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Citation details
Kübler D, Kroneberg D, Al-Fatly B, Schneider G-H, Ewert S, van Riesen C, et al. Determining an efficient deep brain stimulation target in essential tremor - Cohort study and review of the literature. Parkinsonism Related Disorders. [Online] Elsevier BV; 2021;89: 54–62.
DOI: 10.1016/j.parkreldis.2021.06.019

Determining an efficient deep brain stimulation target in Essential Tremor - cohort study and review of the literature

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Number of words:
Abstract: 250
Text: 2975 (+ 633 in supplementary methods)

Tables and figures:
Tables: [1] Literature review
Figures: [1A-C] Change of tremor severity and ADL following DBS, [2A-B] Reconstruction of DBS leads and visualization of active contacts, [3A-D] The tremor-suppressive cluster, its center of gravity and clusters associated with side effects; Prediction of clinical improvement based on the proximity to center of gravity; Coordinates from literature review; Prediction of tremor improvement based on the proximity of the literature-based coordinates to the "sweet spot" of our cohort.
Supplementary methods: [1] Surgical planning and procedure; Electrode localization and volume of tissue activated (VTA) estimation
Supplementary tables: [1] Scores and side effects, [2] Stimulation parameters, [3] Previously published "sweet spots" in MNI space
Supplementary figure [1]: Different VTA maps/methods to generate the probabilistic "sweet and sour spots" [2] Probabilistic stimulation map in axial and sagittal view.

References: 30

Keywords: Essential Tremor, Deep Brain Stimulation, ventral intermediate nucleus VIM, dentato-rubro-thalamic tract DRTT, sweet spot

Financial Disclosure / Conflicts of Interest
AAK reports honoraria and non-financial support from Medtronic, honoraria from Boston Scientific, Ipsen Pharma and Abbott. GHS reports honoraria for lectures by Medtronic, Boston Scientific and Abbott. CVR reports consultancies from AbbVie Pharma. DG reports Honoraria by Medtronic, AbbVie Pharma, Desitin Pharma, Licher GmbH, UCB Pharma. GE reports Honorary for Advisory Boards by AbbVie Pharma, BIAL Pharma, Desitin Pharma, STADA Pharma, Neuroderm Honorary for Lectures by Inc. AbbVie Pharma, BIAL Pharma, Britannia Pharma, Desitin Pharma, Licher GmbH, UCB Pharma, Zambon Pharma and Royalties from Kohlhammer and Thieme Verlag. DKu, DKr, BA and SE have nothing to disclose.

Study Funding
DKu and DKr supported by the BIH-Charité Clinician Scientist Program funded by the Charité-Universitätsmedizin Berlin and the Berlin Institute of Health. BA is funded by a Doctoral Research Grant from the German Academic Exchange Service (DAAD). AAK is supported by the DFG with the project grants KU 2261/13-1 and EXC 2049/1.

Abstract

Introduction

Deep brain stimulation (DBS) is a highly efficacious treatment for essential tremor (ET). Still, the optimal anatomical target in the (sub)thalamic area is a matter of debate. The aim of this study was to determine the optimal target of DBS for ET regarding beneficial clinical outcome and impact on activities of daily living as well as stimulation-induced side effects and compare it with previously published coordinates.

Methods

In 30 ET patients undergoing bilateral DBS, severity of tremor was assessed by blinded video ratings before and at 1-year follow-up with DBS ON and OFF. Tremor scores and reported side effects and volumes of tissue activated were used to create a probabilistic map of DBS efficiency and side effects.

Results

DBS was effective both in tremor suppression as well as in improving patient reported outcomes, which were positively correlated. The "sweet spot" for tremor suppression was located inferior of the VIM in the subthalamic area, close to the superior margin of the zona incerta. The Euclidean distance of active contacts to this spot as well as to 10 of 13 spots from the literature review was predictive of individual outcome. A cluster associated with the occurrence of ataxia was located in direct vicinity of the "sweet spot".

Conclusion

Our findings suggest the highest clinical efficacy of DBS in the posterior subthalamic area, lining up with previously published targets likely representing the dentato-rubro-thalamic tract. Side effects may not necessarily indicate lead misplacement, but should encourage clinicians to employ novel DBS programing options.

Introduction

Essential tremor (ET) is characterized by a progressive bilateral action tremor affecting the upper limbs and less commonly also the head, voice, trunk and lower limbs[1]. Cumulative evidence suggests that ET is not a single entity but rather a syndrome requiring further subclassification[2]. Pharmacological therapy may reduce tremor severity by 50% on average[3,4] but is often limited by side effects. In patients with symptoms refractory to medical therapy, deep brain stimulation (DBS) is a safe and effective treatment, even in the long term[5,6] or with advanced age[7]. After one year of bilateral DBS, tremor severity reduction of 66% - 78%[8] is reported, yet up to 90% tremor suppression can be reached in individual cases[9] while others barely respond to stimulation, for largely unknown reasons.

There is an ongoing debate about the optimal target coordinates, often referred to as the "sweet spot" for DBS in ET resulting in the most efficient tremor reduction. The classical DBS target for ET, the ventral intermediate nucleus of the thalamus (VIM)[10] represents a central node within the suggested tremor network connecting the primary motor cortex with the contralateral dentate nucleus via the dentato-rubro-thalamic tract (DRTT)[11]. Other than in the VIM, a comparable degree of tremor reduction has also been achieved with DBS in the posterior subthalamic area (PSA) and the caudal Zona incerta (Zi, details in table 1). For all of these targets, stimulation induced side effects such as ataxia, dysarthria and paraesthesia have been reported, which often limit the clinical potential of DBS by narrowing the therapeutic window, especially when the disease severity progresses[12]. Few studies have directly compared clinical efficacy on tremor reduction and occurrence of side effects between different target areas, with some indicating a higher prevalence of side effects with VIM-DBS[13].

The comparability of published targets across individuals and centers is complicated due to incongruent standards of how coordinates are reported relative to different anatomical landmarks or stereotactic standard spaces. To address this issue, Horn and colleagues recently proposed a method to transform landmark-based coordinates from individual space in a probabilistic fashion into a standardized stereotactic space[14].

This study aimed to define the areas associated with beneficial effect on tremor obtained from blinded video ratings as well as induction of side effects in standardized stereotactic space from a retrospective cohort. Furthermore, we sought to compare this "sweet spot" of DBS with previously published target coordinates that were reported to be effective for tremor suppression.

Methods

Patient selection

30 patients (12 female, average age 68±11 years) with ET refractory to medical therapy that underwent bilateral implantation of DBS leads between 11/2011 and 08/2017 were included in the retrospective analysis. We included subjects with the following clinical data available: (1) Preoperatively video-documented tremor assessment (PRE DBS) (2) postoperative imaging and (3) postoperative video-documented tremor assessment with DBS switched on (ON DBS) and off (OFF DBS) with documentation of stimulation settings at 1-year follow-up. All patients gave their written informed consent and the ethics committee of the Charité-Universitätsmedizin Berlin approved all study procedures. A detailed description of **surgical planning and procedure** is provided in the supplementary material of this article.

Blinded assessment of tremor severity

Symptom severity was assessed before surgery (PRE DBS) and after one year of chronic DBS (follow-up after 14±4 months, range: 10-35 months) using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) parts A and B[15]. Postoperative assessment was conducted ON and OFF DBS after deactivation for at least one hour. Tremor assessment was videotaped and TRS scores were rated offline by two movement disorder specialists blinded to the stimulation conditions. To ensure comparability of individual improvement with electrode localization across individuals, a subscore of all items addressing the upper limbs (TRS-UL consisting of the TRS items 5,6,11,12,13 and 14) was additionally calculated. The occurrence of stimulation induced side effects was extracted from clinical records. Health-related disability was assessed by the German version of the Bain and Findley Tremor Activities of Daily Living (ADL) scale[16] before surgery and at 1-year follow-up during DBS.

Electrode localization and probabilistic stimulation mapping

A detailed depiction of DBS lead localization, VTA estimation and probabilistic stimulation mapping of beneficial and side effects is provided as supplementary material.

Statistical analysis

IBM SPSS Statistics 25 (SPSS Inc., Chicago) and custom Matlab scripts (Mathworks, R2017a) were used for calculation of all test results. Two-sided p-values <0.05 were considered significant. Kolmorogov-Smirnov tests were used to test for normal distribution of the data. Wilcoxon signed-rank or paired t-tests were used for comparison of pre-and postoperative clinical data. Unpaired t- or Mann-Whitney tests were used to compare x, y and z dimensions of electrode coordinates across subgroups, depending on their normality distribution. We also calculated the Euclidian distance (proximity) of the active contacts of each hemisphere to our "sweet spot". This proximity index was then fed into a linear regression model in order to predict tremor improvement in the contralateral upper limb.

Literature review and relation to our "sweet spot"

A systematic was conducted on https://www.ncbi.nlm.nih.gov/pubmed to identify studies reporting on clinical efficacy of DBS for ET with respect to coordinates in neuroanatomical space (last update 03/22/2020). Search terms were "coordinate* / active contact* / lead location" AND "essential tremor / (sub/thalam*) deep brain stimulation / effect". Publications with less than 5 individuals with ET were discarded. Publications from the functional neurosurgery field usually report coordinates relative to the AC-PC line in an unstandardized fashion. To facilitate spatial comparability, we used Lead-DBS to convert the AC-PC coordinates to MNI space and vice versa following a recently introduced probabilistic conversion algorithm[14]based on our cohort images. This allowed visualizing all coordinates from the literature and results of this study in a common space.

Next, we investigated how these literature-based DBS coordinates can predict tremor improvement in our cohort. Proximity as calculated by Euclidean distances between 59 lateralized active contacts coordinates and each of the 13 literature-based coordinates were used to predict respective contralateral upper limb tremor improvement in a linear regression model. The resulting R-values were attributed to each of the literature-based coordinates indicating the strength of prediction. P-values were corrected for multiple comparison using false discovery rate.

Results

DBS effects on tremor suppression and ADL

Individual pre- and postoperative tremor and ADL scores as well as electrode models and stimulation parameters are summarized in supplementary table 1 and 2. Impedance testing in all patients ruled out malfunctions of DBS leads.

Average symptom severity measured by TRS was 31.6±11.5 PRE DBS. After one year ON DBS, a significant reduction by 57%±22% in the TRS score was observed (average 12.8±8.6, $p<0.001$). After transient deactivation, reemergence of tremor was observed OFF DBS (33.8±19.0, $p<0.001$, figure 1A).

Seven patients with less than 40% improvement at 1-year follow-up (range from -4.0% to 37.5%) were categorized as poor responders and 13 patients with more than 65% clinical improvement (range from 66.7% to 90.0%) as excellent responders. Stimulation amplitudes did not differ significantly between excellent and poor responders (2.3±0.9 vs. 2.3±0.4).

The subscore of all items addressing the upper limbs (TRS-UL) showed a similar degree of tremor suppression from 29.1±7.6 to 11.6±7.4 points (improvement of 57%±23%, $p<0.001$, figure 1B). TRS and TRS-UL showed high congruency when correlated ($R=0.99$, $p<0.001$).

The preoperative ADL score of 23.4±10.0 (range 8-46) was significantly reduced by 54%±31% following DBS (11.2±8.6, $p<0.001$). This reduction showed a significant correlation with the reduction of symptom severity assessed by the TRS and TRS-UL ($R= 0.41$, $p=0.04$, Fig1C).

Determination of the "sweet spot"

Electrode localizations in MNI space and positions of active contacts are shown in figure 2A and 2B. Probabilistic mapping informed a cluster spanning the area of the VIM and Zi (cluster size 278.88 mm^3, supplementary figure 2) including voxels with >10 VTAs and >40% tremor improvement. The MNI coordinates of the cluster's center of gravity were x=-14.5, y=-16.5 and z=-3.5 (with an average tremor improvement of 69.6%) corresponding to x =-14.44±1.20, y=-5.93±1.24 and z=-0.61±0.76 when converted to AC-PC stereotactic space. The resulting spot was inferior to the lower margin of the VIM adjacent to the upper margin of the Zi (red spot in figure 3A). Of note, the MNI coordinates of the voxel with maximum average tremor improvement of 70.5% were x=-12; y=-19.5 and z=-5.5.

The proximity of the active contacts to the center of gravity of the "sweet spot" was significantly predictive of tremor improvement ($R=0.35$, $p=0.006$, Fig3B).

Stimulation induced side effects and determination of "sour spots"

17 patients reported no side effects following DBS. 13 patients reported one or two side effects: Gait ataxia was documented nine times, dysarthria six times and dyskinesias in two cases (see supplementary table 1). Patients with ataxia, the most frequently reported side effect, had a significantly higher stimulation amplitude for left-hemispherical DBS (ataxia: 3.0±1.1V/mA, no ataxia: 2.2±0.7V/mA, $p=0.04$). Side effects occurred more often in patients with excellent but also in some with poor clinical effect of DBS tremor suppression, i.e. of the 13 excellent responders, five patients reported adverse effects (one ataxia, one dysarthria and three ataxia and dysarthria). Of the seven poor responders, one patient reported ataxia and one

dyskinesia. ADL scores in the subgroup with ataxia did not differ significantly from those without ataxia (12.1±3.7 vs. 10.7±10.3, p=0.11).

In patients with ataxia, x-coordinates of the left and right hemisphere were not significantly different after being flipped to one hemisphere for comparability. X, Y and Z coordinates did not differ significantly between patients with and without ataxia.

Clusters of voxels associated with gait ataxia were depicted in an area medial and adjacent to the center of gravity of the probabilistic map (Figure 3A). Of note, both tremor suppressive and gait ataxia clusters ranked 1000/1000 in statistical permutation tests.

Relation to previously reported target coordinates

13 studies on clinical efficiency of DBS for ET reporting corresponding coordinates of active contacts could be included in our literature review (see table 1). Patient characteristics, targets and localization methods differ strongly across publications with reported favorable outcomes for electrodes and/or active contacts located in the VIM as well as in the PSA and Zi. All coordinates extracted from previous studies were transformed to MNI space (supplementary table 3) and plotted along with our "sweet spot" in figure 3C. The average distance of the literature-based spots to the center of gravity of our "sweet spot" was 3.29 mm±1.39, with 7 out of 13 studies reporting coordinates within less than this average distance.

Additionally, we explored how these literature-based coordinates could predict our cohort improvement score. Ten out of thirteen literature-based coordinates were predictive of tremor improvement (refer to supplementary table 3 for respective R and corrected p values). The more proximal the coordinate to our sweet spot center of gravity, the higher the R-value (Figure 3D). The position of predictive coordinates was in the vicinity of our sweet spot center of gravity. Non-predictive coordinates were located dorsally inside the thalamic VIM nucleus. Of note, this analysis was not meant to test the validity of the aforementioned coordinates as targets/spots for tremor control but to investigate the relation of literature-based coordinates to our sweet spot.

Discussion

In this study, we have used a probabilistic approach to delineate a cluster associated with effective tremor suppression in the PSA close to the upper margin of the Zi as well as a cluster associated with gait ataxia located in close vicinity from blinded video ratings and postoperative imaging from a single center cohort of 30 patients. We have further explored the spatial relations to 13 previously published coordinates that were reported to be associated with tremor suppression.

Spatial relations to "sweet spots" from literature

The center of gravity of the probabilistic map of our cohort was in close proximity to 7 of the 13 previously reported coordinates associated with tremor suppression that span beyond the VIM over the adjacent PSA into the Zi. As active contacts were dispersed across VIM to Zi, anatomical variance may explain why the average tremor suppressive effect (57.6%) was less than for most coordinates from our literature review. Active contacts residing within the cluster determined with probabilistic modelling yielded on average 69.9% tremor improvement, yet the probabilistic approach used in this study accounts for the variability of all clinical outcomes including poor and excellent responders alike into the generation of the stimulation map. It must be stressed that the coordinates provided do not represent a suggestion for a stereotactic target rather than a mathematically determined point within a cluster of active contacts of the DBS leads associated with tremor suppression.

To date, only one randomized controlled trial has compared outcomes between targeting VIM and PSA in patients with ET, suggesting the latter to be potentially more efficient[13]. This was further specified by Dembek and colleagues[17], who importantly demonstrated that for both targets, a shorter distance to the DRTT was associated with lower stimulation amplitudes and greater efficiency of tremor suppression. Other authors support the notion that the distance to the DRTT is more relevant in terms of clinical efficacy than a specific set of coordinates[18–20]. Using a different methodology based on structural and functional connectivity profiles associated with favorable clinical outcome, our group has recently concluded that different target regions may in fact be representations of a common anatomical correlate[21] in form of a fiber tract passing along the red nucleus through the Zi, via the PSA towards the thalamus. Of note, the spot associated with the ideal connectivity profile for tremor suppression was located ventrolateral to the thalamus, directly inferior to the VIM, congruent to the entry point of cerebellar efferences to the thalamus. Fiechter and colleagues suggest that effective treatment of tremor in Parkinson's disease might as well be mediated by stimulation of the DRTT[22].

Relation between tremor effect and patient reported outcome

The functional relevance of the degree of tremor reduction was further underlined by the correlation of patient reported outcome (ADL) with tremor suppressive effect. This is an important finding adding to previous studies from our group[21] since the occurrence of stimulation induced side effects may be perceived as an overall unsuccessful therapy despite effective tremor suppression. Only few studies[19,23,24] have included patient reported

outcomes so far, although it is obvious that the patients' perception of clinical improvement is a highly relevant factor for the success of the therapy.

Characteristics of the "sour spot" associated with ataxia

Interestingly, in our cohort the cluster associated with ataxia was in close vicinity to voxels with effective tremor suppression. Although spatial distribution of x,y and z coordinates of active contacts did not differ between subgroups with and without side effects, it needs to be stressed that interindividual neuroanatomical differences regarding structures mediating side effects may not be represented due to the conversion into MNI space. Groppa and colleagues previously demonstrated that an increase of stimulation amplitude beyond the tremor suppressive effect induces limb ataxia[25] presumably conveyed by fibers representing cerebello-rubro-thalamic afferences that are of different myelinization thickness as concluded from analyses of strength-duration curves. In a follow-up study, FDG-PET identified a hypermetabolism in the cerebellar vermis[26] as a correlate of progressive gait ataxia following DBS. VTAs of patients with gait ataxia were located more posteromedial and caudal in the subthalamic area. In line with this, we found significantly higher stimulation amplitudes of the left, but not of the right hemisphere in our nine patients with ataxia compared to those without ataxia, potentially representing supratherapeutic stimulation amplitudes.

Similar to recent reports on pallidal DBS in dystonia[27], our analysis revealed sour spots close to an area with high tremor suppression suggesting that fiber bundles mediating effective tremor suppression and ataxia reside in close vicinity. Describing a similar spatial association of therapeutic and side effects, Dembek and colleagues report that the superior tremor suppression of DBS in the Zi compared to VIM resulted in a higher rate of paresthesia and dizziness[28], side effects that were not reported in our cohort. Further localized mapping of side effects combined with fiber tracking or electrophysiology is needed to dissect these structures.

Implications for DBS programming strategies

Due to the density of neuroanatomical structures in the subthalamic area, the occurrence of stimulation induced side effects requires careful consideration of strategies that allow to focus DBS on structures mediating beneficial effects. Accounting for individual anatomical variances, implantation of DBS leads based on tractography has been shown to result in better tremor control, quality of life and less adverse effects compared to conventional, landmark based implantation[19]. Furthermore, advanced programming strategies may help to reduce side effects[29]. Previously, our group has demonstrated the reversibility of stimulation induced gait ataxia following adaptation of DBS settings to shorter pulse widths that allowed equal tremor suppression to standard settings[43] speculated to differentially activate fiber tracts mediating desired and adverse effects. Another way to focus the electric field are modern directional DBS leads that feature radially segmented electrodes, allowing for steering and shaping of the electrical field in order to increase thresholds for side effects and thereby broaden the therapeutic window[30].

Limitations of the study

A major limitation is the retrospective single center design of this study. In order to minimize limitations, video raters were blinded to the stimulation condition during tremor assessment. As videos focused on tremor assessment, quantitative ataxia measures could not be provided, yet we chose to include binary information on the occurrence of ataxia to include any form of ataxia documented in the patient records.

Conclusions

We provide a probabilistic map of tremor suppression from a single center cohort based on blinded video ratings using probabilistic simulation mapping. Further, we explored spatial relations to previously described coordinates associated with beneficial outcome that were converted to a common neuroanatomical space for this purpose. We conclude that the multitude of coordinates associated with beneficial outcome might be representations of a single neuroanatomical correlate. The occurrence of side effects should therefore not necessarily be interpreted as a misplacement of leads, but rather encourage clinicians to make full use of the range of programming and steering options of DBS.

Acknowledgements

We thank our patients for their consent to include their clinical and imaging data in this study. We gratefully thank Dr. Andreas Horn for providing methodological support, Anne-Christiane Meyer and Bianka Ahmad for their assistance in executing the blinded video ratings and Dr. Julius Hübl for his assistance with clinical duties.

Authors' Roles

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique.

D Kübler: 1A-C, 2A-C, 3A
D Kroneberg: 1C, 2A-C, 3A
B Al-Fatly: 1 C, 2A-C, 3B
GH Schneider: 1C, 3B
S Ewert: 2A, 2B
C van Riesen: 1C, 2C, 3B
D Gruber: 2C, 3C
G Ebersbach: 2C, 3C
A Kühn: 1A, 1B, 2C, 3B

Figure legends

Figure 1: Changes of tremor severity and ADL following DBS. **A:** Fahn-Tolosa-Marin tremor rating scale total score (TRS). **B:** Subscore of items measuring tremor and performance (pouring, drawing etc.) of upper limbs (TRS-UL). Red bars indicate group average and standard deviation. **C:** Pearson's correlation of relative improvement from timepoints preOP to onDBS of TRS-UL and ADL scores.

Figure 2 A: Electrode localizations in MNI space in the area of the thalamus (blue mesh) and its VIM (violet) spanning across the zona incerta (Zi, green) to the subthalamic white and grey matter. The subthalamic nucleus (STN) is shown in yellow. Right-sided electrodes have been flipped to the left side, thus all electrodes are shown on the left hemisphere. **B:** Active contacts shown as red spheres in relation to aforementioned basal ganglia structures.

Figure 3 A: Probabilistic stimulation map of VTAs associated with tremor suppression shown in faint yellow (cluster threshold >10 VTAs and >40% average tremor improvement per voxel). The "sweet spot" represented by the center of gravity (red) was calculated. The clusters of voxels associated with gait ataxia ("sour spots", center of gravity in green) lie within the voxel cluster associated with tremor suppression and in vicinity of its center of gravity. **B:** Euclidean distance of active DBS contacts to center of gravity was predictive of individual relative improvement of TRS scores from PRE DBS to ON DBS. **C:** The center of gravity of our PSM (red) is shown in comparison to previously published AC-PC to MNI converted spots. Median Euclidian distance of literature-based spots was 3.28 mm, with 7/13 spots residing within less than the average distance of 3.29 ± 1.39 mm. **D:** Prediction of

tremor improvement based on coordinates from literature. Using Euclidean distance (proximity) between active DBS contacts and literature coordinates, tremor improvements in our cohort could be predicted from 10 of the 13 coordinates included in this study. More ventral coordinates in the region of posterior subthalamic area were more predictive. Each coordinate has been color coded with its respective R-value. Prediction using proximity of active contacts to center of gravity of current study sweet spot is shown in upper-right. Notably, predictive coordinates tend to cluster around current study sweet coordinate.

Supplementary Figure 1: Different VTA maps to generate probabilistic VTA derived sweet spot. Tremor suppression and gait ataxia associated *p*-maps were generated using the method described in Dembek et al., 2017. A-maps represent the average of tremor improvement in each voxel as described in the method section of the article. The centroid represents the significant peak voxels in each a-map surviving 1000x permutation tests to adjust for multiple comparison. Tremor suppression and ataxia maps were masked for voxels containing >10 and >4 VTAs respectively.

Supplementary Figure 2: Probabilistic map of tremor suppressive effect from threshold of 40% tremor improvement (red colors) up to 70% (yellow colors) in axial (upper panel), sagittal (middle panel) and coronar (bottom panel) slices, superimposed on sections of 7 Tesla MRI of ex vivo human brain at 100 micron resolution (Edlow et al., 2019) with depth of planes provided for each view.

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Table 1

Publication	Main study question	Number of patients	Age at surgery (years)	X ± SD (left / right if given)	Y ± SD (left / right if given)	Z ± SD (left / right if given)	Y given relative to	Main results
Tsuboi et al., 2020[1]	Longitudinal follow-up of tremor suppression and ADL scores in dystonic and essential tremor	- 97 with ET	67.4 ± 9.6	14.3 ± 1.6	-4.3 ± 1.5	2.1 ± 2.3	MCP	- Tremor suppression and effect on ADL remained significant for 4-5 years - After 12 months 55.2% tremor reduction in ET group
Low et al., 2019[2]	Comparison of conventional and DTI-guided PSA-DBS (RCT)	- 17 ET patients, 7 implanted according to DTI, 10 conventionally	Together with PD patients: - DTI: 70.4 ± 8.5 - Conventional: 54.2 ± 18.7	-10.6 ± 1.1 / 10.0 ± 0.9	−7.7 ± 1.6 / −7.4 ± 1.4	−3.8 ± 0.6 / −4.0 ± 0.5	MCP	- Lead implantation according to DTI of the DRTT results in better tremor control and more ADL improvement - After 12 months 85.6% (DTI) and 70.1% (conventional) tremor reduction
Barbe et al., 2018	Comparison of PSA- and VIM-DBS (RCT)	- 13 ET patients, all implanted bilaterally - Crossover design	58.9 ± 17.0	-11.0 ± 1.4	-5.7 ± 1.4	-1.9 ± 0.6	MCP	- Coordinates of PSA contacts with 64% tremor reduction - No difference in tremor reduction between PSA- and VIM-DBS - Lower stimulation amplitudes needed in PSA group for equal benefit
Eisinger et al., 2018[3]	Comparison of Zi- and VIM-DBS	- 47 ET patients - 41 of them implanted unilaterally	64.8 ± 10.8	-14.4 ± 1.4	-4.1 ± 1.5	2.7 ± 1.5	MCP	- Coordinates of VIM-group with better long-term effect - At 3 years 79-94% improvement under VIM-DBS versus 38-73% under Zi-DBS
Fenoy and Schiess, 2017[4] / **Fenoy and Schiess, 2018**[5]	Efficacy of DBS with direct targeting of the DRTT	- 20 ET patients - 2 of them implanted unilaterally	66.8 (41-84)	-13.5 ± 1.8 / 13.5 ± 1.8	-6.3 ± 1.6 / -5.8 ± 1.6	2.9 ± 2.7 / 1.7 ± 2.5	MCP	- Coordinates of contacts planned relative to DRTT - In the 2018 paper compared to 20 ET patients with standard planning - Equal tremor effect but lower stimulation parameters in DRTT group
Cury et al., 2017[6]	Long-term outcome of thalamic DBS for ET, PD and DYT	- 38 ET patients - 3 of them implanted unilaterally	63.6 ± 10.9	-14.7 ± 1.9 / 14.9 ± 2.1	7.1 ± 1.4 / 6.8 ± 1.9	1.8 ± 2.2 / 2.9 ± 2.8	PC	- Coordinates of good responders (25 ET patients with ≥ 60% tremor improvement) - Overall improvement under VIM-DBS for ET 66% after 1 year and 48% after 10 years
Fiechter et al., 2017	Search for common target in tremor dominant PD (STN) and ET (VIM)	- 12 ET patients, 3 of them implanted unilaterally	71 ± 11	-14.3 ± 1.6	-5.0 ± 0.9	0.9 ± 1.2	MCP	- Coordinates of ET patients - 54% overall improvement - improvements in resting 75%, postural 56% and intentional tremors 35%

Fytagoridis et al., 2016 [7]	Efficacy of cZi-DBS	- 50 ET patients with cZi-DBS - 8 of them implanted bilaterally - 2 of them implanted double-ipsilaterally	63.5 ± 13.1	-11.9 ± 1.8	-6.2 ± 1.8	-2.0 ± 2.3	MCP	- Coordinates of group with excellent improvement (≥ 90%) of tremor and hand function
Sandvik et al., 2012[8]	Comparison of PSA- and VIM-DBS	- 36 ET patients - 4 of them implanted unilaterally - 4 of them implanted double-ipsilaterally	56.7 ± 15.3	-12.1 ± 1.8	-5.5 ± 1.9	-1.2 ± 2.9	MCP	- Coordinates of the 40 contacts achieving improvement in hand function and tremor reduction of ≥ 90% - 37 of these contacts were part of the PSA group
Barbe et al., 2011[9]	Comparison of VIM-DBS below and above AC-PC	- 21 ET patients - 2 of them implanted unilaterally	not given	-11.3 ± 1.6	-7.2 ± 1.7	-1.4 ± 1.2	MCP	- 17 electrodes with sub-ICL contacts with 65% tremor reduction - No significant difference compared to above-ICL - Within subject comparison with equal parameter settings showed increased effectiveness of sub-ICL contacts
Pilitsis et al., 2008[10]	Optimal contacts for tremor suppression in VIM-DBS	- 27 ET patients - 22 of them implanted unilaterally	67.0 ± 12.0 (patients with favorable outcome)	-12.9 ± 1.6	5.7 ± 1.5	0.1 ± 1.7	PC	- 26 ET patients (22 of them implanted unilaterally) with satisfactory outcome - No scores or relative change given
Papavasiliou et al., 2004[11] **(reprint 2008)**	Optimal target for tremor improvement	- 37 ET patients - 21 of them implanted unilaterally	66.2 ± 13.6 (31-85)	-12.3 ± 1.7	6.3 ± 1.5	0.8 ± 2.5	PC	- Coordinates of statistically determined optimal electrode location - Leads with less than 2mm distance to this theoretical optimal target had a 64% likelihood of causing ≥ 66% reduction
Murata et al., 2003[12]	Efficacy of DBS for ET relative to active contact	- 8 ET patients with severe involvement of proximal arms - All implanted unilaterally	64.6 (50-72)	-10.9 ± 0.8	-7.6 ± 1.2	-3.9 ± 1.7	MCP	- Coordinates of 7 contacts in the subthalamic white matter (prelemniscal radiation and cZi) resulting in tremor improvement of ≥71%

Results of literature search identifying studies that report on clinical effects of DBS for ET relative to the active contacts used for chronic stimulation. Coordinates that led to the best outcome in terms of tremor control when activated are reported for each of the studies. In the AC-PC system, the x-axis runs from left (negative values) to right (positive values) through AC. Values on the y-axis are given relative to PC or to the midcomissural point (MCP).

DTI: diffusion tensor imaging MR, RCT: randomized controlled trial, PSA: posterior subthalamic area, MCP: midcommissural point, PC: posterior commissure, (c)Zi: (caudal)Zona incerta

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Supplementary table 1

Patient number	Sex	Age at operation (years)	TRS preDBS	TRS onDBS	TRS offDBS	TRS-UL preDBS		TRS-UL onDBS		TRS-UL offDBS		ADL preDBS	ADL postDBS	% TRS improvement onDBS vs. offDBS	% TRS improvement onDBS vs. preDBS	% ADL improvement after vs. before DBS	% TRS-UL improvement onDBS vs. offDBS	% TRS improvement onDBS vs. preDBS	side effects
						R	L	R	L	R	L								
1	f	78.9	44	19	62	16	17	8	10	20	21	46	15	69.4	56.8	67.4	56.1	45.5	-
2	m	73.3	27	5	26	14	9	2	2	13	9	21	17	80.8	81.5	19.1	81.8	82.6	-
3	f	71.5	38	7	46	17	12	4	1	15	18	19	10	84.8	81.6	47.4	84.8	82.8	slight gait ataxia
4	f	25.2	15	11	15	5	7	4	4	7	7	21	8	26.7	26.7	61.9	42.9	33.3	-
5	m	74.5	22	14	36	8	11	5	8	15	15	31	13	61.1	36.4	58.1	56.7	31.6	gait ataxia
6	m	77.6	33	14	29	14	16	6	6	12	10	29	10	51.7	57.6	65.5	45.5	60.0	slight gait ataxia
7	m	74.8	34	12	16	9	16	4	6	8	4	32	2	25	64.7	93.8	16.7	60.0	slight dysarthria
8	f	72.1	19	8	20	8	8	4	3	6	13	27	26	60	57.9	3.7	63.2	56.3	-
9	m	73.9	30	3	38	15	13	0	3	15	15	16	10	92.1	90.0	37.5	90.0	89.3	slight gait ataxia, dysarthria
10	m	55.3	16	10	22	5	9	4	5	8	8	16	7	54.6	37.5	56.3	43.8	35.7	-
11	f	69.8	48	25	38	20	18	9	12	13	18	21	8	34.2	47.9	61.9	32.3	44.7	right-sided dyskinesia
12	f	70.7	39	12	63	18	12	3	6	22	22	44	12	81.0	69.2	72.7	79.5	70.0	gait ataxia, slight dysarthria
13	m	70.7	29	11	18	11	12	2	8	5	8	32	20	38.9	62.1	37.5	23,1	56.5	gait ataxia
14	m	65.5	31	6	18	14	13	5	0	10	5	28	7	66.7	80.7	75.0	66.7	81.5	-
15	m	56.0	25	5	37	12	11	2	2	18	11	33	14	86.5	80.0	57.6	86.2	82.6	gait ataxia, slight dysarthria
16	f	69.9	44	11		15	17	6	4			22	6		75.0	72.7		68.8	-
17	f	69.0	56	7	52	22	18	2	4	23	20		8	86.5	87.5		86.0	85.0	-
18	m	71.1	41	16	32	17	19	5	9	11	18		27	50.0	61.0		51.7	61.1	-
19	f	71.1	19	11	18	8	10	5	6	7	10	10	2	38.9	42.1	80.0	35.3	38.9	-
20	m	66.4	31	10	26	7	19	4	5	7	15	17	5	61.5	67.7	70.6	59.1	65.4	-
21	m	47.5	12	10	18	5	6	7	3	8	7	11	5	44.4	16.7	54.6	33.3	9.1	-
22	m	58.7	36	16	50	14	18	4	11	17	24	17	7	68.0	55.6	58.8	63.4	53.1	ataxia, dysarthria

23	f	76.5	35	13	19	16	5	4	4	8	4	26	13	31.6	62.9	50.0	33.3	61.9	ataxia
24	m	58.2	19	5	19	11	5	2	2	12	3	12	0	73.7	73.7	100	73.3	75.0	-
25	m	75.4	25	26	30	9	13	7	16	9	18	8	10	13.3	-4.0	-25.0	14.8	-4.5	dyskinesia (onDBS only used for eating)
26	f	77.2	20	14	20	9	4	7	3	10	5	32	38	30.0	30.0	-18.8	33.3	23.1	-
27	m	58.8	30	10	19	9	14	2	5	6	10	13	1	47.4	66.7	92.3	56.3	69.6	-
28	m	70.7	45	13	75	15	19	4	4	24	24			82.7	71.1		83.3	76.5	-
29	f	71.1	54	49	84	21	20	16	20	24	24			41.7	9.3		25.0	12.2	-
30	m	75.6	31	10		13	13	4	4						67.4			69.2	slight dysarthria

Supplementary table 2

Patient number	Sex	Age at surgery (years)	Electrode model	Contact(s) right	Amplitude right	Contacts(s) left	Amplitude left	µs left	Hz left
1	f	78.9	Medtronic 3387	C+ 1-	2.1V	C+ 5-	2.0V	60	130
2	m	73.3	Medtronic 3387	C+ 1-	2.0V	C+ 9-	2.3V	90	130
3	f	71.5	Medtronic 3387	C+ 1-	2.4V	C+ 9-	3.6V	60	160
4	f	25.2	Medtronic 3387	0+ 1-	1.5V	9+ 8-	2.5V	90	130
5	m	74.5	Medtronic 3387	C+ 1-	2.8V	C+9-	2.8V	60	130
6	m	77.6	Medtronic 3387	C+ 0-	2.0V	C+ 0-	2.0V	60	130
7	m	74.8	Medtronic 3387	C+ 1-	3.4V	C+ 9-	2.7V	90	130
8	f	72.1	Medtronic 3387	C+ 0-	2.0V	C+ 10-	3.0V	90	130
9	m	73.9	St. Jude Medical 6143	2+ 1-	2.5mA	2+ 1-	5.5mA	100	130
10	m	55.3	Medtronic 3387	C+ 2-	1.6V	C+ 10-	2.4V	60	130
11	f	69.8	Medtronic 3387	C+ 0- interleaved C+ 1-	2.7V 1.3V	C+ 8- interleaved C+ 9-	0.9V 0.8V	60	120
12	f	70.7	Medtronic 3387	C+ 0-	2.0	9+ 8-	2.3	60	180
13	m	70.7	Medtronic 3387	C+ 1-	2.0	C+ 9-	3.1	60	180
14	m	65.5	St. Jude Medical 6143	C+ 3-	2.8mA	C+ 7-	2.8mA	60	210
15	m	56.0	Boston Scientific Vercise Cartesia	C+ 13- 14-	3.0mA	C+ 4- 7-	3.0mA	60	130
16	f	69.9	Medtronic 3387	C+ 0-	2.1V	C+ 8-	3.4V	60	200
17	f	69.0	Medtronic 3387	C+ 2-	2.8V	C+ 9-	2.6V	60	130
18	m	71.1	Medtronic 3387	C+ 0-	1.6V	C+ 11-	1.4V	90	130
19	f	71.1	Medtronic 3387	C+ 1-	2.4V	8+ 10+ 9-	2.9V	150	130
20	m	66.4	Medtronic 3387	C+ 1	2.4V	C+ 9-	1.7V	60	130
21	m	47.5	Boston Scientific Vercise	C+ 15-	3.0mA	C+ 6- 7- 8-	3.0mA	60	174
22	m	58.7	Boston Scientific Vercise Cartesia	C+ 11- 12-	2.4mA	C+ 3- 4-	2.8mA	70	174
23	f	76.5	Medtronic 3387	C+ 10- interleaved C+ 11-	2.1V 4.1V	C+ 3-	2.0V	60	125
24	m	58.2	Boston Scientific Vercise		Off	C+ 1- 2-	1.3mA	60	174
25	m	75.4	Medtronic 3387	2+ 3-	2.8	C+ 9-	1.7V	60	130
26	f	77.2	Boston Scientific Vercise	C+ 13-	1.5mA	C+ 4-	2.5mA	40	130

27	m	58.8	Boston Scientific Vercise	C+ 5- 6-	0.5mA	C+ 3- 4-	0.9mA	60	159
28	m	70.7	Medtronic 3387	C+ 1-	1.5V	C+ 9-	2.8V	90	130
29	f	70.1	Medtronic 3387	C+ 2- interleaved C+ 3-	2.1V 2.5V	C+ 10- interleaved C+ 11-	1.9V 1.8V	120	125
30	m	75.6	Medtronic 3387	C+ 1-	1.7V	C+ 9-	1.7V	60	130

m: male, f: female, C: case (of implantable pulse generator), V: Volt, µs: microseconds, Hz: Hertz

Supplementary table 3

Publication	Coordinates of spot in MNI space (right hemisphere)			Prediction of individual improvement by Euclidean distance to respective spot	
	x	y	z	R	p
Kübler, Kroneberg et al. 2020	-14,5	-16,5	-3,5	***0.35***	***0.006***
Tsuboi et al., 2020	-14,24	-14,77	-5,37	***0.30***	***0.04***
Low et al., 2019	-10,37	-18,26	-7,5	***0.28***	***0.04***
Barbe et al., 2018	-11,52	-17,54	-5,38	***0.30***	***0.04***
Eisinger et al., 2018	-14,38	-14,45	0,4	0.06	0.65
Fenoy and Schiess, 2017 Fenoy and Schiess, 2018	-13,93	-17,75	1,05	0.16	0.23
Cury et al., 2017	-15,50	-16,34	-0,66	0.23	0.09
Fiechter et al., 2017	-14,33	-15,46	-1,73	***0.29***	***0.04***
Fytagoridis et al., 2016	-11,92	-16,85	-5,27	***0.30***	***0.04***
Sandvik et al., 2012	-12,09	-16,09	-4,37	***0.31***	***0.04***
Barbe et al., 2011	-11,38	-17,94	-4,52	***0.31***	***0.04***
Pilitsis et al., 2008	-12,99	-17,59	-2,59	***0.34***	***0.04***
Papavasilliou et al., 2004 (reprint 2008)	-12,81	-16,31	-3,82	***0.34***	***0.04***
Murata et al., 2003	-10,99	-18,39	-7,47	***0.28***	***0.04***

Supplementary table 3: Probabilistic conversion coordinates of DBS targets associated with tremor suppression that were included in this study to MNI space following Horn et al., Neuroimage 2017. R and p values were obtained from linear regression model with individual improvement of TRS (PRE DBS vs. ON DBS) as dependent variable and Euclidean distance from respective coordinate as dependent variable, thus representing strength of prediction. p-values were corrected for multiple comparisons using false discovery rate (Benjamini&Hochberg).

Figure 1

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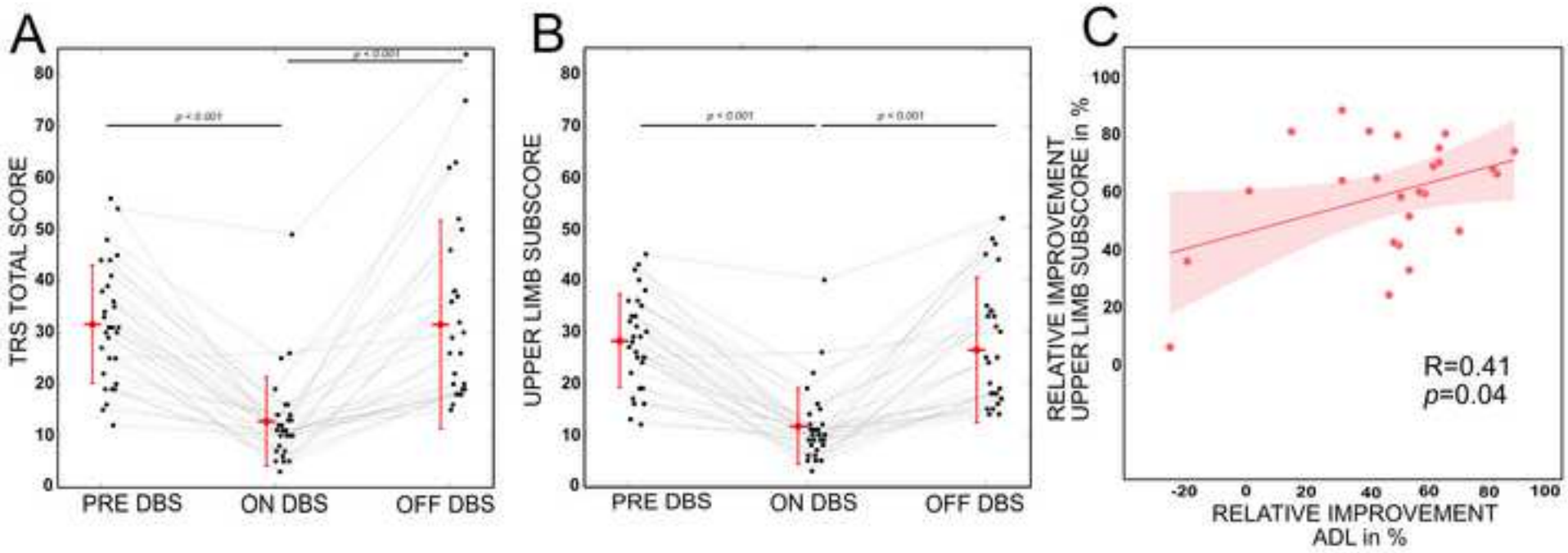

Figure 2

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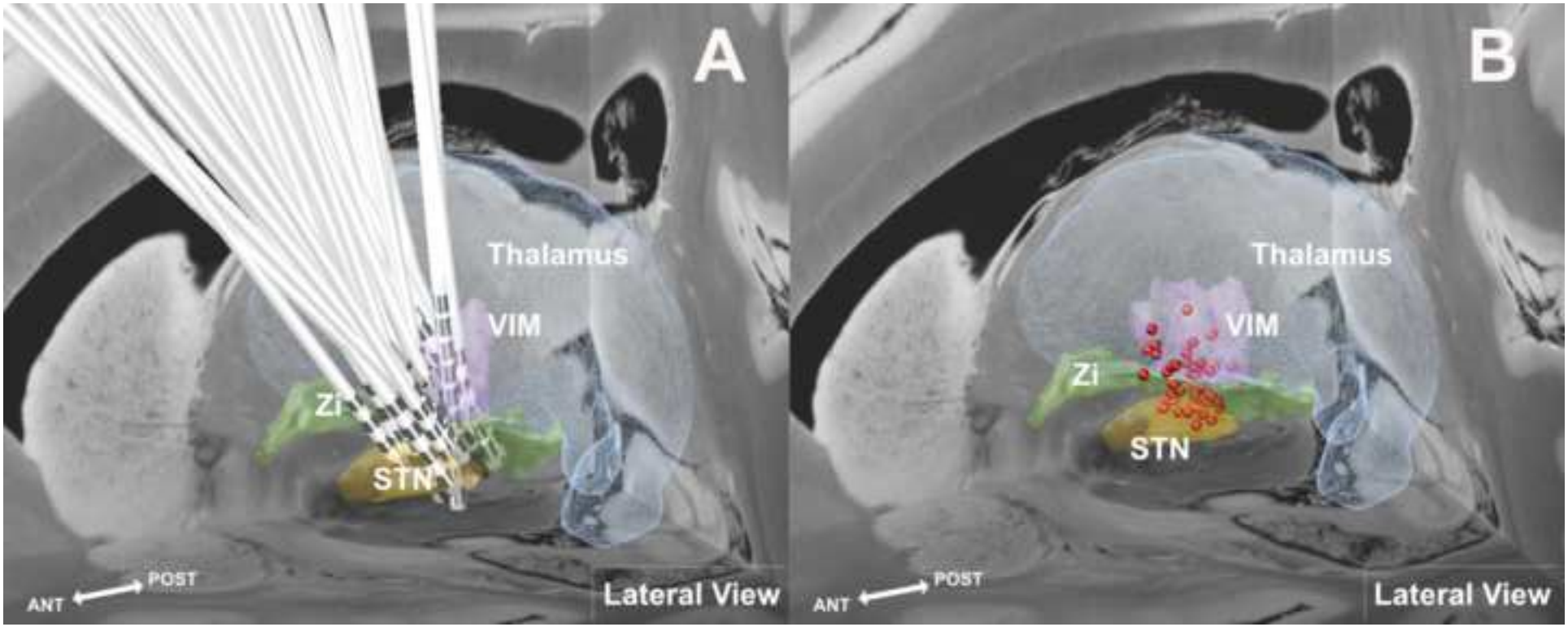

Figure 3

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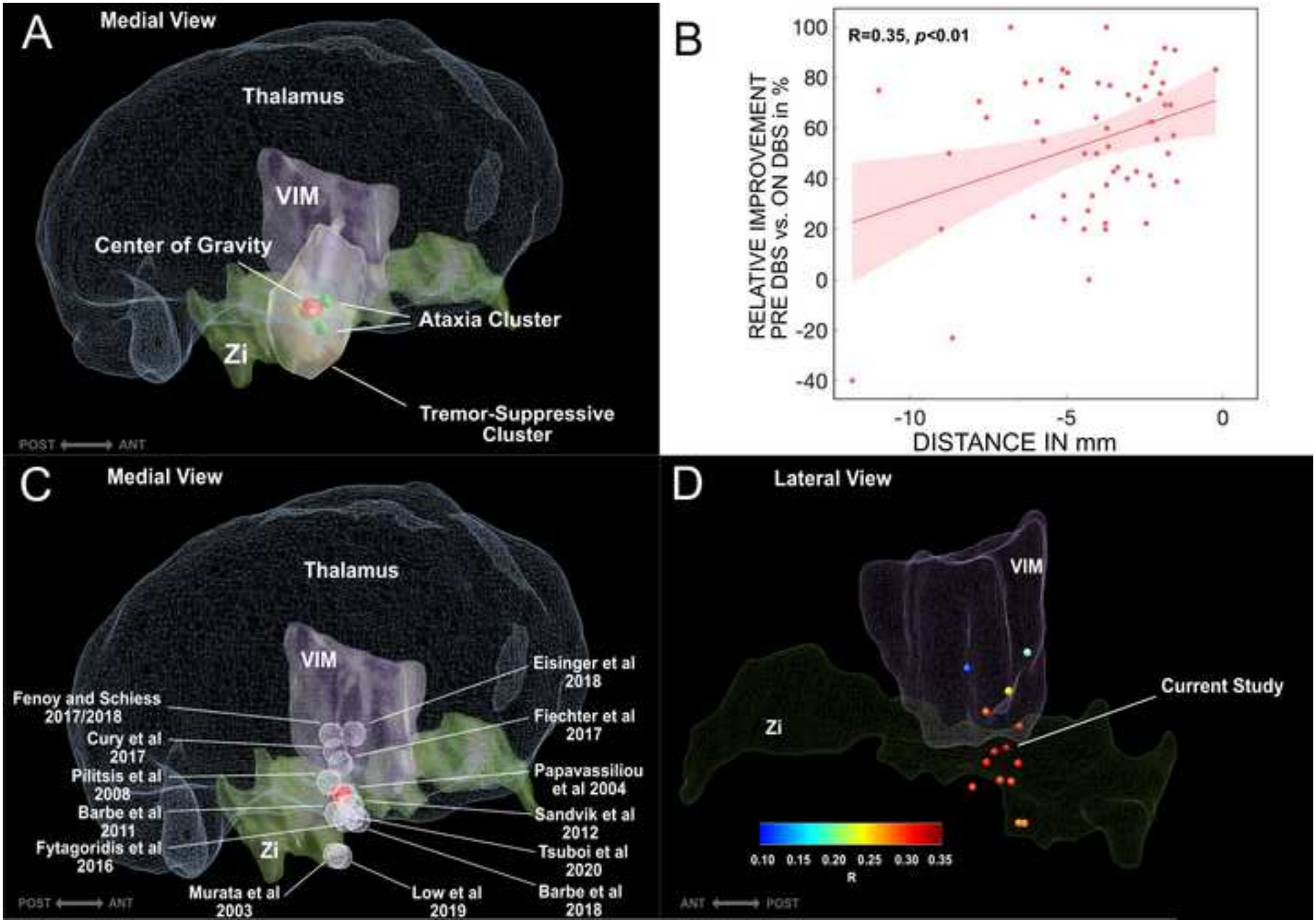

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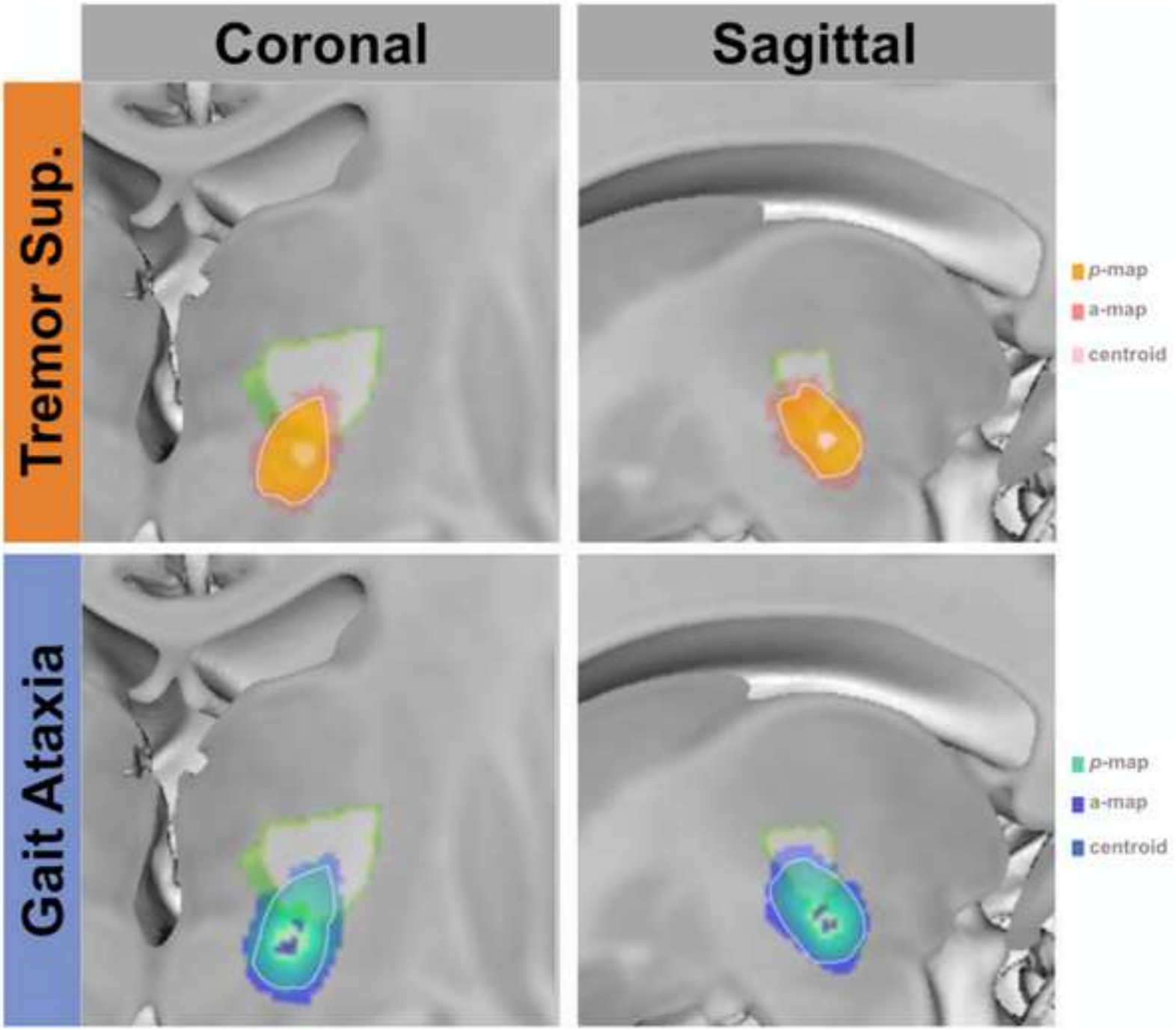

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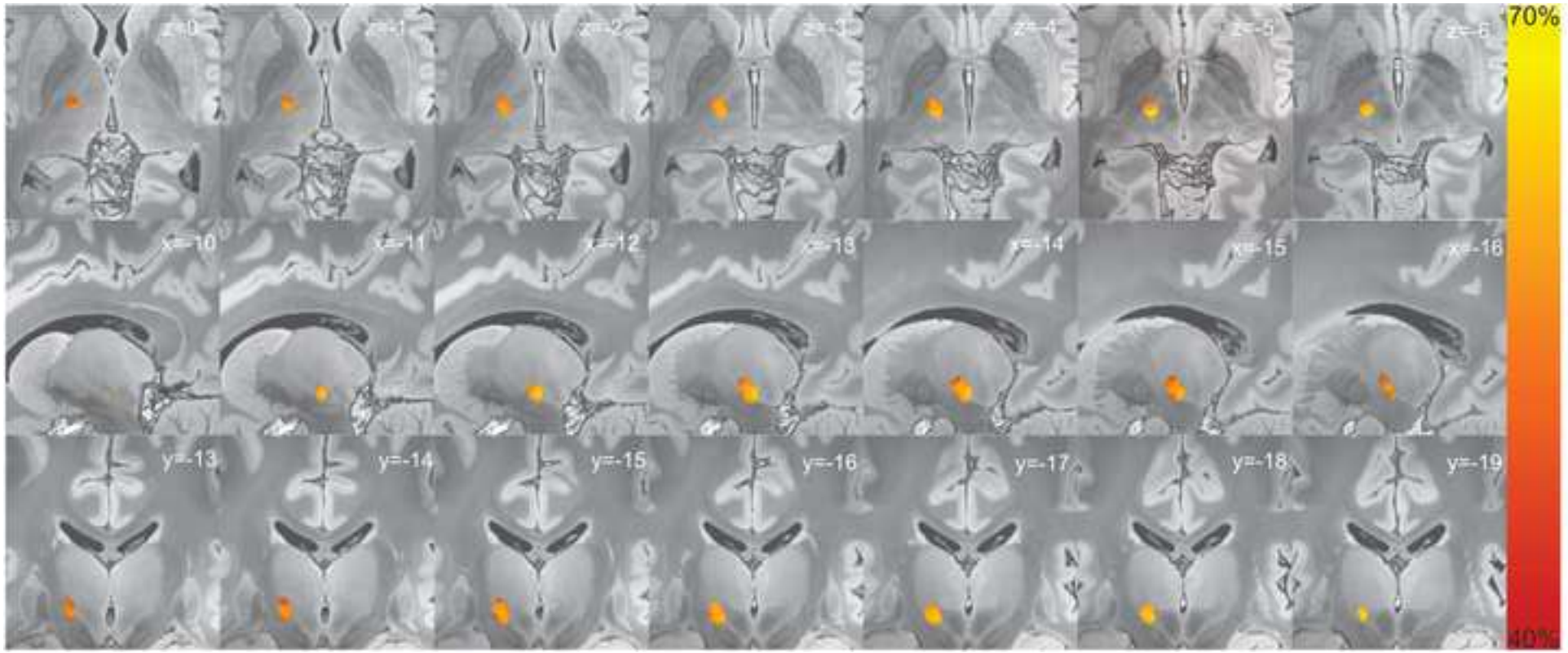

Supplementary methods

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