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Parkinson's disease tremor differentially responds to levodopa and subthalamic stimulation

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Abstract

Background: Tremor in Parkinson's disease (PD) has an inconsistent response to levodopa and subthalamic deep brain stimulation (STN-DBS).

Objectives: To identify predictive factors of PD tremor responsiveness to levodopa and STN-DBS.

Material and Methods: PD patients with upper limb tremor who underwent STN-DBS were included. The levodopa responsiveness of tremor (overall, postural and rest sub-components), was assessed using the relevant UPDRS-III items performed during the pre-operative assessment. Post-surgical outcomes were similarly assessed on and off stimulation. A score for the Rest/Postural tremor ratio was used to determine the influence of rest and postural tremor severity on STN-DBS outcome. Factors predictive of tremor responsiveness were determined using multiple linear regression modelling. Volume of tissue activated measurement coupled to voxel-based analysis was performed to identify anatomical clusters associated with motor symptoms improvement.

Results: 165 patients were included in this study. Male gender was negatively correlated with tremor responsiveness to levodopa whereas the ratio of Rest/Postural tremor was positively correlated with both Levodopa responsiveness and STN-DBS tremor outcome. Clusters corresponding to improvement of tremor were in the subthalamic nucleus, the Zona Incerta and the thalamus while clusters corresponding to improvement for akinesia and rigidity were located within the subthalamic nucleus.

Conclusion: More severe postural tremor and less severe rest tremor were associated with both poorer levodopa and STN-DBS response. The different locations of clusters associated with best correction of tremor and other parkinsonian features suggest that STN-DBS effect on PD symptoms is underpinned by the modulation of different networks.

Tremor is a defining feature of Parkinson's disease (PD) and affects up to 75% of patients (1). The pathophysiology of tremor remains elusive and may be distinguishable from traditional hypodopaminergic signs due to the involvement of both basal ganglia and cerebello-thalamo-cortical pathways (2). Unlike rigidity or akinesia, PD tremor responds variably to levodopa with a small proportion of patients reporting complete resistance to levodopa treatment (3). Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a well-established treatment for PD patients suffering from motor fluctuations (4). This approach tends to result in excellent motor outcomes though tremor responsiveness to this modality can also be variable. The extent of pre-operative levodopa responsiveness has traditionally been used to predict outcomes of STN-DBS. Although this approach may have some merit particularly in predicting DBS effects on gait, akinesia and rigidity, large discrepancies have been noted for tremor response (5,6). Additionally, the contribution of other clinical factors, such as age, gender, or tremor characteristics in predicting responses to levodopa, STN-DBS outcomes and the interplay of these aspects remains poorly understood and warrants further investigation (7). These factors could potentially represent readily available markers for clinicians to consider when determining whether a patient is a good candidate for DBS and the ideal anatomical target.

Here we aimed to clarify some of these aspects by assessing a cohort of PD patients suffering from tremor and treated with STN-DBS. The goals were to measure tremor improvement under levodopa and subthalamic stimulation, explore if dopa-resistant tremor has distinguishing characteristics, and ultimately if specific patient features influence these responses.

Material and methods

Patients

Patients suffering from Parkinson's disease (according to the UK Brain Bank criteria) (8), treated by STN-DBS at the National Hospital for Neurology and Neurosurgery with ≥ 1 point on the UPDRS III (9) tremor items (20, 21) in the 'Off medication' condition during their pre-operative acute levodopa challenge, were included in this study. We excluded patients who showed an improvement of ≤20% on rigidity and akinesia scores after levodopa intake, to avoid the bias of including patients with a 'falsely' negative dopa challenge due to medication absorption problems or patients suffering from conditions other than Parkinson's disease, as previously described (10,11). All included patients had imaging verification of accurate electrode placement within the STN.

Clinical Assessment

Levodopa-responsiveness was evaluated before the surgery for all patients during an acute dopa challenge. Subjects were assessed after overnight dopaminergic treatment withdrawal (OFF-MED condition) and 1 hour after receiving a supramaximal dose of levodopa (the patient's usual morning Levodopa dose +50%) on the same day. The outcome of STN DBS was documented as part of post-operative DBS optimisation between 1 and 5 years following the surgery. Patients were assessed after overnight dopaminergic medications withdrawal, with the stimulation turned off 5 minutes before assessment (OFF-DBS condition), then on (ON-DBS condition). UPDRS II scores, age, duration of the disease, Levodopa equivalent daily dose (LEDD) as well as duration of DBS and stimulation settings were collected at the time of the assessments.

Surgical procedure

DBS leads were implanted under general anaesthesia using a stereotactic MRI-guided and MRI-verified approach without microelectrode recording (using a Leksell frame model G, Elekta Instrument AB, Stockholm, Sweden), as previously reported (12,13).

All patients had bilateral surgery. Electrodes were connected either to a Medtronic® (Activa PC, Kinetra) or Boston Scientific® (Gevia RC, Vercise RC or Vercise PC) device.

Outcome measurement

Levodopa-responsiveness was defined as the difference between the ON-MED and OFF-MED scores on the UPDRS III scale (9). Levodopa response was also specifically calculated for overall tremor (items 20, 21), rest tremor (item 20), postural tremor (item 21), akinesia (items 19, 23, 24, 25, 26, 31), rigidity (item 22), Posture and Gait (items 27, 28, 29, 30) and Speech (item 18) sub scores.

UPDRS II and UPDRS III scores were utilized to classify patients into previously reported motor phenotypes- tremor dominant, Postural Instability and Gait Disturbances (PIGD) dominant or intermediate (14,15).

Patients with a levodopa-response of ≤20% or ≥60% on the tremor score were defined as having a levodopa-resistant and levodopa-responsive tremor, respectively, as previously described (3,11), and further identification of patients with levodopa resistant rest or levodopa resistant postural tremor also used a threshold of ≤20% levodopa response. DBS-responsiveness, defined as the difference between the UPDRS III score measured in the OFF DBS OFF medications and ON DBS OFF medications conditions at the second visit, was similarly calculated. A Rest tremor score/Postural tremor score index was estimated at each visit to measure the contribution of the two components of the tremor on the levodopa and the DBS-responsiveness. For these two ratios, when the denominator was 0, we used a half minimum interpolation approach, and a value of 0.5 was imputed to avoid inappropriately excluding patients with scores of 0, as previously described (16,17).

Imaging procedure

All patients underwent stereotactic MRI pre- and post-lead implantation as part of their routine surgery. For lead localization, the preimplantation T1 MR-scan was co-registered with the post-implantation T1 MR-scan.

The lead trajectory detected on post-lead implantation MRI could then be visualized on the segmented pre-implantation MRI. For patients implanted with directional leads, a post-operative CT scan was performed to confirm the orientation of electrodes using Brainlab Elements software (Brainlab AG, Munich, Germany: http://www.brainlab.com). Automatized segmentation of basal ganglia nuclei was performed using Brainlab Elements software. The segmentation of the STN was then systematically reviewed by a trained operator and manually refined, if necessary, by referring to the visible STN hypointensity on the co-registered T2-weighted preoperative MRI. For Volume of Tissue Activated (VTA) modelling, amplitude of stimulation in mA was calculated for every patient stimulated with Medtronic® implantable pulse generator (Activa PC, Kinetra) using available impedance measurements at the time of the assessment or by imputing a value of 1000 Ω if unavailable (18). Stimulation field models were constructed using a finite element model as previously described (Guide XT version 2.0, Boston Scientific, Marlborough, MA) (19,20). Analysis, processing, annotation, and image segmentation were performed according to standard procedures. Assuming there are spatial locations that correlate with better STN-DBS outcomes, voxels in each VTA were associated with lateralized STN-DBS responses expressed in percentages. These weighed regions of interest (ROIs) were transformed to group average space, averaged and binarised at 75%, which selects the 25% voxels associated with best response, to

determine anatomical clusters associated with best improvement in akinesia, rigidity, tremor and its postural and rest sub-components.

Statistical analysis

Student's t test and Mann-Whitney tests were used for comparisons between normally and non-normally distributed quantitative variables. Chi-square and Fisher's exact tests were used for comparisons between categorical variables.

Pearson and Spearman's coefficients were utilized to identify correlations between quantitative variables for non and linearly distributed covariates, respectively. A hierarchical multivariate linear regression was performed to model the relationship between patients' clinical characteristics, levodopa response, and the STN-DBS effect on tremor. Bonferroni correction was applied for multiple comparisons. All reported p values are two-sided at a significance level of 0.05. All data were analysed using the SPSS statistical package (SPSS, Release V.26.0 Chicago, Illinois, USA).

Results

Preoperative levodopa response assessments

Baseline demographic characteristics of 165 patients who were assessed by a dopa-challenge prior to STN-DBS and the scores for the tremor, rigidity, and bradykinesia sub-items from the UPDRS III scores, OFF and ON medication are reported in Table-1. 13 patients had postural tremor scores of 0 and therefore required imputation to calculate the Rest tremor score/Postural tremor score index. Mean LEDD was 1567.2 mg +/- 791.6.

The absolute and percentage change in scores in response to levodopa challenge for the different UPDRS part III sub-items are presented in Table-2. The overall tremor percentage response to levodopa (81.5 +/- 26.2) was significantly higher ($p<0.01$) than akinesia (64.6 +/- 17.7), rigidity (65.6 +/- 23), speech (55.8% +/- 45.3) or gait and posture (68.8 +/- 21).

Similarly, the postural tremor response to levodopa (70.0 +/- 37.6%) was higher than the dopa-response for akinesia ($p<0.01$) and speech ($p<0.01$), but not gait and posture ($p = 0.30$) while rest tremor dopa-responses (90.8% +/- 21.7%) were also superior to responses for each of these three symptoms respectively ($p<0.01$).

14 patients (8.5%) exhibited a levodopa-resistant tremor while 135 (81.1%) had a dopa-responsive tremor (Table-3). Levodopa resistant patients were exclusively male (M/F ratio at 14/0, (100%) vs 93/42, (68.8%) male patients for dopa-responsive tremor, $p = 0.01$), had a milder rest tremor score than dopa responsive patients (3.5 +/- 4.89 vs 4.81 +/- 3.53; $p = 0.048$) and a lower rest/postural tremor index (0.79 +/- 1.26 vs 2.02 +/- 1.57; $p = 0.001$). This latter finding remained robust after imputation (0.79+/- 1.26 vs 2.34 +/- 2.26; $p = 0.001$). A further 4 (2.8%) and 24 (15.8%) patients showed less than 20% improvement on isolated rest tremor score and postural tremor scores following acute levodopa challenge, respectively. There was a significant male predominance among dopa-resistant postural tremor compared to dopa-responsive postural tremor patients (M/F ratio 21/3 vs 64/34; $p = 0.046$). No other significant differences between dopa-resistant and dopa-responsive tremor patients were noted. Taken as a whole, male patients had a lower percentage response to levodopa than female patients for both total tremor (75.1 +/- 35.5% vs 88.1 +/- 21.5%; $p=0.015$) and postural tremor (65.4 +/- 39.6% vs 81.3 +/- 30.5 %; $p=0.018$). No other significant differences were found for total UPDRS III scores, akinesia, rigidity, or speech responses to dopa according to gender.

We found a negative correlation between severity of the OFF-MED postural tremor score and tremor responsiveness to levodopa (-0.225; $p<0.01$) but a positive correlation between both the native and imputed rest/postural tremor score ratios and tremor responsiveness to levodopa (0.193; $p=0.013$ and 0.196; $p=0.016$ respectively).

Post-operative stimulation response assessments

Of the 165 patients previously assessed 57 were excluded from DBS response analysis due to a lack of formal, detailed post-operative assessments, (partly attributable to the COVID19 pandemic). Clinical characteristics of the 108 patients assessed are provided in Table-4. Mean DBS duration at the time of the visit was 15.5 +/- 8.6 months, mean LEDD reduction was 40.2% +/- 29.7.

Stimulation responses are described in Table-2. For each score, the percentage response to DBS was lower than the respective preoperative Levodopa responses. The overall rest tremor (74.6 +/- 31.2%) and total tremor (66.5 +/- 34.9%) responses to DBS were significantly higher ($p<0.001$) than response to DBS for akinesia (34.8 +/- 66.7%), rigidity (46.4 +/- 32.8%), speech (10.7 +/- 44.1%) and gait (36.4 +/- 45.8%). The postural tremor DBS response (60 +/- 40.8%) was also higher than the DBS responsiveness of akinesia ($p=0.011$), gait ($p=0.002$) and speech ($p<0.001$).

Correlations between the levodopa and DBS responses are presented in Figure-1. We found that the overall motor response (total UPDRS III) to STN-DBS showed only a modest correlation with the overall motor response to levodopa (0.321; $p<0.001$). No correlation between levodopa and STN-DBS responses was noted for motor sub scores except a modest correlation for akinesia (0.288; $p=0.003$).

A positive correlation was noted between the tremor stimulation-response and the mean amplitude of stimulation (0.275; $p=0.01$). Variables correlating to tremor response to STN DBS at a relaxed threshold of $p<0.25$ as previously described (21), namely amplitude of stimulation, pre-operative rest/postural tremor ratio off medication, tremor levodopa response, postural tremor levodopa response, pre-operative speech severity, gait response to levodopa, OFF MED OFF DBS gait severity score, were included in a hierarchical multivariate linear regression analysis. After adjustment for confounders in this multiple linear regression model, a positive association between the tremor response to STN-DBS and the amplitude of

stimulation (unstandardized regression coefficient 0.142, standard error 0.048; p=0.004) was noted as well as an association between the tremor response to STN-DBS and pre-op Rest/Postural off medication tremor ratio (unstandardized regression coefficient 0.047, standard error = 0.022; p=0.038). The inclusion of overall tremor dopa responsiveness did not improve the model.

Volume of tissue activated coupled to statistical voxel-based analysis outcome

Imaging data for 44 patients with available STN-DBS outcome assessments corresponding to 88 electrodes was available for processing. Figure-2A, B and C display the outcome of voxel-based statistical analysis of the VTAs and demonstrate the position of the relevant clusters associated with akinesia, rigidity, and tremor suppression respectively. Akinesia and rigidity clusters were mainly in the posterior and superior part of the subthalamic nucleus, while voxels associated with best tremor correction were in the subthalamic nucleus, the Zona Incerta (ZI) and the thalamus. Some degree of asymmetry was observed between clusters associated with best left and right responses for tremor. Figure-2D and E illustrate the position of clusters associated with best rest and postural tremor suppression. Although some asymmetry was also noted in the position of the relevant cluster, the location of clusters associated with these two components did not significantly differ, both being in the subthalamic nucleus, the ZI and the thalamus.

Discussion

This study assessed the impact of L-DOPA (dopaminergic) medication and subthalamic deep brain stimulation on tremor in a large cohort of patients with Parkinson's disease while comparing this to the treatment responsiveness of other parkinsonian features and exploring the potential roles of tremor characteristics and other patient factors in determining these outcomes. There was an impact of gender on tremor dopa-responsiveness; an association

between higher rest tremor score compared to postural tremor score and both levodopa and STN-DBS responsiveness; a modest correlation between levodopa and STN-DBS response for tremor; and different clusters for tremor and rigidity/akinesia improvements were confirmed. Some degree of asymmetry was noted between hemispheres in the position of the cluster associated with best tremor, best rest tremor and best postural tremor, which could potentially reflect the existence of an asymmetry in the dentato-thalamic tract (DTT), as demonstrated in previous work evaluating the interindividual variability in Vim nucleus and dentato-thalamo-cortical pathways (22).

On balance, this cohort appeared representative of the average population of PD patients presenting with tremor, with patient characteristics (23,24) and treatment outcomes being comparable to other studies (14,25,26). While levodopa responsiveness was strongly correlated with STN DBS response overall, the lack of levodopa responsiveness in predicting STN-DBS outcomes for the specific motor sub-items was interesting, though this observation has previously been reported by a number of other studies (6,7,26–29). The possibility that STN-DBS has additional effects on brain networks, rather than just mimicking the effect of dopamine, could potentially explain this discrepancy, especially for tremor (30). According to the "dimmer-switch model" theory (2), PD tremor is triggered by pathological activity in the striato-pallidal circuit (switch), which is then amplified by cerebello-thalamo-cortical circuit, thus producing the tremor and modulating its amplitude (dimmer). It has been suggested that STN-DBS modulates the cerebello-thalamo-cortical circuitry in addition to the subthalamic nucleus direct projections. In accordance with this model, it has been demonstrated that targeting the DTT during STN-DBS electrode implantation, a structural part of the cerebello-thalamo-cortical circuitry, which is implicated in both Parkinson tremor and essential tremor pathogenicity, was efficient in alleviating Parkinson's disease tremor (31). The modulation of this projection by STN-DBS could partly explain the benefit of this surgery independently from

the "dopa-like" effect generated by the direct stimulation of the subthalamic nucleus. The identification of stimulation clusters associated with tremor suppression, in anatomical correlation with Zona Incerta and the thalamus, namely in the vicinity of the DTT also argues for the hypothesis of an STN-DBS tremor outcome partially mediated by the modulation of cerebello-thalamic pathways. This is in contrast to STN-DBS effect on the other symptoms, namely akinesia and rigidity, whose respective clusters were located within the dorsal part of the subthalamic nucleus.

We found tremor dopa-responsiveness to be superior to the responsiveness of every other PD motor symptom. This result is in accordance with previous work showing excellent tremor responses to dopaminergic medication in most cases (26). Our finding of dopa-refractory tremor being uncommon is also mirrored by another study where only 16 % of the patients met criteria for dopa-resistance (3). The rarity of this clinical presentation combined with the observation of excellent dopa responsiveness for tremor on the majority of the cohort support the hypothesis that dopa-resistant tremor may represent a specific PD motor subtype with potential pathological and prognostic implications (3,10). This hypothesis is further supported by our novel finding in this cohort of a strong association of this trait with male gender. Although this has not been confirmed, two recent studies focusing on the electrophysiological and brain functional connectivity of dopa-resistant tremor showed a trend towards male predominance in this group of patients (3,10). Several factors may contribute to this. Male PD patients may differ in their motor phenotype from females (32) while their disease can also evolve more rapidly (33). Men also seem to be more likely to experience severe motor features over the course of the disease (34), while being less likely to present with the more benign tremor-dominant PD phenotype at the beginning of the disease (32). While the exact mechanisms underlying this differential influence of gender on tremor response to dopa remain to be determined, oestrogen potentially has a positive impact on dopaminergic striatal

function (35,36), and also potentially influences other non-dopaminergic circuits, such as cholinergic (37), noradrenergic or serotoninergic systems (38) that are known to modulate the occurrence and severity of tremor in Parkinson's disease (1,39–41) thus potentially explaining our findings. Further studies exploring the potential role of hormonal factors on the expression of Parkinson's disease tremor may be informative in this regard.

Based on our finding that OFF-MED rest tremor score was lower in patients with dopa-resistant tremor (i.e., a comparatively higher or equivalent postural component), we calculated a ratio Rest/Postural tremor score to reflect the impact of tremor characteristics on the response to the therapies. Among the group of patients with dopa-refractory tremor, this ratio was lower, and prominently correlated with the dopa-responsiveness of the whole cohort. This Rest/Postural tremor score ratio was also confirmed as being independently associated with tremor response to STN-DBS after multivariate analysis to adjust for potential confounders. As the correlation between the ratio and the response to stimulation was positive, this suggests that a more severe rest tremor and a relatively less severe postural tremor, is more likely to respond positively to STN-DBS. These results are in accordance with the response to levodopa and STN-DBS for rest tremor, which were seen to be overall higher (90 and 70%, respectively) than postural tremor (75 and 60%, respectively). Combining this ratio with other predictive factors of STN-DBS outcomes such as detailed clinical phenotyping (25), connectivity imaging (28) and genetic biomarkers known to result in differential STN-DBS outcomes such as *GBA* mutations (42) may inform more precise patient selection or allow more informed patient discussions in the future (43).

Tremor in Parkinson's disease is determined by an interplay of dopaminergic depletion causing abnormal neuronal firing patterns in the subthalamic nucleus and non-dopaminergic pathology causing abnormal firing patterns in the cerebello-thalamo-cortical circuits, the latter also being implicated in 'essential tremor syndromes' (1,44). Given the observed better

response to both levodopa and STN-DBS of rest tremor compared to postural tremor, it could be hypothesized that rest tremor in Parkinson's disease is mainly a reflection of the dopaminergic depletion in the subthalamic nucleus, while the postural tremor primarily results from abnormal activity in cerebello-thalamo-cortical circuits, under lesser influence of the dopaminergic networks. These findings are in accordance with a recent neurophysiological study focusing on postural tremor in Parkinson's disease demonstrating that postural tremor in Parkinson's disease is minimally affected by dopaminergic medication with corresponding non-dopaminergic physiopathology being implicated for this symptom (45). Our VTA voxel-wise analysis could not identify different clusters associated with best postural and rest tremor suppression, both being in the Zona Incerta, near the putative location of the DTT. This suggests that the effect of STN-DBS on rest and postural PD tremor may be at least partially underpinned by the modulation of the same network, namely the cerebello-thalamo-cortical circuitry. Since we found that rest tremor responded better to STN-DBS than postural tremor, we postulate this modulation could potentially be more effective on rest than postural tremor. This hypothesis could explain previous reports from the literature on thalamic stimulation, which demonstrated a better outcome and more long lasting outcome in Parkinson's disease rest tremor patients compared to essential postural tremor patients (30,46).

Several study limitations need to be acknowledged. Firstly, because of the retrospective nature of this work, and because we could only include 108 of the initial 165 patients in the STN-DBS response analysis, and only 44 in the imaging analysis, we cannot exclude the possibility of selection bias, although the demographic composition of the groups was very similar. Secondly, as most patients were seen within two years of surgery, the applicability of these findings is limited to the medium post-surgical follow up period. Additionally, DBS wash out was limited to 5 minutes which may not be truly representative of the Off-stimulation state. Furthermore, as all patients were assessed with the 2008 version of the

UPDRS scale, intention tremor was not quantified in this study. Finally, the small number of patients showing dopa-resistant tremor may have limited our power to detect statistically significant differences with and within the dopa-responsive tremor patient group and to identify factors associated with this condition.

To conclude, we found pre-operative levodopa responses for tremor to be poorly predictive of STN-DBS tremor outcomes. Conversely, a ratio based on the scores related to rest and postural components of tremor appears to have better predictive outcomes, more severe rest tremor with milder postural tremor being associated with a better response to STN-DBS. Our finding of the specific impact of gender on tremor response to levodopa potentially warrants further consideration. These findings in conjunction with other genotypic and imaging biomarkers could potentially inform more predictive models for tremor outcomes with STN-DBS.

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Authors' roles

Research project: (1) A. Conception, B. Design, C. Acquisition of data, D. Analysis and interpretation of data; (2) Manuscript: A. Writing of the first draft, B. Review and critique; (3) Other: A. Subject recruitment, B. Clinical assessment of patients, C. Study supervision.

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Ethical Compliance Statement

Patients' clinical characteristics and UPDRS scores were collated from a dedicated secure database established to audit the outcomes of DBS surgery with institutional approval from the University College London Institute of Neurology. The authors confirm that patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

References

1. Helmich RC, Hallett M, Deuschl G, Toni I, Bloem BR. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? Brain. nov 2012;135(Pt 11):3206-26.
2. Helmich RC. The cerebral basis of Parkinsonian tremor: A network perspective. Mov Disord. 2018;33(2):219-31.
3. Dirkx MF, Zach H, van Nuland A, Bloem BR, Toni I, Helmich RC. Cerebral differences between dopamine-resistant and dopamine-responsive Parkinson's tremor. Brain. 1 oct 2019;142(10):3144-57.
4. Krack P, Benazzouz A, Pollak P, Limousin P, Piallat B, Hoffmann D, et al. Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. Mov Disord. nov 1998;13(6):907-14.
5. Fishman PS. Paradoxical aspects of parkinsonian tremor. Mov Disord. 30 janv 2008;23(2):168-73.
6. Lin Z, Zhang C, Li D, Sun B. Preoperative Levodopa Response and Deep Brain Stimulation Effects on Motor Outcomes in Parkinson's Disease: A Systematic Review. Movement Disorders Clinical Practice. 2022;9(2):140-55.
7. Chen CC. Is outcome of subthalamic nucleus deep brain stimulation in Parkinson disease predictable? Neurology. 05 2019;92(10):453-4.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. mars 1992;55(3):181-4.
9. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 15 nov 2008;23(15):2129-70.
10. Zach H, Dirkx MF, Roth D, Pasman JW, Bloem BR, Helmich RC. Dopamine-responsive and dopamine-resistant resting tremor in Parkinson disease. Neurology. 15 sept 2020;95(11):e1461-70.
11. Albanese A, Bonuccelli U, Brefel C, Chaudhuri KR, Colosimo C, Eichhorn T, et al. Consensus statement on the role of acute dopaminergic challenge in Parkinson's disease. Mov Disord. mars 2001;16(2):197-201.
12. Foltynie T, Zrinzo L, Martinez-Torres I, Tripoliti E, Petersen E, Holl E, et al. MRI-guided STN DBS in Parkinson's disease without microelectrode recording: efficacy and safety. J Neurol Neurosurg Psychiatry. avr 2011;82(4):358-63.
13. Holl EM, Petersen EA, Foltynie T, Martinez-Torres I, Limousin P, Hariz MI, et al. Improving targeting in image-guided frame-based deep brain stimulation. Neurosurgery. déc 2010;67(2 Suppl Operative):437-47.
14. Katz M, Luciano MS, Carlson K, Luo P, Marks WJ, Larson PS, et al. Differential effects of deep brain stimulation target on motor subtypes in Parkinson's disease. Ann Neurol. avr 2015;77(4):710-9.
15. Lewis S, Foltynie T, Blackwell A, Robbins T, Owen A, Barker R. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry. mars 2005;76(3):343-8.
16. Wei R, Wang J, Su M, Jia E, Chen S, Chen T, et al. Missing Value Imputation Approach for Mass Spectrometry-based Metabolomics Data. Sci Rep. 12 janv 2018;8(1):663.
17. Shen M, Chang YT, Wu CT, Parker SJ, Saylor G, Wang Y, et al. Comparative assessment and novel strategy on methods for imputing proteomics data. Sci Rep. 20 janv 2022;12:1067.
18. Satzer D, Lanctin D, Eberly LE, Abosch A. Variation in Deep Brain Stimulation Electrode Impedance

over Years Following Electrode Implantation. Stereotact Funct Neurosurg. 2014;92(2):94-102.
19. Wirth T, Dayal V, de Roquemaurel A, Ferreira F, Vijiaratnam N, Akram H, et al. Endurance of Short Pulse Width Thalamic Stimulation Efficacy in Intention Tremor. Stereotact Funct Neurosurg. 23 nov 2020;1-6.
20. Dayal V, De Roquemaurel A, Grover T, Ferreira F, Salazar M, Milabo C, et al. Novel Programming Features Help Alleviate Subthalamic Nucleus Stimulation-Induced Side Effects. Mov Disord. déc 2020;35(12):2261-9.
21. Grant SW, Hickey GL, Head SJ. Statistical primer: multivariable regression considerations and pitfalls†. European Journal of Cardio-Thoracic Surgery. 1 févr 2019;55(2):179-85.
22. Ferreira F, Akram H, Ashburner J, Zrinzo L, Zhang H, Lambert C. Ventralis intermedius nucleus anatomical variability assessment by MRI structural connectivity. NeuroImage. 1 sept 2021;238:118231.
23. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. New England Journal of Medicine. 31 août 2006;355(9):896-908.
24. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease. New England Journal of Medicine. 13 nov 2003;349(20):1925-34.
25. Xu C, Zhuang P, Hallett M, Zhang Y, Li J, Li Y. Parkinson's Disease Motor Subtypes Show Different Responses to Long-Term Subthalamic Nucleus Stimulation. Front Hum Neurosci [Internet]. 4 oct 2018 [cité 22 sept 2020];12. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6180162/
26. Piboolnurak P, Lang AE, Lozano AM, Miyasaki JM, Saint-Cyr JA, Poon YYW, et al. Levodopa response in long-term bilateral subthalamic stimulation for Parkinson's disease. Mov Disord. 15 mai 2007;22(7):990-7.
27. Zaidel A, Bergman H, Ritov Y, Israel Z. Levodopa and subthalamic deep brain stimulation responses are not congruent. Mov Disord. 30 oct 2010;25(14):2379-86.
28. Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. Connectivity Predicts deep brain stimulation outcome in Parkinson disease. Ann Neurol. juill 2017;82(1):67-78.
29. Lin W, Shi D, Wang D, Yang L, Wang Y, Jin L. Can Levodopa Challenge Testing Predict the Effect of Deep Brain Stimulation? One-Year Outcomes in a Chinese Cohort. Front Aging Neurosci. 2021;13:764308.
30. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol. mars 2019;15(3):148-60.
31. Coenen VA, Sajonz B, Prokop T, Reisert M, Piroth T, Urbach H, et al. The dentato-rubro-thalamic tract as the potential common deep brain stimulation target for tremor of various origin: an observational case series. Acta Neurochir. 1 mai 2020;162(5):1053-6 6.
32. Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. Nat Rev Neurol. 2020;16(2):84-96.
33. Borgström E, Lundin S, Lundeberg J. Large Scale Library Generation for High Throughput Sequencing. PLOS ONE. 27 avr 2011;6(4):e19119.
34. Latourelle JC, Beste MT, Hadzi TC, Miller RE, Oppenheim JN, Valko MP, et al. Large-scale identification of clinical and genetic predictors of motor progression in patients with newly diagnosed Parkinson's disease: a longitudinal cohort study and validation. Lancet Neurol. 2017;16(11):908-16.
35. Rivest R, Falardeau P, Di Paolo T. Brain dopamine transporter: gender differences and effect of chronic haloperidol. Brain Research. 18 sept 1995;692(1):269-72.
36. Lavalaye J, Booij J, Reneman L, Habraken JB, van Royen EA. Effect of age and gender on dopamine transporter imaging with [123I]FP-CIT SPET in healthy volunteers. Eur J Nucl Med. juill 2000;27(7):867-9.
37. Kirshner ZZ, Yao JK, Li J, Long T, Nelson D, Gibbs RB. Impact of estrogen receptor agonists and model of menopause on enzymes involved in brain metabolism, acetyl-CoA production and cholinergic function. Life Sci. 1 sept 2020;256:117975.
38. Luine V, Frankfurt M. Estrogenic regulation of memory: The first 50 years. Horm Behav. mai 2020;121:104711.
39. Qamhawi Z, Towey D, Shah B, Pagano G, Seibyl J, Marek K, et al. Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. Brain. oct 2015;138(Pt 10):2964-73.
40. Pasquini J, Ceravolo R, Qamhawi Z, Lee JY, Deuschl G, Brooks DJ, et al. Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study. Brain. 1 mars 2018;141(3):811-21.
41. Koller WC. Pharmacologic treatment of parkinsonian tremor. Arch Neurol. févr 1986;43(2):126-7.
42. Mangone G, Bekadar S, Cormier-Dequaire F, Tahiri K, Welaratne A, Czernecki V, et al. Early cognitive decline after bilateral subthalamic deep brain stimulation in Parkinson's disease patients with GBA mutations. Parkinsonism & Related Disorders. 1 juill 2020;76:56-62.
43. Roquemaurel A de, Wirth T, Vijiaratnam N, Ferreira F, Zrinzo L, Akram H, et al. Stimulation Sweet Spot in Subthalamic Deep Brain Stimulation – Myth or Reality? A Critical Review of Literature. SFN. 11 juin 2021;1-18.

44. Vijiaratnam N, Wirth T, Morris HR. Revisiting the assessment of tremor: clinical review. Br J Gen Pract. déc 2020;70(701):611-4.
45. Dirkx MF, Zach H, Bloem BR, Hallett M, Helmich RC. The nature of postural tremor in Parkinson disease. Neurology. 27 2018;90(13):e1095-103.
46. Pahwa R, Lyons KE, Wilkinson SB, Simpson RK, Ondo WG, Tarsy D, et al. Long-term evaluation of deep brain stimulation of the thalamus. J Neurosurg. avr 2006;104(4):506-12.

Tables and figures legend

Table-1: Acute levodopa challenge cohort characteristics

Table-2: Response to levodopa and subthalamic stimulation of the different Parkinson's disease symptoms

Table-3: Baseline characteristics of dopa-responsive and dopa-resistant tremor PD patients

Table-4: Subthalamic Deep Brain Stimulation cohort characteristics

Figure-1: Correlation matrix between levodopa and subthalamic stimulation responses for Parkinson's disease symptoms.

Cases in green were significant for corrected p value<0.05

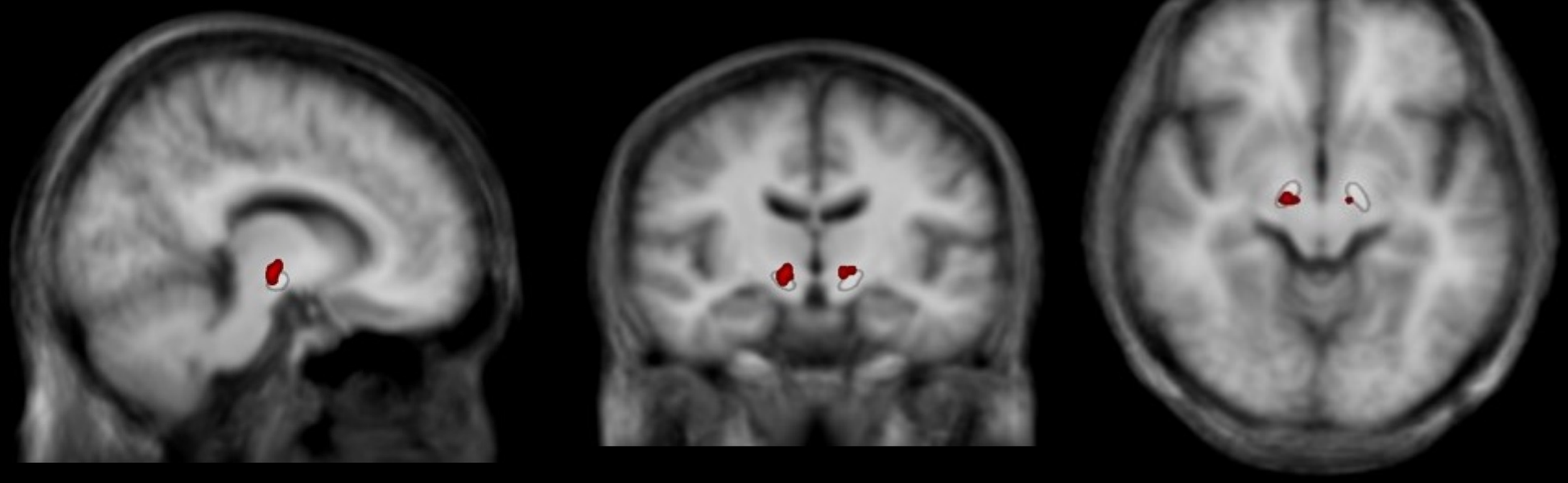
Figure-2: Volume of tissue activated significant clusters associated with lateralized akinesia (A, clusters in red), rigidity (B, clusters in yellow), overall tremor (C clusters in purple), rest tremor (D clusters in green) and postural tremor (E clusters in blue) scores.

Clusters represent the group average spaces, binarised at 75%, which selects the 25% voxels associated with best response.

Absolute	Tremor Response to DOPA	Tremor Response to DBS	Rigidity Response to DOPA	Rigidity Response to DBS	Akinesia Response to DOPA	Akinesia Response to DBS	Gait Response to DOPA	Gait Response to DBS	Speech Response to DOPA	Speech Response to DBS
Tremor Response to DOPA		0.182	0.334	0.007	0.066	-0.017	0.034	0.049	0.036	0.023
Tremor Response to DBS			-0.037	0.072	0.029	0.101	0.119	0.144	0.001	-0.089
Rigidity Response to DOPA				0.183	0.204	-0.018	0.182	0.04	-0.021	0.065
Rigidity Response to DBS					0.270	0.448	0.129	0.331	0.154	-0.001
Akinesia Response to DOPA						0.288	0.540	0.232	0.016	-0.051
Akinesia Response to DBS							0.156	0.613	0.056	0.044
Gait Response to DOPA								0.181	-0.047	0.038
Gait Response to DBS									0.047	0.234
Speech Response to DOPA										0.067
Speech Response to DBS										

Figure-1.tiff

A



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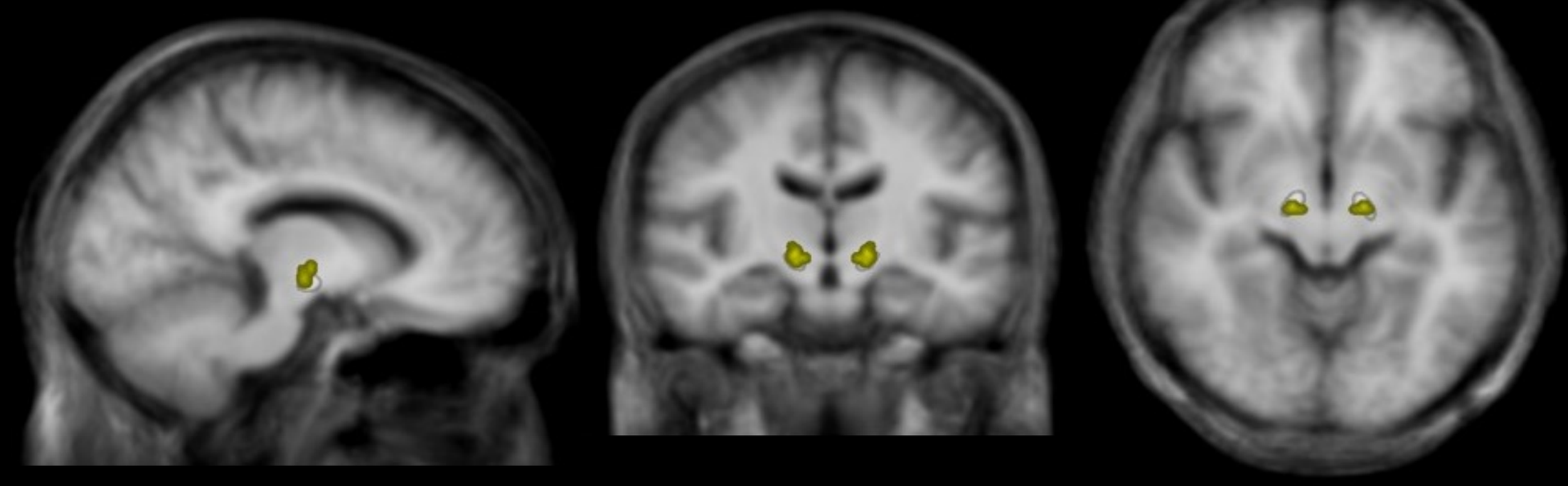

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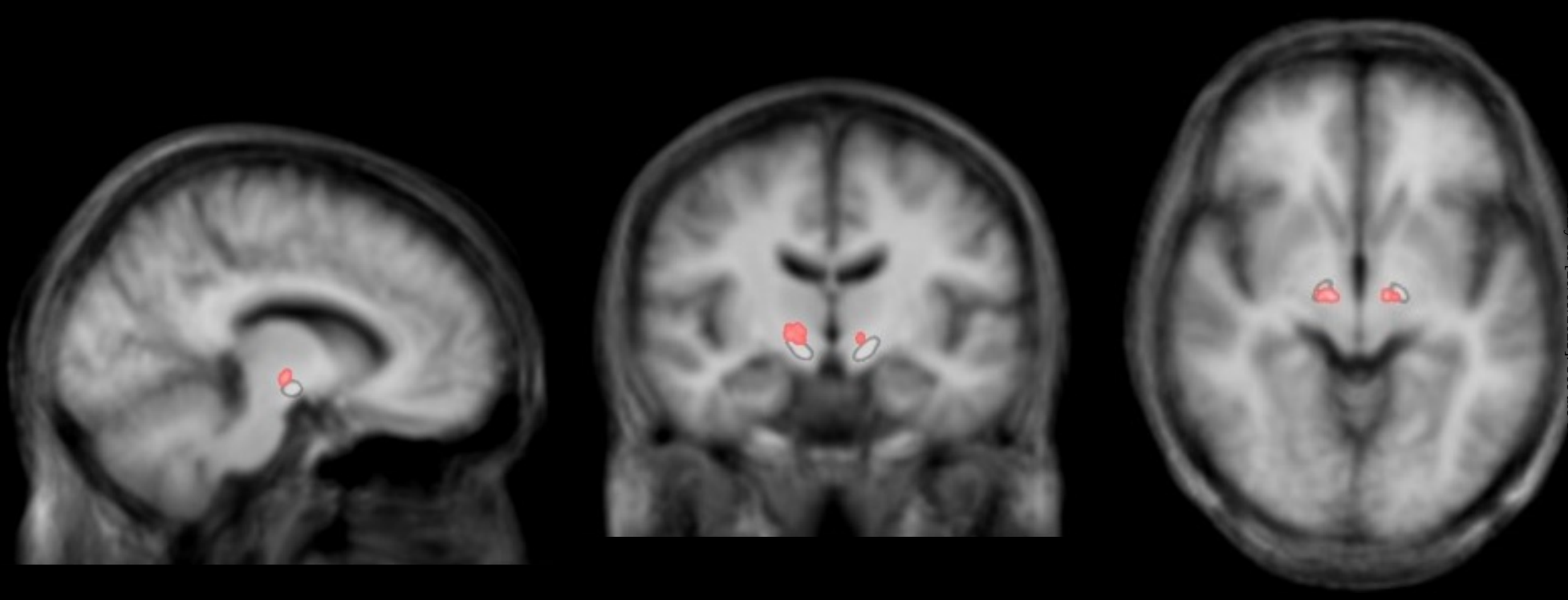

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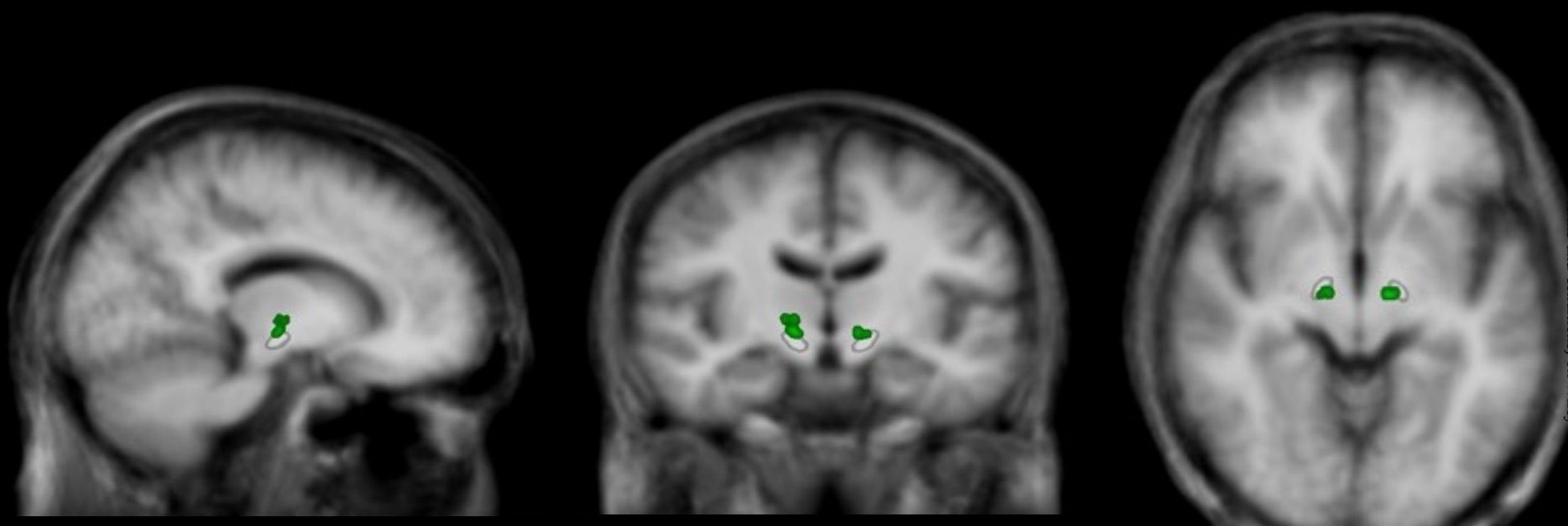

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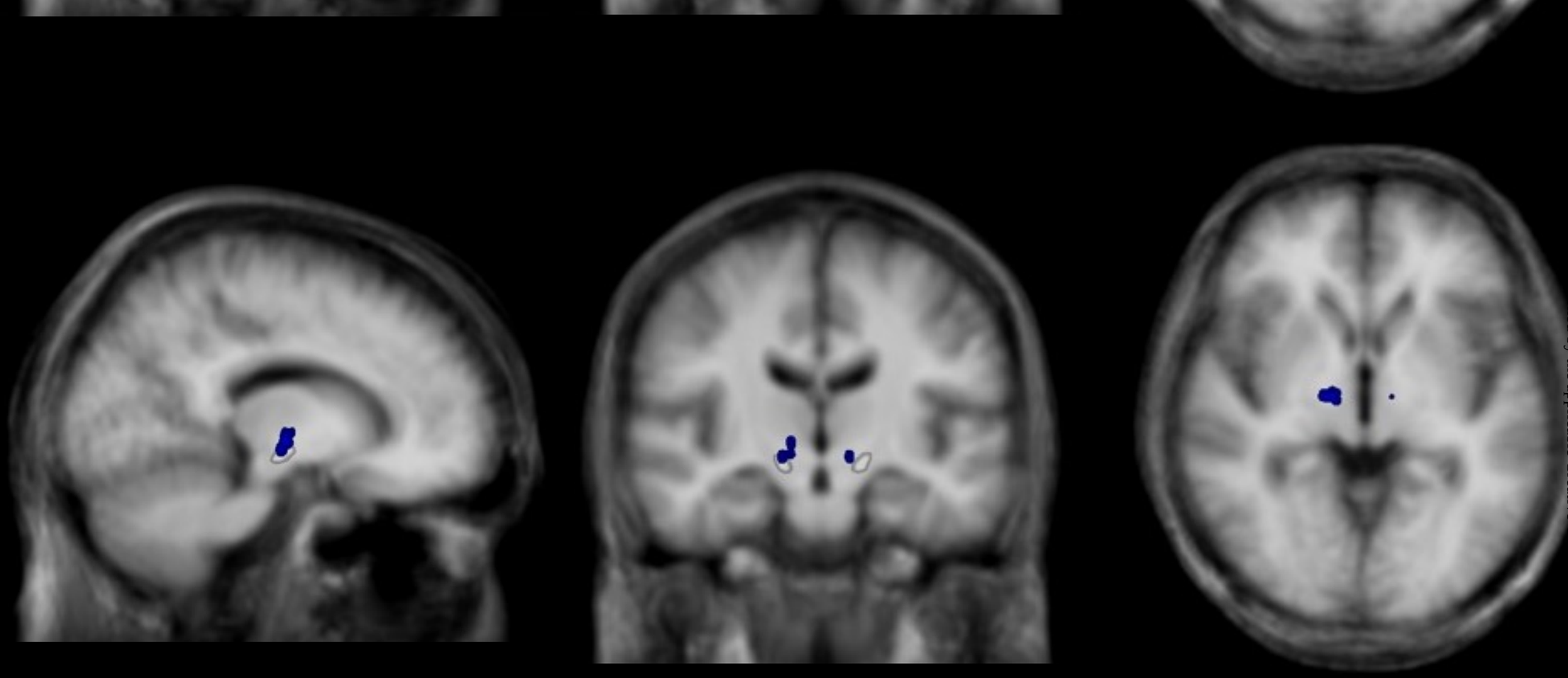

Table-1: Acute levodopa challenge cohort characteristics

	Acute Levodopa challenge cohort Baseline characteristics	
Total number of patients	165	
Sex ratio M/F	2,23	
Phenotype	102 PIGD 21 Intermediate 19 Tremor Dominant	
	Mean Std. Deviation	**Median Interquartile range**
Age (years)	56.5 +/- 7.9	57.8 (52.1 – 63.1)
Duration of disease (years)	10.9 +/- 5.4	10 (9 – 13.8)
LEDD (mg)	1567.2 +/- 791.6	1357 (1060 – 2078.5)
Tremor rest UPDRS III Off	4.8 +/- 3.8	4 (2 – 7)
Tremor postural UPDRS III Off	2.7 +/- 3.8	2 (2 – 4)
Tremor UPDRS III Off	7.5 +/- 5	7 (4 – 11)
Rigidity UPDRS III Off	9.7 +/- 4.3	10 (7 – 12)
Akinesia UPDRS III Off	21.1 +/- 7.2	20.5 (16 – 26)
Gait and Posture UPDRS III Off	7.5 +/- 3.6	7 (5 – 9)
Speech UPDRS III Off	1.4 +/- 0.8	1 (1 – 2)
UPDRS III Off	47.2 +/- 14.4	46 (36 – 56)
Rest/Postural Ratio V0	1.8 +/- 1.5	1.43 (1- 2.5)
Rest/Postural Ratio V0 Imputed	2.1 +/- 2.1	1.55 (1 – 2.5)

Table-2: Response to levodopa and subthalamic stimulation of the different Parkinson's disease symptoms

	Response to Levodopa				Response to STN-DBS			
Number of patients	165				108			
	Absolute value		**Percentage**		**Absolute value**		**Percentage**	
	Mean Std. Deviation	**Median Interquartile range**	**Mean Std. Deviation**	**Median Interquartile range**	**Mean Std. Deviation**	**Median Interquartile range**	**Mean Std. Deviation**	**Median Interquartile range**
Rest Tremor Response	4.03 +/- 3.4	4 (1 – 6)	90.8 +/- 21.7%	100 (100 – 100)%	4.64 +/- 4.38	3 (1 – 8)	74.6 +/- 31.2%	87.5 (50 – 100)%
Postural Tremor Response	1.88 +/- 1.61	2 (1 – 3)	70.0 +/- 37.6%	100 (40.1 - 100)%	1.97 +/- 2.19	2 (0 – 3)	60.0 +/- 48.6%	70.8 (33.3 – 100)%
Tremor Response	5.91 +/- 4.41	5.5 (3 – 8)	81.5 +/- 26.2%	100 (66.7 – 100)%	6.61 +/- 5.97	6 (2 – 11)	66.5 +/- 35%	75 (50 – 100)%
Rigidity Response	6.37 +/- 3.26	6 (4 – 9)	65.6 +/- 23.0%	70 (53 – 83)%	4.92 +/- 3.67	4.5 (2.75 – 7)	46.4 +/- 32.8%	50 (33.3 – 66.7)%
Akinesia Response	13.19 +/- 6.01	12 (9 – 17)	64.6 +/- 17.7%	62.7 (50 – 74.4)%	10.03 +/- 6.95	10 (5 – 14)	34.8 +/- 66.7%	42.9 (21 – 65.2)%
Speech Response	0.75 +/- 0.69	1 (0 – 1)	55.8 +/- 45.3%	50 (33.3 – 100)%	0.19 +/- 0.73	0 (0 – 1)	10.7 +/- 44.1%	0 (0 – 33.3)%
Gait and Posture Response	5.12 +/- 3.16	4 (3 – 7)	68.8 +/- 21.0%	68.8 (52 – 81.8)%	2.66 +/- 2.78	2 (1 – 4)	36.4 +/- 45.8%	42.9 (21 – 65.2)%
UPDRS III Response	31.35 +/- 12.27	31 (23 – 39)	67.7 +/- 14.5%	66.4 (59.4 – 74.3)%	24.4 +/- 14.9	24 (15 – 32)	44.2 +/- 27.3%	46 (34.9 – 61.1)%

Table-3: Baseline characteristics of dopa-responsive and dopa-resistant tremor PD patients

	Dopa-resistant tremor <20%		Dopa-responsive tremor >60%		p
N	15 (8.5%)		135 (81.1%)		/
Phenotype	PIGD: 10 Intermediate: 1 Tremor: 2		PIGD: 95 Intermediate: 17 Tremor: 14		0.779
Sex ratio M/F	**14/0**		**93/42**		**0.01***
	Mean Std. Deviation	**Median Interquartile range**	**Mean Std. Deviation**	**Median Interquartile range**	
Age at V0 (years)	57.6 +/- 7.54	57 (52.7 – 65.4)	56.38 +/- 7.9	57 (51.1 – 62.4)	0.7
Duration of disease at V0 (years)	11.71 +/- 5.48	8.5 (7.7 – 10.9)	11.15 +/- 5.58	10.1 (7.3 – 12.9)	0.402
LEDD	1627.23 +/- 1018.35	1180 (806 – 2164)	1613.64 +/- 766.75	1392.5 (1100 – 2092.5)	0.621
Tremor rest UPDRS III	**3.5 +/- 4.9**	**0 (0 – 8)**	**4.81 +/- 3.53**	**4 (2 – 7)**	**0.048**
Tremor postural UPDRS III	3.07 +/- 2.43	2.5 (1 – 3.75)	2.6 +/- 1.69	2 (2 – 4)	0.795
Tremor UPDRS III	6.57 +/- 6.79	3 (1 – 13.8)	7.41 +/- 4.6	7 (4 -10)	0.182
Rigidity UPDRS III	9.86 +/- 4.28	10 (7 – 13)	9.92 +/- 4.25	10 (7 – 12.5)	0.964
Akinesia UPDRS III	22.43 +/- 6.87	21 (19 – 26)	21.19 +/- 7.05	20 (16 -26)	0.484
Gait and Posture UPDRS III	7.71 +/- 4.76	7 (4 -11)	7.61 +/- 3.39	7 (5 – 9)	0.824
Speech UPDRS III	1.57 +/- 0.94	2 (1 – 2)	1.44 +/- 0.84	1 (1 – 2)	0.518
UPDRS III Total	48.14 +/- 14.94	47 (42 – 50)	47.57 +/- 14.2	46 (37 – 56)	0.917
Rest/Postural Ratio V0	**0.79 +/- 1.26**	**0 (0 – 1.1)**	**2.02 +/- 1.57**	**1.6 (1 – 2.75)**	**0.001**
Rest/Postural Ratio V0 Imputed	**0.79 +/- 1.26**	**0 (0 – 1.1)**	**2.34 +/- 2.26**	**1.8 (1 – 3)**	**0.001**

Table-4: Subthalamic deep brain stimulation cohort characteristics

B	Stimulation assessment cohort Baseline characteristics	
Number of patients	108	
Gender (M/F)	2,18	
Phenotype	74 PIGD 13 Intermediate 13 Tremor Dominant	
	Mean Std. Deviation	**Median Interquartile range**
Age at DBS Implantation (years)	56.6 +/- 7.9	52.8 (52.1 – 63.1)
Disease duration at DBS implantation (years)	13.1 +/- 5.5	10.4 (8 – 13.9)
Duration of DBS at V1 (months)	15.5 +/- 8.6	13.5 (12 – 19.7)
LEDD decrease (%)	40.2 +/- 29.7	44.5 (22.2 – 60.1)
UPDRS III Off Off Rest Tremor Score	6.3 +/- 5.4	5 (2 -10)
UPDRS III Off Off Postural Tremor Score	3.1 +/- 2.3	3 (2 – 4)
UPDRS III Off Off Total Tremor Score	9.4 +/- 7.2	7 (4 – 14)
UPDRS III Off Off Rigidity Score	10.2 +/- 4.7	10 (7- 14)
UPDRS III Off Off Akinesia Score	24.4 +/- 7.6	25 (18 – 30)
UPDRS III Off Off Gait and Posture Score	6.5 +/- 3.8	6 (4 – 9)
UPDRS III Off Off Speech III Score	1.5 +/- 1.1	1 (1 – 2)
UPDRS III Off Off Total UPDRS III	52.0 +/- 18.0	49 (39 – 65)
Rest/Postural Tremor Ratio at V1	2.0 +/- 1.4	1.67 (1 – 2.5)
Rest/Postural Tremor Ratio at V1 Imputed 0,5	2.3 +/- 2.9	1.9 (1 – 2.8)
Amplitude (V)	2.8 +/- 0.7	2.7 (2.2 – 3.35)
Pulse width (us)	60.9 +/- 4.1	60 (60 – 60)
Frequency (Hz)	135.3 +/- 19.9	130 (130 – 130)