting to structures associated with motor control is extremely important for optimal symptomatic benefit of STN-DBS[10,12,15]. These recent DBS reports confirm early lesional studies showing cortical input from the supplementary motor cortex seems crucial, especially for hypokinetic symptoms[6,10,12].

The robust improvements of STN-DBS in patients with mid- and advanced-stage[1,2] PD motivate investigations into whether DBS in very early-stage PD could extend or even enhance those benefits. The first and, to date, only clinical trial to evaluate DBS in early-stage PD randomized 30 patients to DBS plus optimal drug therapy (DBS+ODT) or ODT alone and followed them for two years[16]. In the 'DBS in early-stage PD' pilot trial, a seven-day washout of all PD medications and stimulation was completed to evaluate changes in motor symptoms without the overt influence of symptomatic therapies (i.e., DBS, PD medications). It is important to note that the therapeutic washouts implemented in the 'DBS in early-stage PD' pilot trial did not evaluate neuroprotection. However, in lieu of a biomarker, they allowed changes in motor symptoms after withdrawal of symptomatic therapies for one week to be evaluated over the two-year clinical trial.

Given the known variability of DBS response across individuals with PD[2] and prior associations between electrode localization and outcomes[6–8], this study's objective was to explore relationships between stimulation volumes, fiber tract connectivity, and motor outcomes in the only cohort of patients to receive DBS in early-stage PD.

METHODS

Cohort

This study evaluated early-stage PD subjects (PD medication duration 0.5–4 years) from the 'DBS in early-stage PD' pilot clinical trial (NCT00282152; IDEG050016). Trial design[17], operative and surgical targeting experiences[18,19], and two-year[16], five-year open-label[20] and 11-year open-label[21] results were previously reported. Briefly, 30 early-stage PD patients (90% male, mean age: 60.4±6.6 years) were randomized 1:1 to bilateral STN-DBS plus ODT or ODT. Key enrollment criteria included PD medication duration of 0.5–4 years, Modified Hoehn & Yahr Stage II off medication, and no history or evidence of dyskinesia or motor fluctuations. Fifteen early-stage PD subjects were randomized to DBS and implanted bilaterally with quadripolar electrodes (Model 3389, Medtronic, Minneapolis, MN). One DBS subject was excluded from this analysis due to missing data. Fifteen early-stage PD subjects were randomized to ODT and medically treated throughout the two-year trial. One ODT subject dropped out after the baseline visit and was excluded from this analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was provided by all participants of the 'DBS in early-stage PD' pilot trial (Vanderbilt IRB#040797).

Therapeutic Washout and Motor Assessments

During the two-year trial, subjects were admitted to the Vanderbilt Clinical Research Center for a seven-day washout of all PD therapies at baseline, 6-, 12-, 18- and 24-months. At

washout assessments, the UPDRS-III motor examination was videotaped in two conditions: ON therapy (day 1; MedON/StimON) and 7 days OFF therapy (day 8; MedOFF/StimOFF). After the trial completed, videotapes were scored by an independent rater blinded to treatment assignment, ON/OFF status, and visit sequence. Blinded UPDRS-III scores included all motor items except rigidity which cannot be evaluated by videotape. Unblinded UPDRS-III (including rigidity scores) were also collected ON (day 1) and OFF (day 8) therapy at each visit.

Therapeutic Management

Treating neurologists managed DBS subjects' medication and stimulation parameters. All early DBS subjects were treated using monopolar stimulation with case positive and a single optimal contact negative[16]. Beginning one month postoperatively, the optimal contact was programmed at 130-Hertz and 60-μsec pulse width. Programmed settings were considered effective when clinical improvement in motor symptoms, such as rigidity or tremor, were improved without the presence of stimulation associated adverse effects, such as paranesthesia or involuntary muscle contraction. Levodopa equivalent daily doses (LEDD) were calculated as previously described[22].

Electrode Localizations

Preoperative T1w and T2w MRI scans and postoperative CT scans were acquired in each patient[19]. Electrodes were localized using the advanced processing pipeline in *Lead-DBS* [lead-dbs.org[6]]. Specifically, postoperative CTs were linearly coregistered to preoperative MRI using advanced normalization tools (ANTs[23]). Registrations were carefully inspected and refined if necessary. The brain shift correction step from *Lead-DBS* was applied to account for non-linear deformation of brain tissue and pneumocephalus during surgery. Preoperative volumes were then normalized to ICBM 2009b NLIN asymmetric ("MNI") space applying the ANTs SyN Diffeomorphic Mapping[24] with the "effective: low variance default + subcortical refinement" preset. This method yielded the best performance for STN segmentation with precision comparable to manual expert segmentations[25]. Electrodes were automatically pre-reconstructed using the phantom-validated and fully-automated PaCER method[26] and manually refined if needed. Atlas segmentations in this study were defined based on the DISTAL atlas[25]. Group visualizations were performed using *Lead-Group*[27].

E-field Modeling

Electric field vector magnitudes (i.e., *E-fields*) were used to estimate the volume of tissue modulated around electrodes. E-fields were calculated based on the 24-month DBS programming settings using an adaptation of the SimBio/FieldTrip pipeline as implemented in *Lead-DBS*[6]. E-fields were nonlinearly flipped to the contralateral side since no asymmetric effects were assumed, resulting in 2×14=28 E-fields across the cohort.

Sweet Spot Mapping

To identify the neuroanatomical substrates associated with clinical change, sweet spots associated with outcomes [motor symptom progression (UPDRS-III 7-day OFF Δbaseline ▫ 24 months); symptomatic motor improvement (UPDRS-III ON percent

Δbaseline ▫ 24 months)] were calculated in a voxel-wise manner using *Lead-Group*[27]. Specifically, for each voxel covered by the group of E-fields across the cohort in MNI space, E-field vector magnitudes across subjects were Spearman rank-correlated with clinical outcomes. The area of interest was conservatively restricted to voxels covered by at least 20% of E-fields with a vector magnitude above 0.2 V/mm [a typical value assumed for DBS to activate axons[28]]. For visualization, sweet spots were smoothed using a full-width-half-maximum kernel of 2-mm, while rank-correlation coefficients in color bars of Figures 3 and 5 were derived from unsmoothed files.

Fiber Filtering

Fiber tract connectivity was assessed using a connectome modified from the *DBS Tractography Atlas* which featured additional connections from cortex to STN and from STN to substantia nigra[29]. For the finite set of 6,525,876 fiber tracts represented in the resulting *Netstim Tractography Atlas* and each subject's E-field, a value of probabilistic impact on the tract was calculated as previously described[30]. Tracts were considered connected if the mean E-field magnitude they traversed was >1000 V/m and if they were connected to >5% of E-fields.

Comparison to Other Established DBS Landmarks

To further characterize the anatomical relationship of our identified early-stage PD sweet spots with respect to previously established anatomical targets and boundaries, we searched the literature for landmarks in DBS targeting. The search yielded two established landmarks, namely the metanalytical target by Caire et al.[7] (derived from 171 standard of care PD patients; associated with optimal symptomatic motor improvement[31]) and the Bejjani line[32] (a line connecting anterior aspects of the red nucleus at its maximal diameter at the level of STN on axial slices; commonly used as an anatomical reference in STN-DBS planning).

Statistical Analysis

Strength of structural connectivity was Spearman rank-correlated with change in motor outcome which yielded a connectivity map showing positive and negative tract associations with each outcome [motor progression (UPDRS-III 7-day OFF Δ baseline to 24 months) or symptomatic motor improvement (UPDRS-III ON %Δ baseline to 24 months)]. The robustness and generalizability of identified tract models were evaluated using leave-one-patient-out, 5-fold, and 10-fold cross-validations. To visualize the null-distribution of these cross-validation experiments, we repeated the leave-one-patient-out design after permuting motor progression values across subjects 1,000 times. To study the (in)dependence between motor progression scores we calculated their correlation across the group. Further, we repeated main analyses (sweet spot and fiber filtering experiments) on the motor progression scores after regressing out symptomatic improvement scores. To evaluate motor progression including rigidity, blinded UPDRS-III scores were combined with unblinded UPDRS-III rigidity scores to provide the 'full UPDRS-III'. In a sensitivity analysis, two-year progression of the 'full UPDRS-III' was used as an additional outcome for the fiber tract connectivity model. Relationships between motor progression (UPDRS-III 7-day OFF Δ baseline to 24 months) and PD therapies (LEDD Δ baseline to 24 months; 24-month stimulation voltage) were assessed using Spearman's correlation, with internal validation

using a bootstrapping resampling procedure (1000 replications; seed: 2023) in STATA 17.0 (StataCorp LP, College Station, TX).

RESULTS

Demographics and baseline characteristics of subjects from the 'DBS in early-stage PD' pilot clinical trial are summarized in Table 1, with details about the trial reported elsewhere[16,20,21]. Subjects in this electrode localization study were randomized to DBS and operated on in early-stage PD (mean baseline disease duration 2.6±1.9 years) with mean baseline age of 60.9±6.9 years (n=14).

Relationship Between Motor Progression and Stimulation Site

Sweet Spot Analysis—Electrode localization revealed placement of active contacts within the STN and surrounding areas in all subjects (Fig. 1), as previously reported[33]. The aggregate volume derived from voxel-wise probabilistic mapping in the DBS cohort (correlating two-year change in motor progression with E-field magnitude) revealed the strongest slowing of motor progression in the dorsolateral STN (Fig. 2 A–C). The peak location (i.e., the location most strongly associated with the least amount of motor progression) was located at **MNI coordinates**: +11.25, −13.56, −7.44 mm (Spearman's rank correlation coefficient at peak: R=0.67). Expressed in **functional (AC/PC) coordinates**[31], this maps to 11.07±0.82 mm lateral, 1.83±0.61 mm posterior, and 3.53±0.38 mm inferior to the midcommissural point. In contrast, involvement of more anterior and dorsal regions that primarily encompassed zona incerta, was associated with a greater degree of motor progression. The N-map of stimulation volumes covered a larger area encompassing the entire motor STN (Fig. 2 D–F).

Fiber Filtering Analysis—To interrogate the structural networks implicated in motor progression, E-fields derived from the DBS cohort were used to seed from a structural connectome (*Netstim Tractography Atlas*). Rank-correlation of E-field magnitudes with motor progression scores revealed distinct fiber tracts associated with differential clinical outcome (Fig. 3A). Specifically, positively-correlated fibers projected from supplementary motor area (SMA) and primary motor cortex (M1) to the STN (Fig. 3A–B). In contrast, negatively-correlated fibers originated from pre-SMA and cerebellum, reaching more anterior aspects of STN with the sensorimotor/associative transition zone and posterior subthalamic area, respectively (Fig. 3A–B). Of note, tracts originating from SMA on average received a slightly higher fiber score than the ones originating from M1 (0.41 vs. 0.38, $t = 3.6$, $P<0.01$).

Tracts were weighted by the degree of how much their modulation correlated with motor progression across the DBS cohort. This model was validated using leave-one-patient-out (Fig. 3D, R=0.56, P=0.02), 5-fold (R=0.50, P=0.03), and 10-fold (R=0.53, P=0.03) cross-validations. To investigate the relative contribution of positive and negative tracts, analyses were repeated using only positive tracts [leave-one-patient-out CV: R=0.48, P=0.05), 5-fold CV: (R=0.41, P=0.07), and 10-fold (R=0.46, P=0.05)] and again using only negative tracts [leave-one-patient-out CV: R=0.35, P=0.12), 5-fold CV: (R=0.34, P=0.12), and 10-fold (R=0.42, P=0.07)]. Repeating the leave-one-patient-out analysis 1,000 times after permuting

motor progression values across subjects revealed the null-distribution for this experiment (Fig. 3E), which was centered around an R ~ 0 (the R value of the unpermuted case, R = 0.56 ranked significantly at p = 0.039). Motor progression distributions for each randomization group from the 'DBS in early-stage PD' pilot trial are shown in Figure 3D. Of note, motor progression scores for one-third of early DBS subjects were the same or better two years after baseline (5/14; Fig. 3D). A sensitivity analysis using 'full UPDRS-III' motor progression scores (blinded scores + unblinded rigidity score) produced a similar tractography profile and cross-validations as the primary analysis [leave-one-patient-out CV: R=0.49, P=0.04), 5-fold CV: (R=0.38, P=0.10), 10-fold CV (R=0.47, P=0.04)].

Relationship Between Symptomatic Motor Improvement and Stimulation Site

While a key focus of this study was to determine the relationship between stimulation site and changes in motor progression across subjects who received STN-DBS (i.e., comparing 7-day MedOFF scores before surgery and MedOFF/StimOFF scores 2 years after surgery), it is important to evaluate these results in the context of the sweet spot and connectivity profile associated with symptomatic motor improvement (i.e., comparing MedON scores before surgery with MedON/StimON scores 2 years after surgery). This was done to determine whether the optimal sites and networks for these two distinct measures agree – or whether each would require stimulating a distinct spot/network.

Therefore, the sweet spot analysis was repeated using motor improvement scores (Fig. 4A–B) instead of motor progression scores. Overall, the location associated with motor improvement and slower motor progression overlapped at the subthalamic level. The motor improvement sweet spot map peaked at +11.2, −13.7, −7.4 mm (**MNI coordinates**; peak Spearman's rank correlation coefficient, R=0.92), close to the motor progression sweet spot (Fig. 2; Euclidean distance: 0.12mm). Expressed in **functional (AC/PC) coordinates**[31], this maps to 11.08±0.82 mm lateral to, 1.93±0.60 mm posterior to, and 3.48±0.38 mm inferior to the midcommissural point.

The fiber filtering analysis was also repeated using the symptomatic motor improvement outcome. Results converged on a very similar network to the motor progression outcome results (Fig. 4C) and again showed robust correlations [leave-one-patient-out CV: R=0.68, P<0.01), 5-fold CV: (R=0.62, P=0.01), and 10-fold (R=0.69, P=0.04)]. Independent validation of positive and negative tracts revealed significant correlations when using positive tracts [leave-one-patient-out CV: R=0.70, P<0.01), 5-fold CV: (R=0.67, P<0.01), and 10-fold (R=0.72, P<0.01)] but not negative tracts [leave-one-patient-out CV: R=0.02, P=0.468, 5-fold CV: R=0.11, P=0.36, and 10-fold CV: R=0.10, P=0.36]. To further explore (in)dependence of motor progression scores and symptomatic improvement outcomes (R=0.46, P=0.03) in relationship to our main results, we repeated the sweet spot and fiber filtering analyses on motor progression scores that were cleaned from motor improvement outcome scores (Fig. 4D–F). This showed highly similar results, suggesting that the two scores did share additional, not the same, variance on group level.

Relationships Between Motor Progression and PD Therapies—To explore whether slower motor progression across subjects who received STN-DBS could be

explained by receiving more stimulation voltage and/or more PD medications, we assessed correlations between motor progression and the symptomatic therapies that were withdrawn during the seven-day washouts. Critically, *lower* stimulation amplitude at 24 months correlated with slower motor progression (R=−0.52, P=0.02; Fig. 5A), and there was also a significant correlation between greater *reductions* in LEDD (change from baseline to 24 months) and slower motor progression for DBS subjects (R=−0.59, P=0.01; Fig. 5B). There was no relationship between change in LEDD and motor progression for subjects randomized to ODT (R=0.16, P=0.54; Fig. 5B). These results, in combination with our electrode localization analyses, suggest that stimulation location, not the amount of PD therapy given, drives motor benefit.

Comparison to Other Established DBS Landmarks—Figure 6 features spatial relationship between landmarks in DBS targeting and the motor progression and motor improvement sweet spots identified in this early-stage cohort. Comparison of target locations revealed intersection of both our early-stage PD sweet spots and the advanced-stage PD location identified by Caire et al.[7] with the Bejjani line[32]. The early-stage PD sweet spots, however, revealed variability in the mediolateral and ventrodorsal planes indicating a more ventral and lateral position of our targets with respect to the metanalytical location of advanced-stage PD from Caire et al.[7] (Figure 6A; mean Euclidean Distance: 2.2±0.01 mm).

DISCUSSION

This study reports relationships between electrode localization and motor outcomes from the ‘DBS in early-stage PD’ pilot clinical trial. There are four main conclusions that can be drawn from this study. First, slower motor progression across subjects who received STN-DBS significantly correlated with stimulating cortical tracts from SMA and M1 but not pre-SMA. Second, the sweet spot and tracts associated with slower motor progression in early-stage PD largely coincided with those associated with early-stage PD symptomatic motor improvement. In other words, the network subserving optimal clinical response in early-stage PD was also associated with slower motor progression. Third, slower motor progression significantly correlated with lower levels of stimulation voltage and PD medications. Finally, the sweet spot and tracts identified for optimal motor benefit in early-stage PD were similar to yet slightly more ventral and lateral than previously-reported efficacious locations from studies of patients who received DBS in advanced-stage PD[6,10,12].

It is important to clarify that the effect on “motor progression” reported here does not provide evidence of neuroprotection, which cannot be shown without a validated biomarker. In lieu of a biomarker to track neurodegeneration, the pilot trial utilized seven-day therapeutic washouts to evaluate changes in underlying motor symptoms after removing the overt effects of symptomatic therapies (DBS and PD medications). While DBS symptomatic effects are reported to wash out within hours[34], lingering symptomatic effects from PD medications can persist beyond seven days. Symptomatic effects of levodopa, for example, can last weeks or even months[35]. However, for a clinical trial evaluating DBS in early-stage PD, a seven-day washout strikes an appropriate balance between scientific rigor (i.e., how

long is needed to wash out the majority of symptomatic effects of the intervention being tested?) and reasonable burden to study participants (i.e., what is practically and ethically feasible to ask early-stage PD patients to endure?). Importantly, in the pilot trial, ODT subjects received more medications throughout the study[16] and are therefore expected to have more lingering symptomatic effects compared to DBS+ODT subjects. Of relevance to this study which evaluated variance in motor outcomes within the DBS group, DBS subjects with slower motor progression required less stimulation voltage and PD medications than DBS subjects with typical motor progression. This is consistent with prior studies evaluating optimal stimulation location in patients with advanced-stage PD[36,37]. Therefore, notwithstanding limitations of this washout and the lack of a PD biomarker, data presented here showing strong correlations between slower motor progression and stimulating the dorsolateral region STN receiving hyperdirect input (M1 and SMA; not pre-SMA) are intriguing and warrant further investigation.

Our results could play a role to change clinical practice if further validated in prospective trials. First, the sweet spot and optimal tract profile, while calculated on a group level, can be registered to brains of novel patients using accurate spatial co-registrations[38]. Hence, in the future, this could guide both surgical planning (as an initial step that can be further refined by experienced personnel) and DBS programming (guiding initial contact selections). Moreover, after replication on larger samples, the latter part could become critical, since one cannot observe motor progression during the programming session itself (since it unfolds over years).

As noted, neuroprotection cannot be demonstrated by this study design or others currently available, but these results suggest sustained effects on motor symptoms after a prolonged withdrawal of stimulation and medications in early-stage PD. It is currently unclear how such an effect might occur, but previous work may shed light on potential mechanisms. Specifically, in human studies, long-term plasticity with DBS in the sensorimotor network has been suggested by prolonged beta band attenuation after DBS withdrawal from two longitudinal reports[39,40]. Since the hyperdirect pathway may be the prominent source of high STN beta activity[41], the association of this pathway with slowing motor progression is intriguing. However, it is likely that indirect projections pointing to the same subthalamic loop would play a similar role but went undetected by our analysis. Anatomically, these correspond to comb fibers that are not visible on dMRI-based tractography datasets[42]. Chronic sensing-enabled DBS systems now permit longitudinal electrophysiological recordings, and future studies exploring how electrode location affects beta band activity and motor progression could help elucidate potential mechanisms. Additionally, preclinical studies point to brain-derived neurotrophic factor (BDNF) signaling as a potential mediator of these effects: STN stimulation increases BDNF in the striatum, substantia nigra, and M1 cortex[43] and BDNF signaling via its high-affinity receptor tropomyosin-related kinase type B (trkB) is associated with neuroprotection and symptomatic efficacy of STN-DBS. As suggested by Fischer and Sortwell[43], increases of this prominent neurotrophic growth factor could promote neuron survival, maintenance of the cortical-basal ganglia circuitry or even decrease alpha-synuclein.

The early-stage PD sweet spots identified here map closely to previously published sweet spots associated with motor symptom improvement in advanced-stage[6,10]. This dorsolateral region of the STN location aligns with the anterior border of the red nucleus, known as the Bejjani line, a common surgical targeting landmark for STN-DBS for PD[32]. Since DBS is intendend to be used throughout PD progression, it is a key finding that precise surgical targeting to this established location for advanced-stage PD is expected to provide superior motor benefit in patients with early-stage PD.

While targeting focal sites of the STN (defined by local relationships to anatomical landmarks) is commonly used for surgical planning[32], there is an increasing paradigm shift in conceptualizing benefit in relationship to the global networks modulated by DBS[11,12]. Indeed, our structural connectivity analysis revealed robust correlation of motor improvement in early-stage PD with hyperdirect pathway fiber tracts, reaching STN from M1 and SMA but not pre-SMA. Given prior strong associations of the hyperdirect pathway with symptomatic motor improvement for STN-DBS patients with advanced-stage disease[10,12,15], it is not surprising that these tracts would also impart motor benefit for early-stage PD patients. Evidence continues to accumulate that stimulation or ablation of connections from M1 improve tremor while those from SMA improve hypokinetic symptoms[10,13,44] which confirms knowledge established by early lesional work. There is less clarity on the exact division between hyperdirect input from SMA vs pre-SMA in DBS for PD. These neighboring cortical regions are not directly connected to each other, and they also show notable differences in their functional roles and connectivity profiles[45]. Interestingly, here, modulating hyperdirect tracts originating from pre-SMA were *negatively* associated with both slowing motor progression and clinical improvements. The same negative association applied to fibers of passage corresponding to the non-decussating dentatothalamic tract. It is unclear whether these negative tracts play a causal role or result from spurious correlations (i.e., subjects with poorer outcomes happened to modulate these connections by chance), but the causal ingredient was that they did *not* modulate the beneficial connections. Notably, leaving out negative tracts or positive tracts (and repeating the analysis) led to inferior results for slowing motor progression, suggesting that both modulating positive tracts and not modulating negative tracts could play a role in mediating effects. Critically, this was not the case for tracts associated with symptomatic motor improvements, where only stimulation overlaps with positive tracts showed significant predictive value (while reanalyzing the data using only the negative tracts did not yield significant results). We must emphasize, however, that these findings should not be overinterpreted. First, as mentioned, negative fiber scores do not mean negative (causative) effects, but, more likely, lack of positive effects. In other words, based on these data, we don’t conclude that stimulating cerebellar tracts will cause faster motor progression. Second, even if causative effects were at play, we are unable to conclude further implications (i.e., on VIM DBS targeting, or similar) at this point. Additional prospective studies are needed to resolve those relationships.

Limitations of this study should also be discussed. First, differences in clinical phenotype between early- and advanced-stage PD could shift optimal stimulation location as PD advances. However, optimal stimulation sites reported here are in line with published reports on advanced-stage PD cohorts (for a review, see [46]). Patient-specific tractography data were

not collected in the pilot, and instead, normative connectome data were used. Although this approach lacks patient-specific anatomical features, test-retest studies show that larger fractions of differences observed in individualized tractography data are due to noise (and not true anatomical variations across patients)[47] and that, for instance, the effect of the MRI scanner can be larger than the one of the patient in DBS[48]. Furthermore, normative connectome data has been shown to yield similar results to patient-specific data in PD[49]. Future studies collecting patient-specific connectivity data may be able to explain more variance. Similarly, reconstruction of electrode placements and aggregation in a common space that allows comparisons leads to bias due to imaging resolution, so reconstructed electrodes do not exactly match reality. To maximally counteract this bias, an established pipeline was used that was specifically created for this task, using concepts such as brain shift correction, multispectral normalizations[6], phantom-confirmed electrode localizations[26], and a validated segmentation framework[50]. Moreover, recently, bias introduced by the user localizing *Lead-DBS*, as well as postoperative imaging modality was quantified and remained below the magnitude of imaging resolution[51]. All subjects included in this analysis provided written informed consent to participate in the 'DBS in early-stage PD' pilot clinical trial, which included a detailed, expanded informed consent procedure designed to address ethical considerations for enrolling in a surgical trial as an early-stage PD patient[52]. Notably, the pilot trial was limited to 30 subjects by the FDA (IDEG050016). Since this is the only cohort implanted with DBS early-stage PD and also the only study evaluating changes in motor symptoms seven days after stopping PD therapies, we were unable to independently validate findings in a separate cohort. However, for such a small study of only 14 DBS patients, the robustness of the structural connectivity profile was demonstrated across multiple cross-validations (leave-one-patient-out, 5-fold, and 10-fold). One key strength of this study is the meticulously collected longitudinal, blinded clinical ratings of the UPDRS-III motor examination (ON therapy and seven days OFF therapy); however, blinded ratings inherently rely on videotaped recordings for scoring, which precludes evaluation of rigidity. Since rigidity is often a symptom used for DBS programming, excluding this cardinal motor feature may have biased results. To address this concern, a sensitivity analysis was conducted by combining the unblinded rigidity scores with the blinded UPDRS-III motor score which yielded a similar tractography profile to our primary analysis and similarly showed significant correlations. Finally, taken alone, correlations between slower motor progression and lower stimulation amplitude as well as greater reduction in dopaminergic medication could speak to underlying effects of milder progression or higher sensitivity to therapies in some patients. However, our results indicating that subjects with the least amount of motor progression were (i) stimulated at a specific site (sweet spot) which (ii) received cortical input from M1 and SMA (but not pre-SMA) speak against this alternative hypothesis. Given the robustness of our connectivity analysis when subjected to cross-validations, we conclude that motor progression depends on the stimulation site, which subsequently influences the required stimulation voltage and the required medication dosage.

This study analyzed relationships between electrode location and motor outcomes from the 'DBS in early-stage PD' pilot trial. Results suggest that DBS electrodes stimulating the dorsolateral region of the STN, specifically the zones of the nucleus receiving input from

M1 and SMA (but not pre-SMA), is associated with slower motor progression in early-stage PD. This finding is hypothesis-generating and must be prospectively confirmed in larger study.

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Summary for Social Media If Published:

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What is the current knowledge on the topic?

- Electrode/stimulation location are key determinants of deep brain stimulation efficacy. In Parkinson's disease, stimulating the dorsolateral/sensorimotor region of the subthalamic nucleus is associated with superior symptomatic motor improvement.

What question did this study address?

- This is the first study to evaluate relationships between stimulation site and motor progression in patients who received deep brain stimulation in very early-stage Parkinson's disease.

What does this study add to our knowledge?

- These results suggest that stimulating the dorsolateral region of the subthalamic nucleus receiving input from primary motor (M1) and supplementary motor areas (SMA; but not pre-SMA) is associated with slower motor progression and superior symptomatic motor improvement in early-stage Parkinson's disease.

How might this potentially impact on the practice of neurology?

- Deep brain stimulation is currently only applied investigationally in patients with early-stage Parkinson's disease. This finding is hypothesis-generating and must be prospectively tested in larger prospective study.

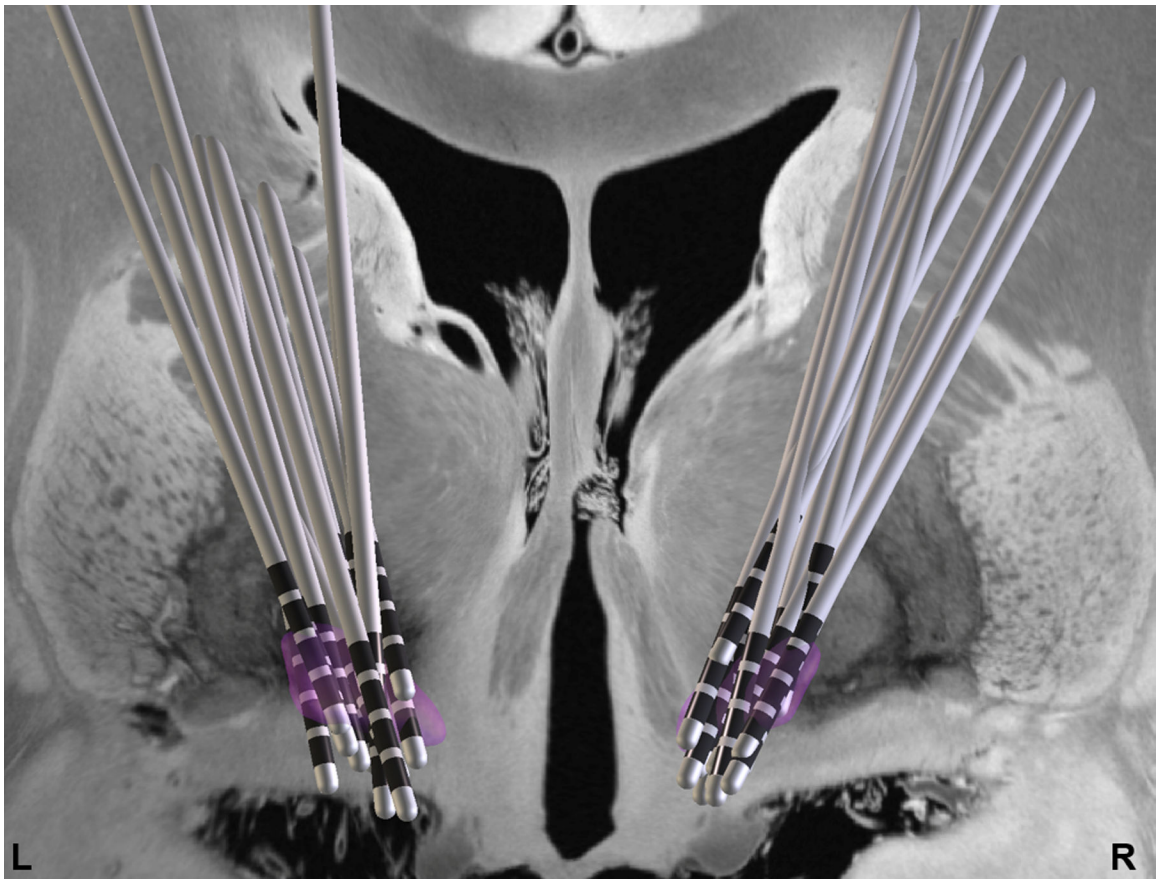

Figure 1: Anatomical distribution of DBS electrodes at the mesencephalic level.

Reconstructions of investigated leads in the 'DBS in early-stage PD' cohort (n=14 subjects) are featured in the coronal plane. The STN, derived from the DISTAL Minimal Atlas[25], is superimposed on slices of a 100-μm, 7 T brain scan in MNI 152 space[53].

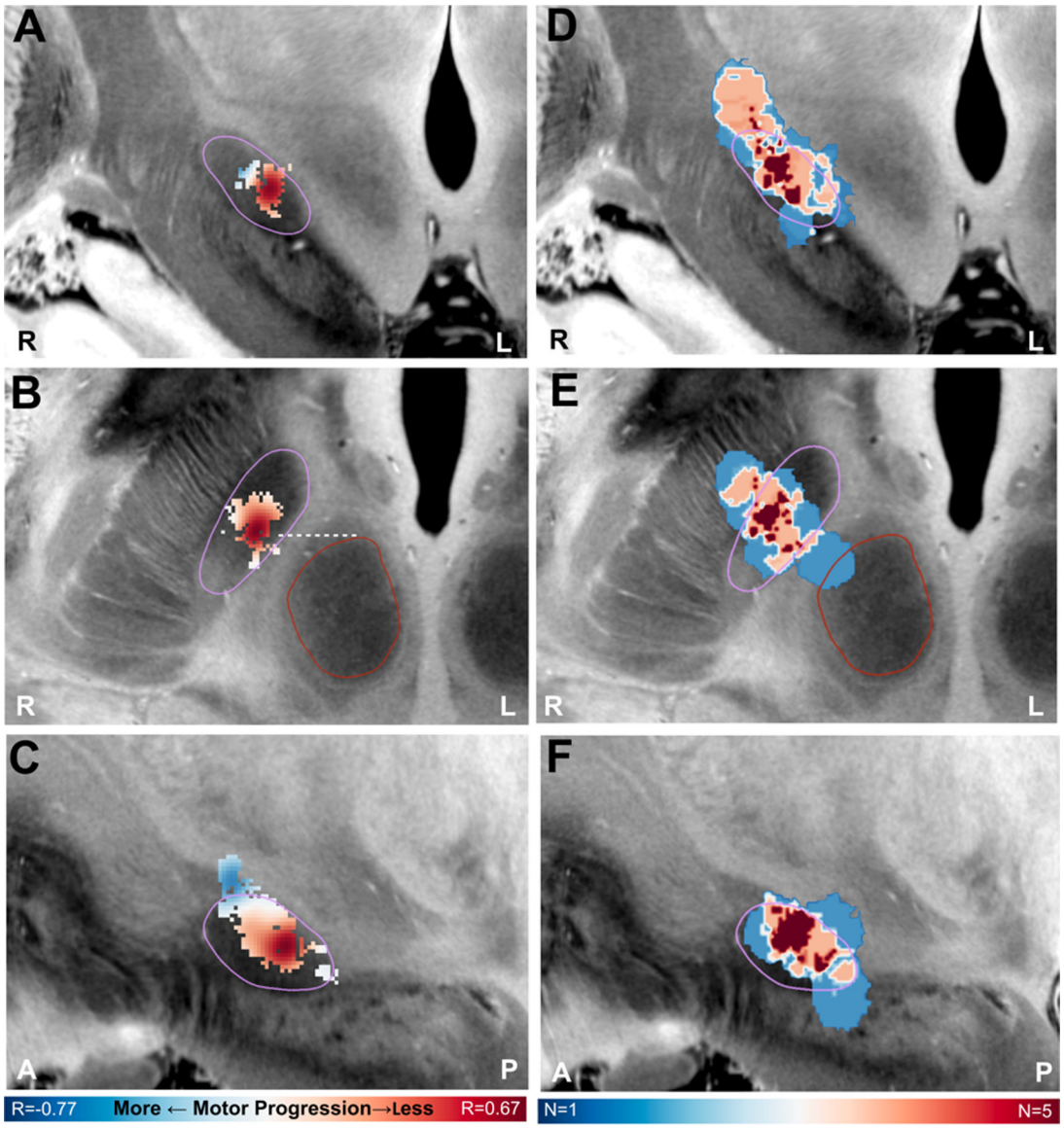

Figure 2: Sweet spot associated with slower motor progression in early-stage Parkinson's disease.

(A-C) Electric field vector magnitudes of all DBS subjects were rank-correlated with motor symptom progression scores in a voxel-wise manner. (A) Coronal, (B) axial, and (C) sagittal views are centered on the functional coordinates: 11.07 ± 0.82mm lateral, 1.83 ± 0.61mm posterior to, and 3.53 ± 0.38mm inferior to the midcommissural point (MNI peak coordinates: 11.4, −13.7, −7.6mm). STN outlined in purple. Red nucleus outlined in red. Bejjani line = white dashed line[32]. (D-F) N-image of stimulation volumes showing broad coverage across the STN on a group level.

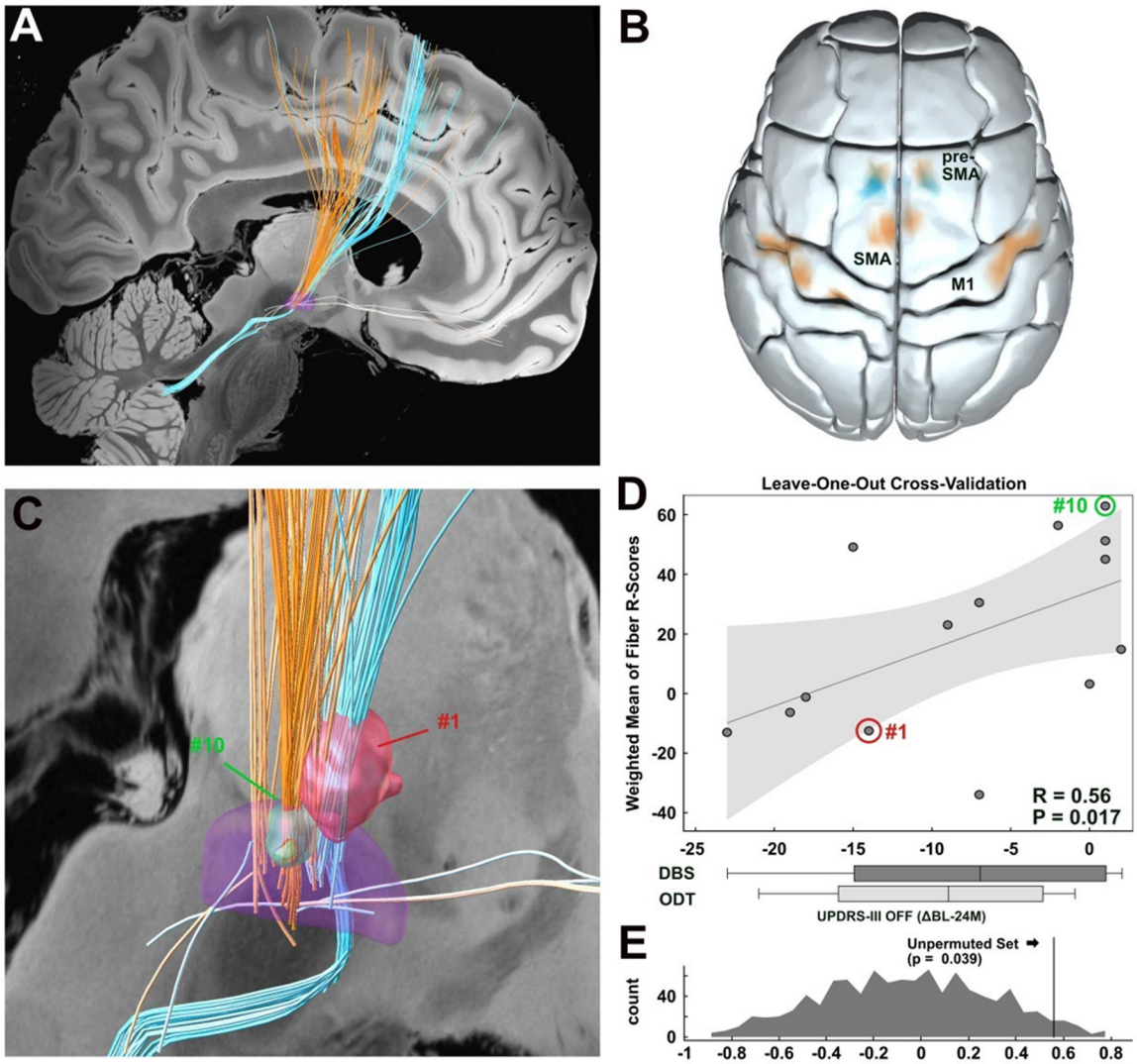

Figure 3: White matter tracts associated with motor progression in early-stage Parkinson's disease.

(A) The degrees of fibers modulated by E-fields were rank-correlated with slower motor progression scores across the entire DBS cohort (UPDRS-III 7-day OFF baseline to 24-month scores). Orange fibers correlate positively with slower motor progression [R between 0.06 and 0.58], while cyan fibers correlate negatively [R between −0.53 and −0.01]. Subthalamic nucleus (STN), purple. (B) Density maps of cortical fiber projections (positive/orange and negative/cyan) are overlayed onto an MNI space template [Johns Hopkins University (JHU) atlas parcellation: M1 (JHU: 25 & 26, precentral gyrus), SMA & pre-SMA (JHU: 1 & 2, superior frontal gyrus, posterior segment)] using Surf Ice software (https://www.nitrc.org/projects/surfice). (C) Stimulation sites of top (green) and poorly responding (red) illustrative example subjects and their relationship to fibers associated with slowed motor progression (orange). (D) Top: Leave-onepatient-out Cross-Validation of the fiber tract model shown in Panels A-C to estimate outcomes in unseen data. The analysis was iteratively repeated, each time leaving out one patient and estimating their outcomes by relating their stimulation site to the positively and negatively weighted fiber

tracts. Repeating the same analysis in a 5-fold or 10-fold cross-validation also led to significant correlations (R = 0.50, P = 0.033 and R = 0.53, P = 0.027, respectively). Data from illustrative example subjects from Panel C are featured. Bottom: distribution of motor progression scores by randomization group from the 'DBS in early-stage PD' pilot clinical trial. DBS, n=14. ODT, n=14. (E) The null-distribution of the leave-one-patient-out experiment from Panel D (which was calculated by repeating the analysis 1,000 times after permuting motor progression values across subjects).

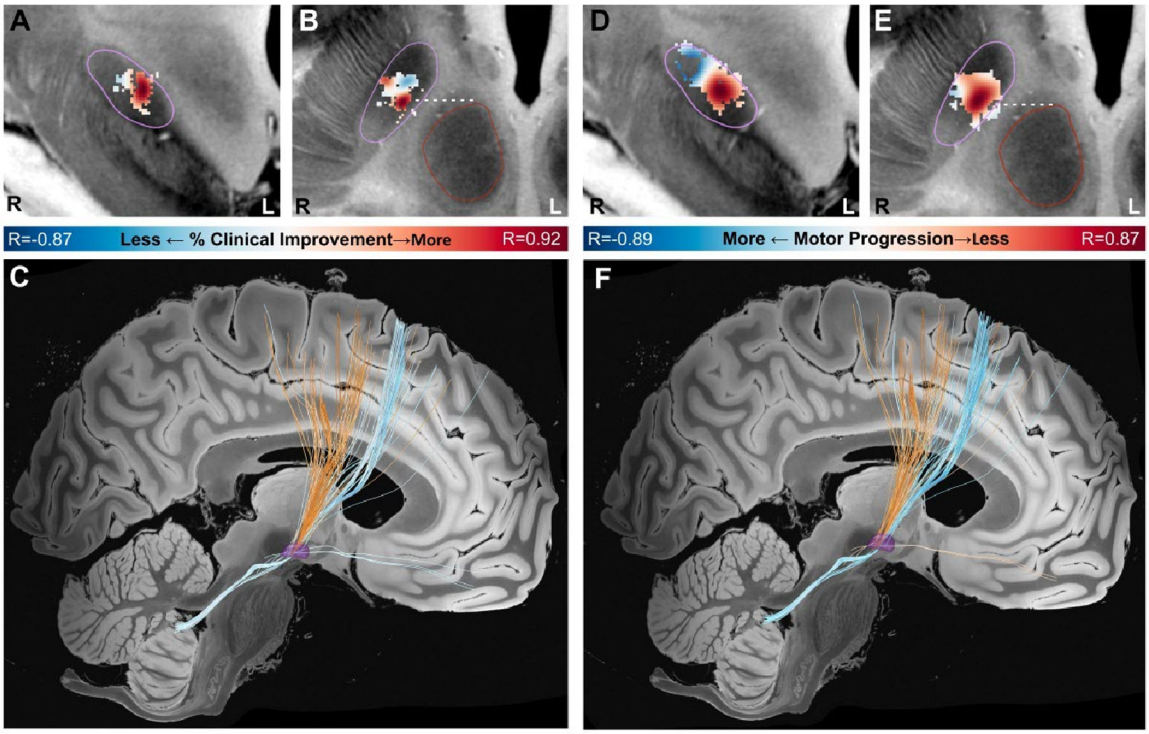

Figure 4: Symptomatic Motor Improvement Sweet Spot and White Matter Tracts.

A-C: Electric field magnitude values of all early-stage PD subjects were rank-correlated with percent symptomatic motor improvement (UPDRS-III MedON baseline to 24-month MedON/StimON scores), corresponding to the same analysis carried out with motor progression scores shown (Figure 2). (A) Coronal and (B) axial views centered on the peak functional coordinates: 11.08 ± 0.82 mm lateral, 1.93 ± 0.60 mm posterior, and 3.48 ± 0.38 mm inferior to the midcommissural point (MNI coordinates: 11.2, −13.7, −7.4 mm). STN outlined in purple. Red nucleus outlined in red. Bejjani line[32] = white dashed line. (C) The degrees of fibers modulated by E-fields were rank-correlated with symptomatic motor improvement across the cohort (UPDRS-III ON baseline to 24-month scores), corresponding to the same analysis with motor progression scores shown in Figure 3. Orange fibers are positively associated with symptomatic motor improvements [R between 0.00 and 0.59], cyan fibers show negative correlations [R between −0.53 and 0.00]. D-F: Analysis of Figure 2 repeated after regressing out symptomatic improvement (MedON/StimON) scores (as analyzed in panels A-C) from motor progression scores.

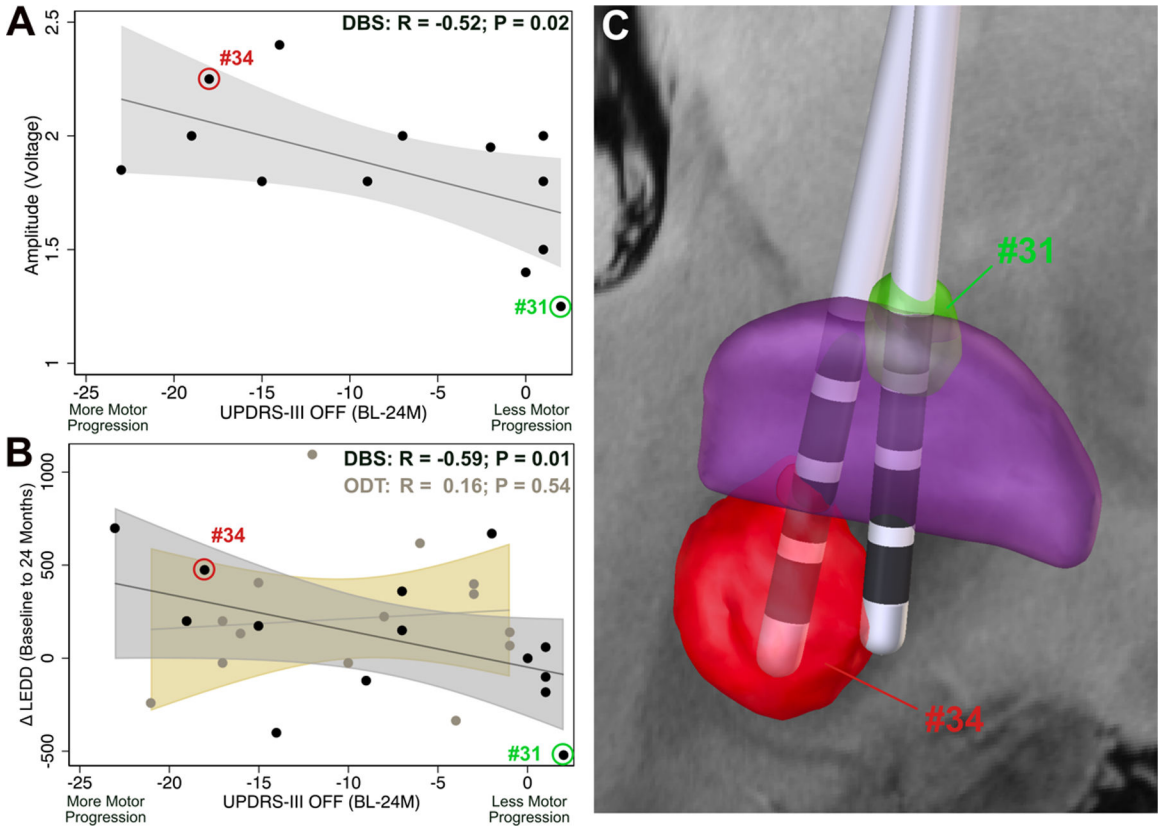

Figure 5: Correlations Between Motor Progression and PD Therapies.

(A) Slower motor progression correlates with lower stimulation amplitude (24-month voltage) for DBS subjects; R=−0.52, P=0.02. Amplitude shown as average of left and right leads. V = voltage. (B) Slower motor progression is also associated with greater reductions in LEDD after surgery for DBS subjects (black dots; R=−0.59, P=0.01). There is no correlation for ODT subjects (tan dots; R=0.16, P=0.54). (C) Stimulation sites of top (green) and poorly responding (red) illustrative example subjects. Stimulation and PD medication data from illustrative example DBS subjects from are featured in Panels A and B.

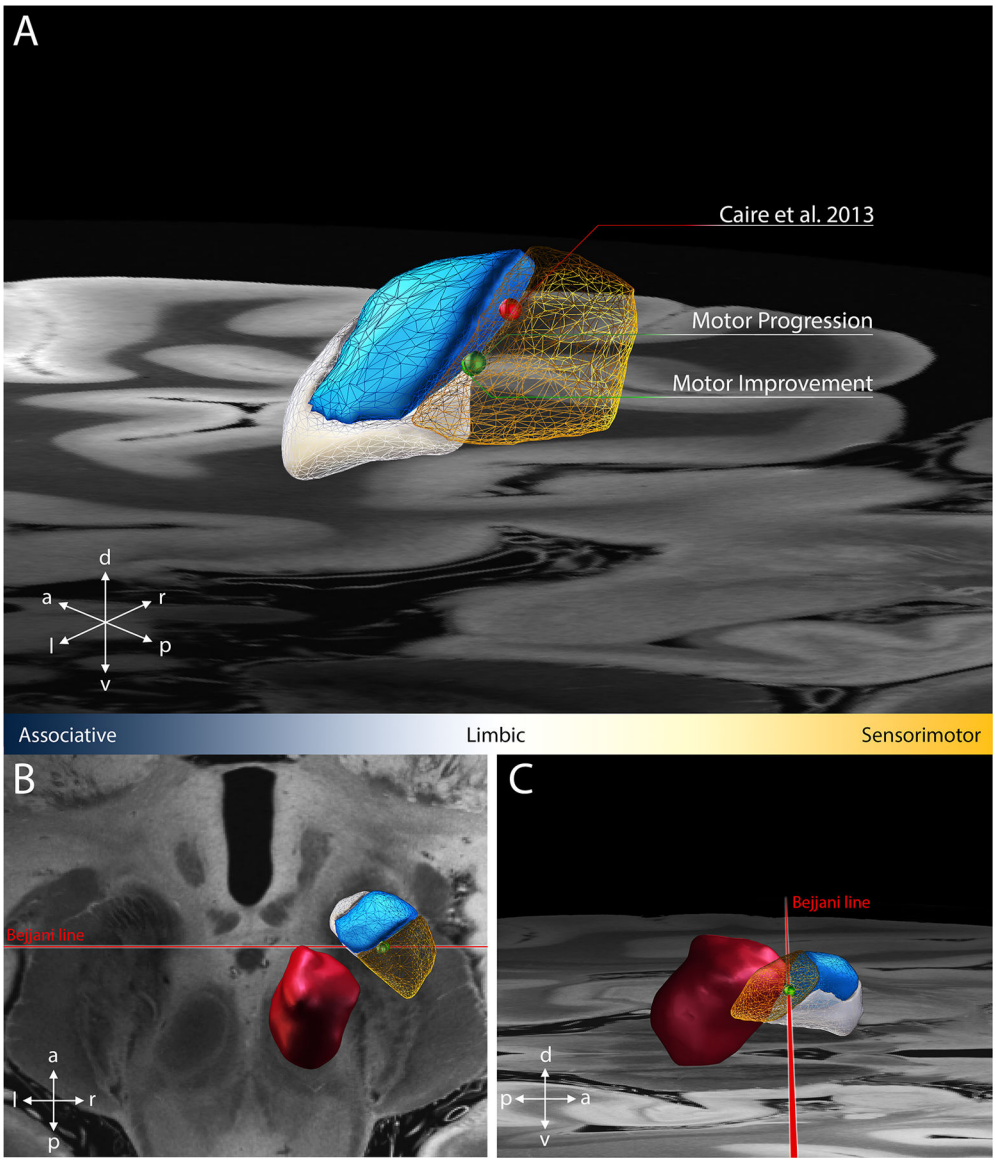

Figure 6: Spatial Relationship Between Early-Stage Parkinson's Disease Sweet Spot and Established Landmarks in DBS Targeting for Parkinson's disease.

(A) Visualization of the optimal early-stage PD locations associated with motor progression (dark green sphere) and symptomatic motor improvement (light green sphere) and their relationship to mean coordinates derived from a meta-analysis of 171 standard of care PD electrodes (red sphere)[7]. The mean Euclidean distance between the advanced-stage PD metanalytic sweet spot and the early-stage PD sweet spots in the current study was 2.2 ± 0.01 mm. Axial (B) and sagittal (C) sections featuring the peak coordinates in MNI space, with the Bejjani line[32] drawn in red. STN functional regions: associative (blue), limbic (white), sensorimotor (orange). Red nucleus (red).

Table 1:

Baseline Characteristics of the ‘DBS in Early-Stage PD’ Pilot Clinical Trial

Baseline Characteristics	**DBS (n=14)**	**ODT (n=14)**
Sex, Male – no. (%)	13 (93%)	12 (86%)
Age (Years)		
Mean ± SD	60.9 ± 6.9	60.7 ± 6.6
Range	52.2 – 74.5	50.2 – 69.8
Medication Use		
Mean Duration (Years)	2.6 ± 1.9	2.0 ± 1.0
Mean LEDD (mg)	429.9 ± 314.1	490.7 ± 216.2
Handedness, Right – no. (%)	14 (100%)	12 (86%)
Side of Onset, Right – no. (%)	10 (71%)	7 (50%)
UPDRS-III (Mean ± SD)		
Blinded Only[~]		
ON	23.1 ± 12.6	21.3 ± 9.2
OFF (7 Days)	28.0 ± 10.2	29.5 ± 8.7
Full[^]		
ON	26.9 ± 14.2	24.4 ± 9.8
OFF (7 Days)	35.4 ± 12.4	35.8 ± 10.0
Total UPDRS ON (Mean ± SD)	35.0 ± 16.3	33.4 ± 13.3

LEDD, levodopa equivalent daily dose

UPDRS, Unified Parkinson’s Disease Rating Scale

[~]Blinded scores (excluding rigidity)

[^]Full UPDRS-III = blinded scores (excluding rigidity) + unblind rigidity score