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Striatal Dopaminergic Function and Motor Slowing in Essential Tremor Plus

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Essentiaalinen vapina (ET) on yksi yleisimmistä aikuisten liikehäiriösairauksista, jolle tyypillistä on yläraajojen molemminpuolinen kannatus- ja liikevapina. Osalla ET:tä sairastavista potilaista esiintyy myös Parkinsonin taudille (PD) tyypillisiä oireita, kuten lepovapinaa, bradykinesiaa ja rigiditeettiä (essentiaalinen vapina plus, ET+). ET+-potilaiden bradykinesia ja rigiditeetti oireiden vuoksi on keskusteltu taudin määrittelystä, sekä mahdollisesta yhteydestä Parkinsonin tautiin (PD). Lisäksi ET-potilailla on todettu kohonnut riski sairastua Parkinsonin tautiin, mikä on herättänyt kiinnostusta erityisesti dopamiinitoimintaan liittyvästä yhteydestä sairauksien välillä. Aikaisemmat kuvantamistutkimukset ovat osoittaneet, että striataalisen dopamiini transportterin (DAT) sitoutuminen on normaalia ET-potilailla verrattuna terveisiin verrokkeihin. Tutkimusnäyttö ET:n mahdollisesta osittaisesta dopaminergisesta mekanismista on kuitenkin viime vuosien aikana lisääntynyt.

Tämän tutkimuksen tarkoituksena on selvittää, onko ET+-potilaiden dopaminerginen toiminta osittain samanlaista kuin PD-potilailla.

Tutkimukseen sisältyi 43 ET+-potilasta, 115 PD-potilasta sekä 40 tervettä verrokkia. Kaikki potilaat kuvattiin [^{123}I]FP-CIT SPECT-kuvantamisella sekä tutkittiin kliinisesti. Kliiniset ET+- ja PD-diagnoosit varmistettiin keskimääräisesti 3,0 vuoden seurannan jälkeen. Lisäksi ET+-potilaiden diagnoosia seurattiin 7,7 vuotta kuvantamisen jälkeen. Striataalisten alueiden DAT-sitoutumisen arvoja vertailtiin kliinisten oireiden kanssa eri potilasryhmien välillä.

Päätuloksena havaittiin, että kokonaismääräinen bradykinesia oli negatiivisesti yhteydessä posteriorisen putamenin DAT-sitoutumiseen sekä ET+- että PD-potilailla. Tulos oli erityisen selkeä sormien liikkeiden bradykinesian suhteen ($F=10,71$, $p=0,001$). ET+-potilailla liikevapinan asymmetria oli lisäksi yhteydessä posteriorisen putamenin DAT-sitoutumisen asymmetriaan ($r=0,33$, $p=0,043$). Nämä tulokset tukevat osittaisen dopaminergisen toiminnan osuutta ET+:n patofysiologiassa ja saattavat selittää, miksi nämä potilaat eivät aina saa hyvää vastetta ei-dopaminergisille hoidoille.

Striatal Dopaminergic Function and Motor Slowing in Essential Tremor Plus

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ABSTRACT

Background

While previous imaging studies have generally shown normal striatal dopamine transporter (DAT) binding in ET, emerging evidence suggests a partial dopaminergic mechanism in this condition and an epidemiological link between ET and PD. This link seems particularly meaningful in ET patients with additional neurological signs, such as slowness of movements, rigidity, or rest tremor (ET+).

Objectives

To investigate the potential dopaminergic pathophysiology of essential tremor (ET) plus (ET+) and to compare it to Parkinson's disease (PD).

Methods

43 ET+ patients, 115 PD patients and 40 healthy controls were studied using [^{123}I]FP-CIT SPECT imaging and clinical examinations. A median follow-up of 3.0 years was carried out to confirm the diagnoses. ET+ patients underwent an extended follow-up with a median of 7.7 years (range 4.3-9.8 years). Region-specific binding ratios of striatal DAT binding were compared among the groups and correlated with the MDS-UPDRS motor scores.

Results

Bradykinesia scores were negatively associated with posterior putamen DAT binding in both the ET+ and PD groups, with the strongest correlation observed in finger tapping ($F=11.1$, $\beta=-0.10$, 95%CI -0.16 to -0.04, $p=0.001$). In ET+ patients, kinetic tremor asymmetry correlated with posterior putamen DAT binding asymmetry ($r=0.33$, $p=0.043$), indicating a relationship between more severe tremor and subtle contralateral DAT loss.

Conclusions

In ET+, subtle increases in bradykinesia scores correlate with striatal dopaminergic dysfunction, while kinetic tremor asymmetry is associated with hemispheric DAT

binding asymmetry. These findings support the concept of partial dopaminergic involvement in the pathophysiology of ET+.

INTRODUCTION

Essential tremor (ET), a prevalent movement disorder in adults, is characterized by bilateral postural and kinetic tremors that are typically unaccompanied by other neurological symptoms or signs.[1] Nevertheless, a subgroup of individuals with ET presents additional neurological manifestations, such as slowness of movements and rest tremor. The nomenclature “essential tremor plus” (ET+) has been proposed to delineate a distinct subtype of ET characterized by these supplementary neurological signs beyond simple action tremors.[2] According to this classification, ET+ patients meet the criteria for ET but also manifest rest tremor or other neurological signs of uncertain clinical significance (i.e., “soft signs”), including impaired tandem gait, questionable dystonic posturing, and memory impairment or other mild signs that are not sufficient for additional syndrome classification or definitive diagnosis.[2] However, the classification of ET+ and its potential relationship with PD remain uncertain and debated, particularly for patients who exhibit rest tremor or other motor symptoms commonly associated with PD[3, 4]. The manifestation of parkinsonian symptoms also poses diagnostic challenges as it is difficult to distinguish between the two conditions based on their clinical phenotypes.[5, 6] Epidemiological studies have also suggested that individuals with ET have an increased risk of developing PD[5, 7], raising questions about a potential pathophysiological connection, especially regarding dopamine function[5, 8].

Despite the high prevalence of ET, our understanding of its underlying pathophysiology remains incomplete. A recent systematic review identified 14 functional brain imaging studies that found no alterations in the dopaminergic system in ET patients, and longitudinal studies have indicated that ET patients exhibit relatively stable dopaminergic function over time.[9] However, in the context of ET+, one previous study reported mild substantia nigra neuronal loss in six ET patients with resting tremor compared to the substantia nigra neuronal population in control subjects (n=21).[10] In addition, the systematic review identified four studies that revealed striatal dopaminergic dysfunction, particularly in the caudate nucleus, in ET patients.[9] Furthermore, a recent study with 16 ET patients suggested that striatal

dopaminergic tone alterations could be associated with bradykinesia, specifically regarding finger tapping.[11]

Considering the previous evidence suggesting potential dopaminergic involvement in ET+ patients and the hypothesis that some patients might represent a transitional state between ET and PD[4,11], the present study aimed to investigate whether ET+ has similarities with PD in terms of striatal dopaminergic function. We hypothesized that a link between striatal dopaminergic function and the manifestation of motor symptoms on the International Parkinson and Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[12]—specifically, slowness of movements or rigidity—could be observed in ET+ patients.

Furthermore, we anticipated that dopamine function in ET+ patients could be observed through symptom asymmetry, since in PD, it is well established that asymmetries in dopaminergic function are correlated with asymmetrical motor symptoms. We hypothesized that, although overall striatal dopamine transporter (DAT) binding is generally within normal ranges in ET+ patients, asymmetries in motor symptoms might still be present and could potentially correlate with contralateral variations in DAT binding. The patients were assessed for an extended clinical follow-up period to uncover possible phenotypic changes and to identify ET+ patients who might have subsequently progressed to PD.

METHODS

Participants. A total of 43 ET+ patients, 115 PD patients, and 40 healthy controls were enrolled in this study. The study subjects were individuals referred for diagnostic brain DAT imaging using [^{123}I]FP-CIT SPECT due to clinically uncertain parkinsonism and/or tremor. All patients underwent diagnostic brain imaging for clinical purposes at Turku University Hospital or Helsinki University Medical Imaging Center in Finland, as part of the NMDAT project (ClinicalTrials.gov NCT02650843). Inclusion criteria required participants to be aged 18 or over and capable of understanding and completing questionnaires in Finnish. The initial cohort comprised 455 individuals scanned between 2014 and 2019. After a median interval of 3.0 years post-imaging (range 0.1-5.9 years), diagnostic evaluations were retrospectively performed by two movement disorder specialists using electronic health records, medication responses, symptoms, signs, and laboratory and imaging results. Based on these evaluations, 115 patients were categorized as having PD and were unmedicated with antiparkinsonian drugs at the time of imaging, while 43 patients were categorized as unmedicated ET+ patients (for classification criteria, see below). The remaining 297 subjects from the original cohort were excluded from the analysis because they were either dopaminergically medicated or diagnosed with other conditions, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal syndrome (CBS), drug-induced parkinsonism, dystonia, clinically undetermined tremor, or clinically undetermined parkinsonian syndrome. The cohort has been described in detail in previous publications (e.g., references [13, 14, 15]). For healthy controls, see supplementary material.

The differential diagnosis between ET+ and PD was based on the MDS clinical diagnostic criteria for PD, which incorporate striatal DAT imaging results. Consequently, individuals exhibiting normal DAT binding were diagnosed as non-PD. Consistent with prior literature on the classification and differentiation of ET and ET+[2, 16, 3], a participant was classified as having ET+ if he or she fulfilled the diagnostic criteria for ET, showed normal striatal DAT binding as evaluated visually by a nuclear medicine physician blinded to the diagnoses and confirmed by a semi-quantitative region-of-interest-based analysis, and obtained scores greater than zero in resting tremor, rigidity or bradykinesia on the MDS-UPDRS motor scale during the

clinical examination. All ET+ patients were referred for clinical DAT-SPECT by a neurologist due to observed slowness of movements, rigidity or resting tremor. For ET+ patients, a second diagnostic evaluation was performed retrospectively by two movement disorder specialists after a median follow-up of 7.7 years (range 4.3-9.8 years) using the same procedure and same diagnostic criteria as for the first evaluation. The aim of this second evaluation was to assess whether disease progression or phenoconversion to PD had occurred over the follow-up period.

Clinical evaluation procedures. All participants underwent a comprehensive series of clinical examinations 2–4 h prior to imaging. The assessments included a clinical interview and the administration of Part III of the MDS-UPDRS[12], which includes tremor ratings and rigidity and bradykinesia subscores. The MDS-UPDRS bradykinesia subscores included finger and toe tapping, hand movements, pronation-supination movements of the hand, leg agility and global bradykinesia (Items 3.4 to 3.8 and 3.14), with the bradykinesia score representing the sum of these subscores. The rigidity subscores included neck rigidity and rigidity of the upper and lower limbs on the MDS-UPDRS (Item 3.3), with the rigidity score representing the sum of these items. Tremor ratings included postural tremor, kinetic tremor of the hands, and rest tremor of the upper and lower limbs (Items 3.15 to 3.17), with the total tremor score representing the sum of these items. The MDS-UPDRS training program and exercise were completed successfully by all examiners.

The Mini-Mental State Examination (MMSE)[17], the Beck Depression Inventory (BDI)[18] and the Parkinson's Disease Questionnaire (PDQ-8)[19] were also used to assess participants. The demographic and clinical characteristics of the participants are presented in Table 1.

Standard protocol approvals, registrations and patient consent. The study received approval from the Ethics Committee of Turku University Hospital (decision No. 3/1801/2021). Written informed consent was obtained from all participants, and the study adhered to the principles of the Declaration of Helsinki.

SPECT imaging and data analysis. For technical details of SPECT imaging, see supplementary material. Reconstructed SPECT images were analyzed using BRASS semiautomated analysis software (version 2.6, Hermes Medical Solutions AB, Stockholm, Sweden), and scanner-specific corrections were performed based on our calibrations. Specific binding ratios (SBRs) were calculated for six striatal subregions including the left and right anterior putamen, posterior putamen, and caudate using the occipital cortex as the reference tissue; these areas were the regions of interest (ROIs). The SBRs were calculated using the following formula: $SBR = (SBR_{caudate\ or\ putamen} - SBR_{occipital})/SBR_{occipital})$[20]. The mean level of DAT binding in the putamen was obtained by averaging the SBRs of the anterior and posterior putamen.

Voxel-based analyses. The significant associations between motor symptoms and striatal SBRs in the ROI analyses were confirmed voxelwise using Statistical Parametric Mapping software (SPM12).[21] For details, see supplementary material.

Statistical analyses. IBM SPSS Statistics version 29 (SPSS Inc., Chicago, IL, USA) was used for all the statistical analyses outside of the voxelwise analyses. The normality of variables was assessed visually through histograms together with Shapiro–Wilk tests. Descriptive statistics are presented as the mean (SD), median (IQR) or n. Group differences were determined using chi-square or Fisher's exact tests for categorical variables, while Mann–Whitney U tests or Kruskal–Wallis tests were performed for continuous variables. Related-Samples Wilcoxon Signed Rank Test was used to study changes between the baseline and follow-up visit. An ANCOVA model was used in the main analyses to investigate the relationships between clinical symptoms and striatal DAT binding, with age, sex, total motor MDS-UPDRS score, and group (ET+ vs. PD) as covariates, unless specified otherwise. In addition, the same statistical model was applied only for the ET+ group with the identical covariates (age, sex, and total MDS-UPDRS score, excluding the group covariate). Healthy controls were not included in the model due to their low scores in MDS-UPDRS, bradykinesia scores, and finger tapping. Interaction effects between clinical evaluations and groups were also explored. Spearman's correlation coefficients were calculated to assess associations between SBRs and rigidity, bradykinesia, and tremor. To evaluate the correlation between tremor and DAT asymmetry, a DAT binding asymmetry index was computed based on the SBRs

([right-left]/[right+left]). To adjust for tremor severity, a severity asymmetry index (SAI) was calculated for kinetic, postural and resting tremors: ([right-left]/[right+left] × MDS-UPDRS item score from the predominant tremor side). Correlations between tremor SAIs and DAT-binding asymmetries were assessed using Spearman's correlation coefficients. The level of statistical significance was set at $p < 0.05$.

Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Group differences

The main differences in demographic and clinical variables among the groups are summarized in Table 1 and Figure 1. Distribution of different tremor types in patient groups are presented in Supplementary Table 1. Compared with PD patients, ET+ patients had a longer motor symptom duration, less rigidity and more total, postural and kinetic tremors, without differences in the total motor symptom severity score (motor MDS-UPDRS) or other demographic or clinical variables (Table 1, Figure 1). Compared with both ET+ patients and healthy controls, PD patients had clearly lower DAT binding values (the mean binding value in the caudate was 18.1% lower in PD patients than in healthy controls and 26.9% lower in PD patients than in ET+ patients; the mean binding value in the posterior putamen was 53.9% lower in PD patients than in healthy controls and 56.9% lower in PD patients than in ET+ patients; $p<0.001$). Compared with those of ET+ patients, SBRs in the caudate nucleus that were 10.8% lower in healthy controls ($p=0.018$), but there were no significant differences in putamen DAT binding between ET+ patients and healthy controls (Table 1, Figure 1). None of the ET+ patients converted to PD during a median follow-up of 7.7 years.

Associations between DAT binding, age and sex

Age was negatively associated with the mean caudate nucleus and posterior putamen SBRs in all groups (β=-0.03, CI, -0.033 to -0.016, $p<0.001$ in the caudate nucleus; β=-0.01, CI, -0.02 to -0.01, $p<0.001$ in the posterior putamen; no group interaction; sex and group were used as covariates). The SBR in the caudate nucleus was greater in females than in males (adjusted mean difference 0.30, 95% CI 0.11 to 0.48, $p=0.002$; no group interaction, age and group used as a covariates). Posterior putamen SBRs did not differ between females and males (adjusted mean difference 0.88, 95% CI -0.06 to 0.24, $p=0.24$; no group interaction, age and group used as a covariates).

Associations between clinical findings and DAT binding in ET+ and PD patients

There were no relationships between the mean caudate nucleus or posterior putamen SBRs and motor total MDS-UPDRS scores ($F<0.73$, $p>0.42$; no group interaction; age, sex and group used as covariates), BDI scores ($F<3.71$, $p>0.055$; no interaction), or motor symptom duration ($F<0.18$, $p>0.67$, no interaction).

Bradykinesia score was related to the mean posterior putamen SBR in both the ET+ and PD groups ($F=4.29$, $\beta=-0.22$, 95% CI -0.42 to -0.01, $p=0.040$; no interaction, Figure 2). No associations with clinical findings and caudate nucleus SBRs were observed ($F=3.10$, $\beta=-0.23$, 95% CI -0.48 to 0.03, $p=0.080$; no interaction). Among the specific bradykinesia items on the MDS-UPDRS, finger tapping (total for the left and right hands) was significantly associated with the posterior putamen SBR in both the ET+ and PD groups ($F=11.11$, $\beta=-0.10$, 95% CI -0.16 to -0.04, $p=0.001$; no interaction, Figure 2). Additionally, the pronation-supination score was associated with the posterior putamen SBR in both the ET+ and PD groups ($F=10.51$, $\beta=-0.10$, 95% CI -0.16 to -0.04, $p=0.001$; no interaction), but there were no associations with the hand movement, toe tapping or leg agility subscale outcomes. Rigidity (more specifically, the mean score for all rigidity items) was not related to SBRs in the caudate or posterior putamen ($F<3.83$, $p>0.05$; no interaction).

In the analyses only including the ET+ patients, finger tapping was significantly related to right caudate nucleus DAT binding ($F=4.5$, $\beta=-0.16$, 95% CI=-0.31 to -0.01, $p=0.040$). Furthermore, finger tapping of the left hand was significantly related to mean caudate nucleus DAT binding ($F=6.2$, $\beta=-0.32$, 95% CI=-0.58 to -0.06, $p=0.018$), both right and left caudate nucleus DAT binding ($F=6.8$, $\beta=-0.33$, 95% CI=-0.59 to -0.07, $p=0.013$ on the right side; $F=5.2$, $\beta=-0.31$, 95%CI=-0.58 to -0.03, $p=0.029$ on the left side), left anterior putamen DAT binding ($F=4.8$, $\beta=-0.31$, 95%CI=-0.59 to -0.02, $p=0.035$), mean striatum DAT binding ($F=4.6$, $\beta=-0.26$, 95% CI=-0.51 to -0.01, $p=0.039$) and both right and left striatum DAT binding ($F=4.4$, $\beta=-0.77$, 95%CI=-1.53 to -0.02, $p=0.044$ on the right side; $F=4.6$, $\beta=-0.79$, 95%CI=-1.54 to -0.05, $p=0.038$ on the left side). Bradykinesia scores remained stable in the follow-

up visit (baseline 13.00 [6.50] vs follow-up 9.00 [16.25], p=0.39, n=18). For tremor associations, see supplementary material.

In ET+ patients, posterior putamen DAT binding asymmetry correlated with the kinetic tremor SAI (r=0.33, p=0.043, more severe tremor side associated with contralateral DAT loss) (Figure 2). Similar results were not observed for postural or rest tremor asymmetry (r=-0.06 to -0.16, p>0.36) or for the caudate nucleus. In PD patients, the rest and postural tremor SAIs were greater than those in ET+ patients (p<0.03), indicating greater asymmetry. Additionally, the striatal DAT-binding asymmetry was greater in PD patients than in ET+ patients (p<0.001), and it correlated strongly with postural, kinetic and rest tremor SAIs in PD patients (r>0.60, p<0.001).

Voxel-based analysis

According to the results of the voxelwise analyses, PD patients had lower striatal SBRs than ET+ patients and controls, but there was no difference between ET+ patients and controls (Figure 3A). There was no significant interaction between diagnosis and bradykinesia scores. The severity of left, but not right, bradykinesia score was significantly associated with lower SBRs in the contralateral putamen according to the model that included both PD and ET+ patients (Figure 3B). This association was also present and was significant in all groups except the ET+ patient group (Figure 3B). This association was also present but did not reach significance in ET+ patients only (Figure 3B).

DISCUSSION

The present findings revealed that, while the presynaptic putaminal dopaminergic function in ET+ patients generally mirrors that of healthy individuals, higher bradykinesia scores on the MDS-UPDRS scale in both ET+ and PD patients are associated with posterior putamen DAT binding. This association is particularly pronounced for finger tapping. Notably, kinetic tremor scores showed a comparable asymmetrical association with dopaminergic function in both ET+ and PD patients. Collectively, the results indicate that the clinical phenotype of ET+ patients is, to some extent, influenced by nigrostriatal dopaminergic neurotransmission.

Bradykinesia has consistently demonstrated a robust association with nigrostriatal dopamine function in PD patients, and dopaminergic pharmacotherapies have demonstrated particular efficacy in treating bradykinesia in PD.[22,23,24] The present results align with previous findings on bradykinesia, as it emerged as the sole cardinal motor symptom correlated with DAT binding in both ET+ and PD patients.[22,23,24] However, it is important to consider that the nature of elevated bradykinesia scores in ET+ and PD may differ. In ET+ patients, the increased MDS-UPDRS bradykinesia subscores may be influenced by factors other than typical slowness of movements and decrement seen in PD. Nevertheless, the analyses focusing solely on the ET+ group revealed that while the specific regions of correlation differed slightly from those in the analyses including the PD group, the overall direction and relationship between DAT binding and finger tapping in ET+ remained consistent. It is important to highlight that putaminal DAT binding was within the normal range in ET+ patients compared to healthy individuals. Additionally, caudate binding was marginally greater in ET+ patients than in healthy controls. This observation may suggest a functional upregulation of DAT in some ET+ patients, a potential selection bias introduced during clinical utilization of DAT binding, or self-selection biases inherent in healthy volunteer populations.[25] The ET+ population in the present study may have been subject to selection bias, as these patients were specifically referred for DAT imaging due to diagnostic uncertainty. This selection process likely resulted in the inclusion of individuals with more pronounced symptoms, which may have contributed to higher bradykinesia scores on the MDS-

UPDRS rating scale compared to what might be observed in the broader ET+ patient population.

Among the various bradykinesia items on the MDS-UPDRS rating scale, finger tapping had the most notable association with DAT binding. The present findings underscore the significance of finger tapping in both ET+ and PD patients, aligning with a recent study that demonstrated an association between finger tapping and dopaminergic function in the putamen among 16 ET patients.[12] However, our study extends these observations by identifying relationships between finger tapping and DAT binding not only in the posterior putamen but also in the caudate nuclei and striatum. These results suggest that the dopaminergic association with finger tapping extends beyond the most affected posterior putamen to encompass the entire striatal region. It should be noted that the previous study focused exclusively on finger tapping and included a sample with a milder ET phenotype in terms of general motor symptom severity. Furthermore, the clinical evaluations differed between studies; while the previous study utilized kinematic recordings, our study relied on MDS-UPDRS ratings. The MDS-UPDRS-scale is inherently subjective, and its evaluation of finger tapping is also related to the concept of decrement. In our study, rather than employing the scale as a diagnostic tool, we used it as an indicator of functional differences in specific signs commonly associated with bradykinesia. These signs were assessed by trained examiners, who were blinded to the final diagnoses and DAT results. Despite the methodological differences between the previous kinematic study and the present study, both studies collectively implicate subtle hand bradykinesia as a symptom modulated by dopaminergic mechanisms in ET+ patients. This convergence of findings from independent studies highlights the dopaminergic involvement in subtle bradykinesia within this patient population. In future studies involving healthy controls, kinematic analyses would be a valuable tool for detecting subclinical variations in motor function, as they offer greater precision compared to the MDS-UPDRS scale, which is primarily designed for assessing PD patients.

Significant, yet divergent, effects on tremor were observed between ET+ and PD patients. In PD patients, there was a positive correlation between the severity of total

tremor and rest tremor and putaminal DAT binding, a phenomenon not observed in ET+ patients. Kinetic tremor scores displayed a positive association in both patient groups, and the asymmetry of kinetic tremor correlated with posterior putamen DAT binding asymmetry in both cohorts. The contrasting mechanisms of tremor in ET and PD, including cerebello-thalamo-cortical projections, dopaminergic neuron degeneration in the retrorubral area of the midbrain in PD[24] and cerebellar neurodegeneration, abnormal functioning of the inhibitory neurotransmitter GABA, and/or oscillating networks in ET[9, 26], may elucidate variations in their respective associations with striatal dopamine. In PD patients, the subtle yet apparent positive correlation between putaminal DAT binding and tremor could be a manifestation of a negative feedback loop or reflect the recruitment of additional monoaminergic circuits to compensate for the dopamine deficit.

A crucial question arises concerning the potential efficacy of dopaminergic treatment for patients with ET+. Our findings suggest that ET+ patients with elevated bradykinesia scores on the MDS-UPDRS scale, in addition to typical postural and kinetic hand tremors, may benefit from targeted dopaminergic pharmacotherapies. It is noteworthy that patients in this study were not taking dopaminergic medications, underscoring that the dopaminergic system was not altered pharmacologically. Identifying the specific subset of ET+ patients with mild bradykinesia-type clinical features and limited or no response to current treatment options that might benefit from a dopaminergic medication trial is essential. Limited studies on dopaminergic medications in patients with ET have reported inconclusive results. Although no objective levodopa-induced motor symptom benefit was reported in patients with a normal substantia nigra at autopsy, including ET patients, some patients reported subjective benefits[27]. Another study revealed improved tremor amplitude in levodopa-treated patients who presented features of both ET and PD[28], while a pilot study reported positive outcomes for tremor, activities of daily living and health-related quality of life in ET patients treated with pramipexole.[29] Importantly, there are no reported studies on the efficacy of dopaminergic drugs on motor symptoms other than tremor in patients with ET.

Another key consideration for this study is the possibility of ET+ patients later converting to PD. The debate persists on whether the presence of features such as

resting tremor in ET signifies a manifestation of ET+ or marks the initiation of PD.[5] Although our ET+ patients underwent clinical follow-up for several years post-imaging, the possibility of delayed PD conversion cannot be fully dismissed, especially for ET+ patients with striatal dopaminergic function at the lower end of the normal spectrum. Evidence on postmortem counts of dopaminergic striatal neurons do not support the hypothesis that ET, in general, represents early PD,[30] and a study including 237 autopsied ET patients suggests that Lewy bodies in ET are rather incidental than pathological[31]. However another prospective clinicopathological study of 231 ET brains resulted in evidence suggesting that 25.1% of patients had Lewy body pathology and that 6.1% of patients developed possible PD or PD after a latency of 5 or more years.[32]

In conclusion, the findings of this study suggest that the slowness of movements and/or decrement of movement amplitude observed in some ET+ patients is partly influenced by nigrostriatal dopaminergic changes, thereby presenting avenues for therapeutic interventions. However, due to limited data in healthy controls, further studies are required to clarify the clinical relevance of this relationship and to determine whether the observed dopaminergic alterations in ET+ represent true pathological changes or fall within a range of normal dopaminergic variation. It is possible that the reduced central dopaminergic tone in ET+ could indirectly reflect the neurodegeneration primarily affecting the cerebellum, consequently resulting in reduced central dopaminergic tone at the level of the basal ganglia.[33] Given the retrospective nature of the present study, future prospective controlled trials investigating the efficacy of dopaminergic treatments for the ET+ phenotype are warranted. Furthermore, the definition and classification on ET+ remains controversial and further studies are needed to assess the clinical relevance of ET+ and its relation to other conditions.

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ETHICAL COMPLIANCE STATEMENT

The study received approval from the Ethics Committee of Turku University Hospital (decision No. 3/1801/2021). Written informed consent was obtained from all participants, and the study adhered to the principles of the Declaration of Helsinki. 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

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FIGURES

Figure 1. Differences among the studied groups in specific binding ratios (SBRs) of DAT binding in the studied striatal regions. A. Right caudate nucleus. B. Left caudate nucleus. C. Right posterior putamen. D. Left posterior putamen. E. Lower posterior putamen. F. Higher posterior putamen. *<0.05, **<0.01, ***<0.001, ****<0.0001; ns = not significant.

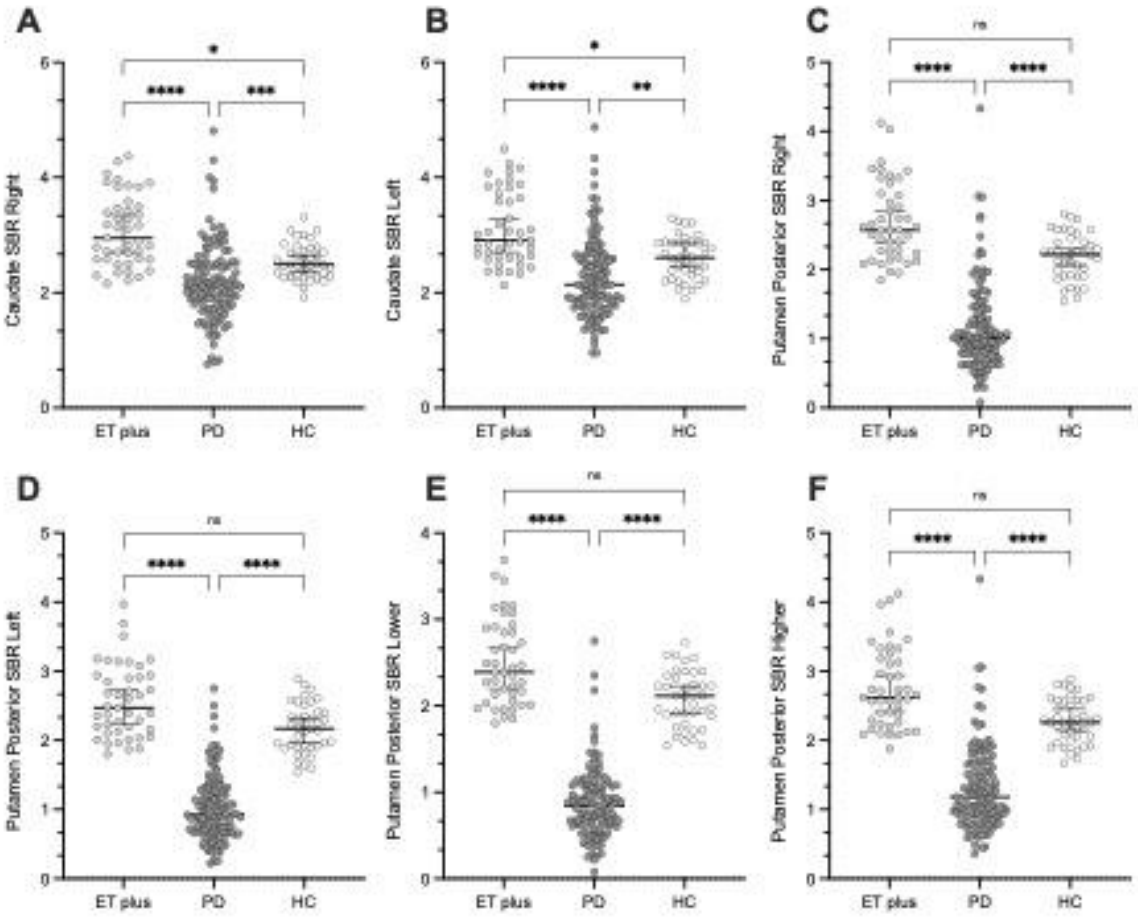

Figure 2. Scatter plots showing correlations between scores in clinical findings and specific binding ratios (SBRs) of putaminal DAT binding in the ET+ and PD groups. A. Total bradykinesia. B. Finger tapping. C. Total tremors. D. Postural tremor. E. Rest tremor. F. Kinetic tremor. G. Kinetic tremor severity asymmetry index (SAI) in ET+ patients. H. Kinetic tremor severity asymmetry index (SAI) in PD patients.

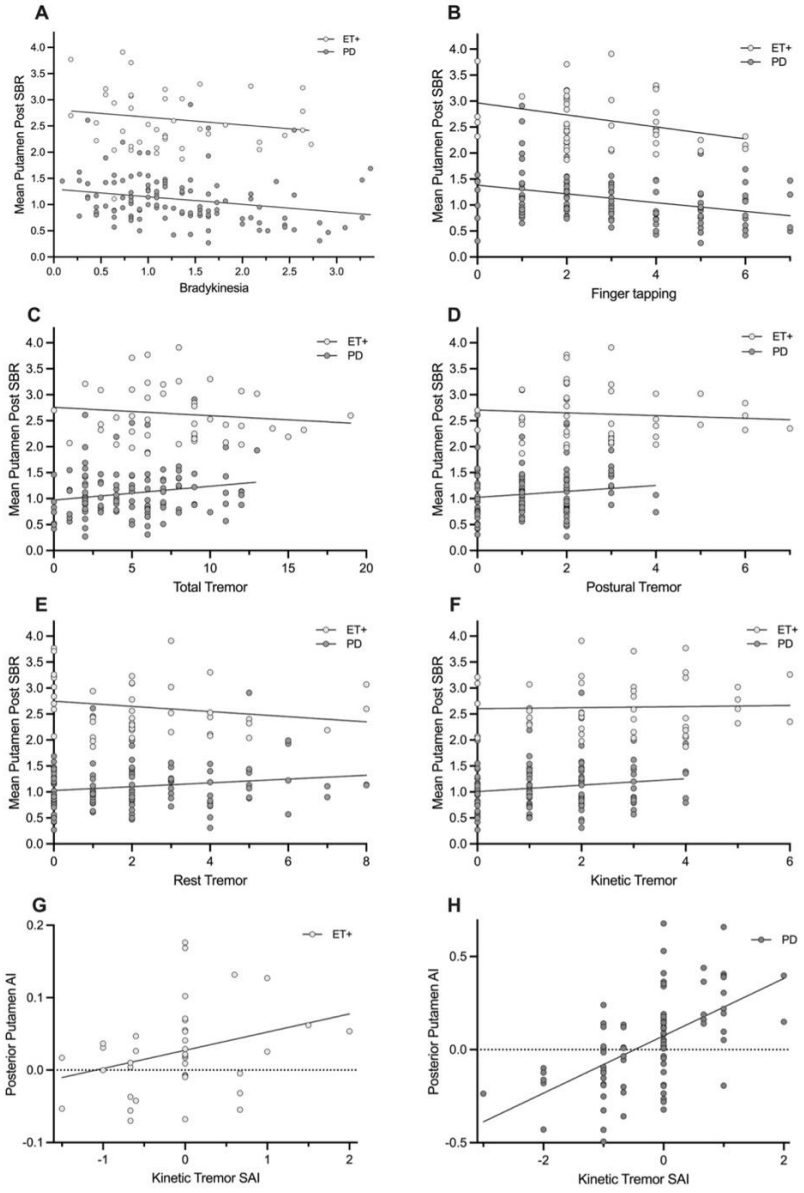

Figure 3. Striatal [^{123}I]FP-CIT-specific binding ratios (SBRs). A. Average striatal voxelwise SBRs in healthy controls and ET+ and PD patients. B. Significant association between a lower SBR in the right putamen and left-sided bradykinesia score in ET+ patients and PD patients (1099 voxels, P_{FWE}=0.003, peak at MNI coordinates 30-14 10 mm) (left) and between uncorrected striatal maps of both left- and right-sided bradykinesia in ET+ patients only. The red–yellow scale indicates a negative association (lower SBR, greater bradykinesia score), and the blue-light blue scale indicates a positive association.

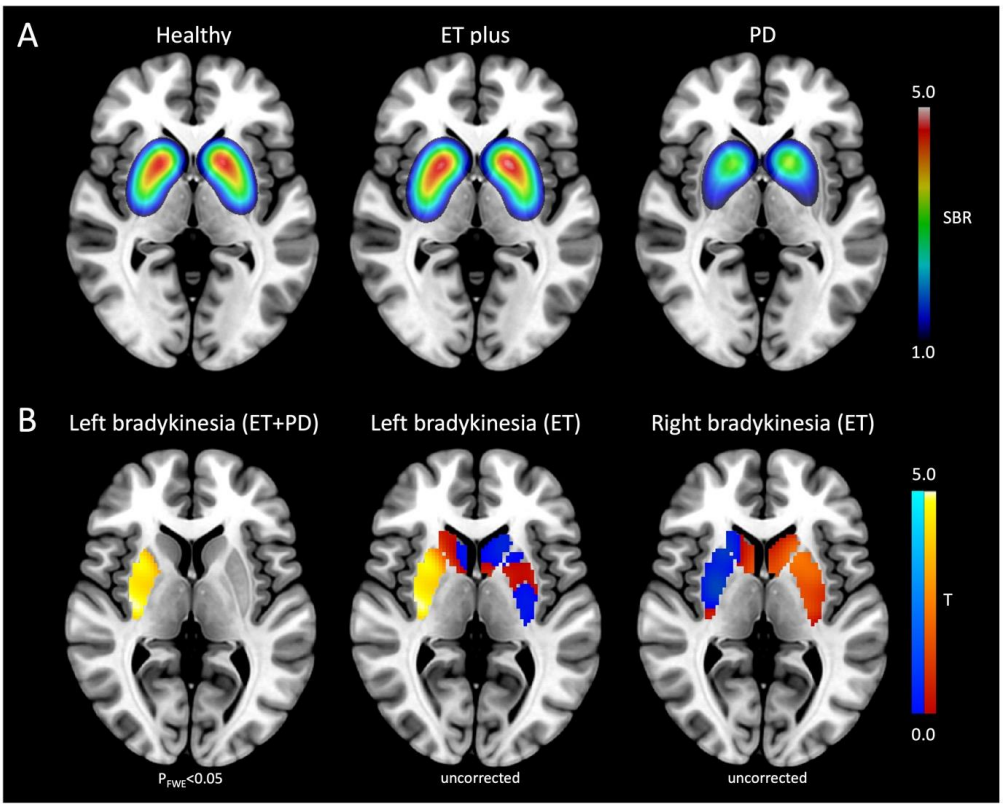

Table 1. Main demographic and clinical characteristics of the studied groups.

Class	Variable	Groups			p value	Pairwise comparisons		
		ET+	PD	HC		ET+ vs. PD p value	ET+ vs. HC p value	PD vs. HC p value
Sample size	n	43	115	40	-	-	-	-
Demographics	Age (yr)	66 [19]	66 [15]	67.5 [12.5]	0.68	ns	ns	ns
	Sex (m/f)	21/22	53/62	21/19	0.78	ns	ns	ns
Cognition	MMSE	27 [3]	28 [3]	28.5 [2.75]	0.052	ns	ns	ns
Mood	BDI	7.0 [9.5]	6.0 [7.0]	0.5 [4.5]	<0.001	1.0	<0.001	<0.001
Motor symptom duration (months)		27 [96]	15 [15]	-	<0.001	<0.001	na	na
Motor examination	Motor MDS-UPDRS total	33 [20]	34 [20]	5 [7]	<0.001	1.0	<0.001	<0.001
	Bradykinesia	12.00 [9.00]	13.00 [9.00]	3.50 [5.75]	<0.001	1.0	<0.001	<0.001
	Rigidity	5.00 [5.00]	7.00 [7.00]	0 [1.00]	<0.001	0.031	<0.001	<0.001
	Tremor total	8.00 [5.00]	5.00 [5.00]	0 [0]	<0.001	0.001	<0.001	<0.001
	Tremor postural	2.00 [2.00]	1.00 [1.00]	0 [0]	<0.001	<0.001	<0.001	<0.001
	Tremor kinetic	3.00 [2.00]	2.00 [1.00]	0 [0]	<0.001	<0.001	<0.001	<0.001
	Tremor rest	2.00 [3.00]	2.00 [3.00]	0 [0]	<0.001	1.0	<0.001	<0.001
DAT binding	Caudate nucleus mean	2.97 [1.04]	2.17 [0.76]	2.65 [0.54]	<0.001	<0.001	0.018	0.001
	Putamen posterior mean	2.48 [0.89]	1.07 [0.57]	2.32 [0.51]	<0.001	<0.001	0.21	<0.001

No subjects were treated with antiparkinsonian dopaminergic medications. Values are medians [IQRs] or n. P values are from Kruskal–Wallis tests or Mann–Whitney U tests, with pairwise comparisons Bonferroni corrected. ET+ = essential tremor plus, PD = Parkinson's disease, HC = healthy control; MMSE = Mini-Mental State Examination, BDI = Beck Depression Inventory, MDS-UPDRS = International Parkinson and Movement Disorder Society's Unified Parkinson's Disease Rating Scale, DAT = dopamine transporter.

Supplementary Table 1. MDS-UPDRS scores of different tremor types and their distribution in patient groups.

Tremor type	Distribution	Group	
		ET+	PD
	n	43	115
Kinetic tremor	Right hand	81 %	57 %
	Left hand	81 %	66 %
Postural tremor	Right hand	86 %	56 %
	Left hand	84 %	58 %
Rest tremor	Right upper extremity	63 %	43 %
	Left upper extremity	58 %	38 %
	Right lower extremity	12 %	23 %
	Left lower extremity	12 %	17 %

Values are n or % of the patients with the score of > 0 on the MDS-UPDRS rating scale. ET+ = essential tremor plus, PD = Parkinson’s disease; MDS-UPDRS = International Parkinson and Movement Disorder Society's Unified Parkinson's Disease Rating Scale.