Preserved noradrenergic function in Parkinson’s disease patients with rest tremor

Martin B. Kinnerup a,⁎, Michael Sommerauer a,b, Malene F. Damholdt a,c, Jeppe L. Schaldemose a, Rola Ismail a, Astrid J. Terkelsen d, Kristian Ster a, Allan Hansen a, Tatiana D. Fedorova a, Karoline Knudsen a, Casper Skjærbæk a, Per Borghammer b, Nicola Pavese a,e, David J. Brooks a,e,f, Adjmal Nahimi a,g

a Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, 8200 Aarhus N, Denmark
b Department of Neurology, University Hospital Cologne and Faculty of Medicine, University of Cologne, 50937 Köln, Germany
c Department for Psychology and Behavioural Sciences, Aarhus University, 8000 Aarhus, Denmark
d Department of Neurology, Aarhus University Hospital, 8200 Aarhus N, Denmark
e Translational and Clinical Research Institute, Newcastle University, Newcastle NE1 7RU, United Kingdom
f Department of Brain Sciences, Imperial College London, London SW7 2AZ, United Kingdom
g Department of Neurology, Restorative Parkinson Unit, Universitetssjukhuset, 22184 Lund, Sweden

ARTICLE INFO

Keywords:
Parkinson’s disease
Tremor
11C-MeNER
Positron emission tomography (PET)
Noradrenaline transporter

ABSTRACT

Noradrenergic neurotransmission may play an important role in tremor modulation through its innervation of key structures of the central tremor circuits. Here, Parkinson’s disease (PD) patients with (PD+T) or without (PD-T) rest tremor had 11C-methylreboxetine(11C-MeNER) positron emission tomography (PET) to test the hypothesis that noradrenaline terminal function was relatively preserved in PD+T compared to PD-T. Methods: Sixty-five PD patients and 28 healthy controls (HC) were scanned with 11C-MeNER PET. Patients were categorized as PD+T if subscores in UPDRS-III item 3 or MDS-UPDRS-III item 17 ≥ 2; remaining were categorized as PD-T. Simplified reference tissue model 2 distribution volume ratios (DVR) for 11C-MeNER were calculated for thalamus, dorsal and median raphe, locus coeruleus (LC) and red nucleus using time activity curves (TACs) obtained from volumes of interest (VOI). Data were statistically interrogated with a general linear mixed model using ‘region’ as factors and the interaction of ‘region x group’ was examined. Results: Tremor positive PD patients had a significantly higher mean 11C-MeNER DVR compared to PD-T in LC and thalamus. The PD+T mean LC DVR was similar to that of HC. PD+T mean 11C-MeNER DVRs were significantly lower than HC in the dorsal raphe while the PD-T group showed significantly lower mean 11C-MeNER DVR across all regions compared to HC. Conclusion: While both PD+T and PD-T groups showed a significant loss of noradrenaline terminal function compared to controls, noradrenergic neurons were relatively preserved in PD+T in LC and thalamus. The greater loss of noradrenergic transporters in PD+T in LC and thalamus compared with PD-T is in line with earlier in-vitro studies and could potentially contribute to their tremor negative phenotype.

1. Introduction

Parkinson’s disease (PD) is characterised by insidious onset of limb bradykinesia, rigidity, and tremor in association with Lewy body degeneration of dopaminergic neurons. Dopamine replacement therapy with levodopa or dopamine agonists significantly alleviates bradykinesia and rigidity, while its effect on tremor is less consistent (Asenbaum et al., 1998; Brooks et al., 1990; Eggers et al., 2011; Mishina et al., 2011). Several phenotypes of PD have been identified by their clusters of clinical symptoms. The most prevalent phenotypes are the akinetic-rigid with or without postural instability and gait difficulty (PIGD) and the tremor-predominant phenotypes (Jankovic et al., 1990; Lees et al., 2009). Imaging studies have reported that the pattern and severity of striatal dopamine dysfunction differs between tremor-predominant...
patients and akinetic-rigid patients, the latter having more severe posterior putamen involvement (Eggers et al., 2011). In line with this, akinetic-rigid patients have a more severe loss of dopamine neurons in the ventrolateral part of substantia nigra pars compacta (SNPC) while the medial part of SNPC is more affected in tremor-predominant patients (Jellinger, 2002).

Tremor prevalence was studied in a clinicopathologic study, in which 68% of patients examined presented with tremor symptoms at disease onset and this gradually increased to 75% with disease progression (Hughes et al., 1993). In a follow-up study on 47 idiopathic PD patients, Rajput et al. observed rest tremor in all subjects (Rajput et al., 1991). Rest tremor is often described as a 4–6 Hz pill-rolling finger-thumb movement that initially is observed as an episodic motor oscillation but gradually manifests itself as a continuous problem.

Interestingly, the presence of tremor may predict a more benign course of disease, at least in the first 10 years, as several studies have shown a lower prevalence of co-morbid non-motor symptoms in patients with tremor predominance (Thanhant and Jankovic, 2014). This observation has led to the hypothesis that non-dopaminergic neurotransmitters, including serotonin and noradrenaline, may also be differently affected by the degenerative processes in patients with tremor-predominant PD compared to other subtypes (Isaias et al., 2012; Pasquini et al., 2018).

The locus coeruleus (LC) sends noradrenergic projections throughout the brain including to structures that have been implicated in generation of tremor in patients with PD (Isaias et al., 2012; Lindvall and Bjorklund, 1974). The ventral intermediate (Vim) nucleus of the thalamus, which plays a central role in tremor circuits, receives dense noradrenergic innervation. Thalamic noradrenergic terminals undergo significant degeneration in patients with PD (Pifl et al., 2012). Interestingly, pathologic studies of the noradrenergic system have suggested that noradrenaline producing neurons in LC are relatively preserved in patients with tremor-predominant PD compared to akinetic-rigid PD patients (Jellinger, 1999; Paulus and Jellinger, 1991). We have shown that loss of noradrenaline terminals in PD patients can be detected in-vivo with C-methyl-benztropine (11C-MeNER) positron emission tomography (PET) (Nahimi et al., 2017) – particularly if REM sleep behaviour disorder is also present (Sommerauer et al., 2018). Our initial 11C-MeNER study suggested a role for noradrenaline in tremor genesis, with a higher preservation of noradrenaline transporters in thalamus in the tremor pre-dominant patient group (Nahimi et al., 2017).

Noradrenergic projections are, in addition to the above, observed in the dorsal and median raphe nuclei (Ordway et al., 1997) and studies suggest that these projections modulate serotonin function (Cassano et al., 2009; Vj, 1979). A recent study of PD using 11F-flupaname-fluoropropyl-carboxymethoxy-3-beta-4-iodophenylpropene (11F-FP-CIT) SPECT reported that serotonin transporter availability in the median raphe (raphe/putamen ratio) was inversely correlated with severity of rest tremor (Pasquini et al., 2018). Loss of raphe serotonin HT1A receptor binding sites has also been linked to PD rest tremor (Doder et al., 2003). This suggests that the noradrenergic system through its modulatory projections to the raphe nuclei, could be an instrumental part of rest tremor in PD.

In this current cross-sectional study, we used 11C-MeNER PET to further investigate our previously reported potential relation between tremor severity and density of noradrenergic terminals in a large cohort of PD patients. Specifically, we tested the hypothesis that the presence of tremor would be associated with greater preservation of the noradrenergic system compared to PD patients without tremor.

2. Materials and methods

2.1. Participants

Sixty-five PD patients (71% male) and 28 healthy age-matched controls (HC) (60% male) were recruited. Twelve PD patients and 8 HC were included from our previous study (Nahimi et al., 2017), 30 PD and 12 HC were included from another earlier study (Sommerauer et al., 2018), and 23 PD and 8 HC were recruited specifically for this study. They were rated with the mini-mental-state-examination (MMSE) (Folstein et al., 1975) or Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) score and excluded if the scores were below 24 or 22, respectively, or if clinical depression was present. Their levodopa equivalent daily dosage (LEDD) was calculated using recent conversion factors (Tomlinson et al., 2010).

2.1.1. Measures

The rapid eye movement (REM) sleep behaviour disorder screening questionnaire (RBDSQ) was used to calculate a total RBDSQ score (Stiasny-Kolster et al., 2007). Motor function was either assessed using the original Unified Parkinson’s Disease Rating Scale UPDRS part III (UPDRS-III) or the Movement Disorder Society Revised Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III). Subjects were rated in the “OFF” state after overnight withdrawal of medication. Rest tremor classification was performed using a slightly modified version of the method described by Pasquini et al. (Pasquini et al., 2018). Patients with rest tremor were classified as PD+ – score ≥ 2 on any of the sub-scores in UPDRS-III item 3.3 or MDS-UPDRS-III item 3.17, while the other patients were classified as tremor negative (PD–). Rest tremor, rigidity and bradykinesia were calculated using the following items for MDS-UPDRS-III and UPDRS-III respectively: rest tremor - 3.17 and 3.3, rigidity - 3.3 and 3.5, bradykinesia - 3.4, 3.5, 3.6 and 3.8 and 3.6–3.9.

Total UPDRS is calculated as the sum of all items in part III; to ensure comparability between the UPDRS and MDS-UPDRS scales we added seven points to the total UPDRS-III score according to established conversion methods (Hentzel et al., 2015).

2.1.2. Procedures

PD patients were recruited in collaboration with the Departments of Neurology at Aarhus University Hospital, Aalborg University Hospital, Viborg Hospital and Odense University Hospital. The ethics committee of Central Denmark region approved the study. Prior to participation, subjects provided written informed consent.

2.2. Imaging

2.2.1. Imaging methods

Each subject was scanned with an ECAT HRRT camera (CTI/Siemens, Knoxville, TN, USA) following the scan protocol described in Nahimi et al. (Nahimi et al., 2017). The scanning session was initiated with a transmission scan to allow attenuation correction followed by a bolus injection of C-MeNER (614 ± 125 MBq) at the start of which the dynamic emission PET scan was initiated. The PET scan was recorded in 3D list mode with 27 dynamic time frames with increasing duration over 90 min. A detailed description of the synthesis of the PET tracer 11C-MeNER has been published previously (Nahimi et al., 2017). PD patients were scanned either in an “ON” or “OFF” condition. Magnetic resonance imaging (MRI) was performed with the Siemens 3 T MAGNETOM PRIMA or 3 T MAGNETOM TRIO using a combined 32-element head and neck coil. A magnetization prepared rapid gradient-echo with two gradient echo images (T1-MP2RAGE) (Marques et al., 2010) was used for segmentation and co-registration.

2.2.2. Image pre-processing and delineation of volumes of interest

PET images were processed with PMOD™ 3.6 software using the PNEURO and PKIN toolboxes. Individual PET and MR images were co-aligned using rigid matching and then normalized into Montreal Neurological Institute (MNI) stereotaxic space.

Volumes of interest (VOIs) were assigned using the Hammers N30883 1 mm atlas in PMODs maximum probability atlas tool (Hammers et al., 2003). Substructures defined in the Hammers atlas were visually inspected and VOIs manually corrected where necessary.
Additional VOIs were defined for the median and dorsal raphe by tracing their borders defined by the Talairach atlas; the red nucleus VOIs was defined from the surrounding anatomical structures; the LC VOI was defined according to previously published details (Nahimi et al., 2017; Sommerauer et al., 2018). See Fig. 1 for a detailed view of the VOIs created.

Thalamus was selected as a VOI based on previous findings reported by Nahimi et al. (Nahimi et al., 2017); dorsal and medial raphe based on serotonin’s role in tremor genesis (Pasquini et al., 2018) and the binding of $[^3]H$nisoxetine (Ordway et al., 1997) in the nuclei; the red nucleus based on MR research showing a significantly increased iron accumulation (Guan et al., 2017) and the red nucleus being reported to play a role in the cerebello-thalamo-cortical system. We were unable to include substantia nigra due to negligible $[^3]H$nisoxetine and MeNER binding reported by Ordway et al. and Ghose et al. respectively (Ghose et al., 2005; Ordway et al., 1997).

2.2.3. Image analysis

Following pre-processing of PET images with a 4 mm Gaussian filter, time activity curves (TACs) were extracted for each VOI sampled using the PKIN toolbox in PMOD. The $^{11}$C-MeNER distribution of volume ratios were computed from TACs using a simplified reference tissue model 2 (SRTM2) with caudate as the reference region. A global value of 0.021 for the clearance rate constant for the reference region ($k_2$) was used as previously described (Nahimi et al., 2017; Sommerauer et al., 2018).

2.3. Statistical analysis

Data were interrogated with the statistical package for the social sciences (SPSS) version 27 and results are presented as mean ± standard deviation if not otherwise stated. Differences in demographic traits between groups were assessed with one-way ANOVA with Welch correction or Students t-test. Normal distribution was assessed with the Shapiro-Wilk test and Q-Q plots.

Volume of interest-based analysis was performed using a linear mixed model for repeated measures with fixed factors: ‘group’, ‘region’ a ‘region x group’ interaction and random effect ‘subjects’. Covariates assessed in the analysis were ‘age’, ‘sex’, ‘LEDD’, ‘injected doses’, ‘total UPDRS’, ‘disease duration’, and the total score of ‘RBDSQ’. A Bonferroni correction for repeated measures was applied.

Correlations between $^{11}$C-MeNER DVR values and rest tremor as well as rigidity and bradykinesia scores were investigated with non-parametric Spearman rank correlation statistics. Rest tremor correlations were performed on subjects with a score greater than zero in items 3.3 or 3.17 in UPDRS-III and MDS-UPDRS-III, respectively.

3. Results

3.1. Clinical findings

Healthy subjects, PD$^+$, and PD$^-$ subjects were comparable in their demographic characteristics. A significant difference was observed
between the mean LEDDs of PD+ and PD-. For the subgroup of patients examined with MDS-UPDRS III (n = PD+ 11, PD- 19) the PD+ group scored significantly higher in gait, postural tremor, kinetic tremor, rest tremor amplitude and constancy of rest tremor. See Table 1 for an overview of the demographic of the population and Table 2 for an overview of the UPDRS assessment.

3.2. Volume of interest analysis

The linear mixed model for repeated measures showed significant mean differences between the three groups (group effect P < 0.0001, values below reported as mean ± standard error of mean). The interaction ‘region x group’ was significant (p = 0.013) and we observed significant differences across specific regions between the two groups of PD patients. PD+ had significantly higher 11C-MeNER DVR values compared to PD- in LC (PD+ 1.28 ± 0.04 | PD- 1.14 ± 0.03) and thalamus (PD+ 1.32 ± 0.02 | PD- 1.24 ± 0.02). The 11C-MeNER DVR value in PD+ was comparable to HC in the LC (HC 1.26 ± 0.04 | PD+ 1.28 ± 0.04) and was significantly lower in the dorsal raphe (HC 1.53 ± 0.06 | PD+ 1.30 ± 0.05). PD+ showed a significant DVR decrease compared to HC in all sampled regions. Asymmetry analysis in the thalamus, showed an average difference between the left thalamus and right thalamus of 2% (range 0% to 7%). In addition, we found no significant difference between congruent and incongruent side with regard to the lateralised disease symptoms. See Fig. 2 for a visualization of 11C-MeNER DVR uptake.

We found no correlation between 11C-MeNER DVR values and rigidity or bradykinesia scores for the regions sampled in this paper. However, a significant correlation was found between rest tremor score and 11C-MeNER DVR values in median raphe (coef. 0.387, P = 0.029), thalamus (coef. 0.396, P = 0.023), and red nucleus (coef. 0.393, P = 0.024). See Table 4 and Fig. 3.

4. Discussion

In the current study, we examined the relationship between rest tremor and availability of noradrenaline transporters by quantifying the latter with 11C-MeNER PET in PD patients with and without tremor. We found that noradrenergic transporter density was decreased in all sampled regions in PD-. PD- had a similar mean 11C-MeNER DVR compared to HC in the LC but...
significantly lower values in the dorsal raphe (see Table 3 and Fig. 2), suggesting that noradrenaline producing neurons are relatively preserved in PD T+ . The disparity between loss of noradrenergic neurons in LC and its terminals in the dorsal raphe may be a reflection of the "dying back" pathology of PD (Bellucci et al., 2017). Noradrenergic innervation of raphe nuclei is topographically organized and facilitates serotonergic neurotransmission. Impairment or dysfunction of noradrenergic facilitation of serotonergic neurons could contribute to a functional impairment of serotonergic neurotransmission and aggravate tremor occurrence. This is in line with previous imaging studies that show an inverse relation between serotonergic transporter binding in raphe nuclei and rest tremor in tremor-predominant PD patients (Qamhawi et al., 2015). In the current study we observed a positive association between rest tremor and 11C-MeNER DVR values in median raphe which is in contrast to the inverse relation between serotonergic transporters and rest tremor. This may illustrate the highly selective binding of 11C-

Table 3

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>PD T+ (†)</th>
<th>PD T- (‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal Raphe</td>
<td>1.53 ± 0.06††</td>
<td>1.30 ± 0.05</td>
<td>1.24 ± 0.04</td>
</tr>
<tr>
<td>Median Raphe</td>
<td>1.46 ± 0.05†</td>
<td>1.38 ± 0.05</td>
<td>1.26 ± 0.04</td>
</tr>
<tr>
<td>Locus Coeruleus</td>
<td>1.26 ± 0.04‡</td>
<td>1.28 ± 0.04§</td>
<td>1.14 ± 0.03</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>1.57 ± 0.04††</td>
<td>1.45 ± 0.04</td>
<td>1.36 ± 0.03</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.39 ± 0.02¶</td>
<td>1.32 ± 0.02</td>
<td>1.24 ± 0.02</td>
</tr>
</tbody>
</table>

Mixed linear model analysis. Labels † HC v PD T+, ‡ HC v PD T-, †† PD T+ v PD T-, § p < 0.05, ¶ p < 0.01, ††† p < 0.001.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Rigidity</th>
<th>Bradykinesia</th>
<th>Rest Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal Raphe</td>
<td>0.102</td>
<td>-0.102</td>
<td>0.205</td>
</tr>
<tr>
<td>Median Raphe</td>
<td>0.014</td>
<td>-0.058</td>
<td>0.387*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.028</td>
<td>0.024</td>
<td>0.396*</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>0.145</td>
<td>0.041</td>
<td>0.393*</td>
</tr>
<tr>
<td>Locus Coeruleus</td>
<td>0.001</td>
<td>-0.007</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Spearman rank correlation – two-tailed. Values reported are spearman correlation coefficients. * p < 0.05.
MeNER to noradrenergic transporters with negligible binding to serotonergic transporters and their hypothetically differential roles in tremor generation (Ghose et al., 2005). Thus, noradrenergic, and serotonergic neurons may interact at multiple levels in the generation of rest tremor in PD patients, i.e. through their reciprocal innervations at the levels of LC and raphe nuclei and in thalamus. Future studies that combine in vivo imaging of both noradrenergic and serotonergic transporters in tremor-predominant PD patients could further elucidate these interactions.

In the present study, 43% of our included PD patients presented with mild to severe rest tremor symptoms. The PD⁺ group showed relatively preserved integrity of thalamic noradrenergic terminals compared to PD⁻, which supports the preliminary finding reported by Nahimi et al. (Nahimi et al., 2017), who showed a difference in binding in thalamus between patients with significant tremor (n = 5) and patients without tremor (n = 10). These findings are also in line with previous in vitro pathology studies that show a lower level of degeneration of noradrenergic neurons in LC in tremor-predominant PD patients compared to akinetic-rigid PD patients (Paulus and Jellinger, 1991). However, it is important to note that noradrenergic neurons and terminals undergo significant degeneration across selected regions in both PD groups compared to HCP (Pifl et al., 2012). Loss of neurons from the LC may influence dopaminergic neurotransmission as preclinical studies show that preservation of noradrenergic function in LC leads to a slowed degeneration of dopaminergic neurons in animal models of PD and stimulates dopamine release from dopaminergic terminals (Mavridis et al., 1991; Rommelfanger et al., 2007). Thus, the more benign disease progression observed in tremor-predominant PD patients, at least in the first 10 years of disease, could in part be due to a relatively preserved noradrenergic system with its stimulatory effect on the dopaminergic system.

A number of pathophysiological models attempting to explain the origin of tremor have been proposed (Jahnsen and Llinás, 1984; Paré et al., 1987; Plenz and Kital, 1999). Helmich et al. have provided an in-depth review of the proposed models, in which PD tremor genesis is proposed to be the product of changes in thalamus and basal ganglia function (Helmich et al., 2012). Helmich et al. suggested a dimmer switch tremor network, in which depletion of dopaminergic terminals triggers tremor frequency oscillations in the cerebello-thalamo-cortical circuit due to input-output mismatch in the motor cortex (Helmich et al., 2012). The cerebello-thalamo-cortical circuit receives dense projections from LC, allowing the noradrenergic system to have a direct modulatory role on the tremor generating circuitry.

Loss of noradrenaline in some thalamic subregions changes the firing pattern of the thalamic neurons from single spike firing with a fast responsibility of relay neurons and high fidelity, to burst firing (Buzsáki et al., 1991). Buzsáki et al. showed that yohimbine, an alpha-2-adrenergic antagonist, changed the thalamic firing pattern from single spike to burst firing. In addition to this, higher background noise appears as noradrenaline innervation deteriorates (Hirata et al., 2006). Lower preservation of the noradrenergic system in the PD⁻ compared to PD⁺ could diminish the ability of the thalamus to relay pathological tremor signals generated in the motor cortex and basal ganglia, as suggested by Helmich et al. (Helmich et al., 2012). This is supported by a study which showed that administration of yohimbine reduced tremor and rigidity in rats with reserpine induced PD (Colpaert, 1987). A more recent study investigated cognitive stress, believed to increase noradrenergic levels in the brain, in relation to rest tremor (Zach et al., 2017). In this study, Zach et al. assessed rest tremor severity when subjects were ON and OFF levodopa medication and during rest and cognitive stress.

Interestingly, while the increased noradrenergic levels induced through cognitive stress significantly increased tremor intensity, it also significantly decreased the tremor variability. A recent study by Dirkx et al. showed an increase in pupil diameter, heart rate and tremor amplitude during cognitive load (Dirkx et al., 2020). Pupil diameter and heart rate changes have been associated with activity in LC (Costa and Rudebeck, 2016; Murphy et al., 2011). This is in line with a rodent study, showing that activation of LC leads to a more synchronized firing pattern (Sara, 2015). The subthalamic nucleus (STN) also showed increased local gamma frequency field potentials during strong tremor (Weinberger et al., 2008). Foffani and Priori suggested that an increased activity in STN could overload downstream processes and contribute to tremor genesis (Foffani and Priori, 2007).

While rest tremor has been attributed to a decrease of pallidal dopamine and may be facilitated by the presence of intact noradrenergic innervation of the thalamus, serotonergic dysfunction may also play a role in rest tremor generation. Recent imaging studies have reported a correlation between tremor severity in PD and serotonin 5-HT₁A receptors or transporter availability in the median raphe (Pasquini et al., 2018). Using ¹²⁵I-WAY100635 PET, Doder et al. showed a correlation between tremor severity and reduced median raphé 5-HT₁A receptor availability (Doder et al., 2003). Rest-tremor severity has been reported to correlate with raphé 5-HT transporter availability in PD (Pasquini et al., 2018; Qamhawi et al., 2015). As with pallidial dopaminergic loss, a pathological change of firing pattern arising due to changes in the serotonergic function could be amplified by preservation of noradrenergic integrity.

5. Conclusion

We found a significant positive correlation between thalamic, red nucleus, and median raphe ¹¹C-MeNER DVR values and rest tremor. Further research into the role of noradrenaline using more sensitive MDS-UPDRS ratings in a larger longitudinal study could elucidate a possible role of noradrenaline in the generation of both action and postural tremor as well as rest tremor. Interestingly we failed to find a correlation between ¹¹C-MeNER DVR values and rigidity or bradykinesia. Rigidity has been linked to oscillatory changes in the 8–35 Hz band in the STN (Kühn et al., 2009) correlating with loss of putamen dopaminergic function in contrast to tremor, which has been linked to oscillations in the gamma frequency range > 35 Hz (Weinberger et al., 2008).

6. Limitations

Although the PD⁺ and PD⁻ groups had different levels of exposure to L-DOPA, the main effect ‘group x region’ was still significant after covarying out the treatment effect. ¹¹C-MeNER DVR reductions in LC and thalamus have also been associated with sleep disorders. A recent study demonstrated a strong correlation between the presence of REM-sleep behaviour disorder (RBD) and noradrenergic dysfunction (Sommersauer et al., 2018). We screened for RBD with the RBDSQ but did not perform a PSG examination, which will be important in future studies to provide a definite diagnosis of RBD.

This study is limited by our use of UPDRS-III, which has a lower sensitivity than MDS-UPDRS-III to detect subtypes of tremor in patients with PD. Therefore, we were not able to perform some subclassifications of tremor in this cohort of PD patients, as the UPDRS-III does not include the appropriate items to do this. In this study, we pooled PD patients assessed with UPDRS-III and MDS-UPDRS-III. In MDS-UPDRS-III the scoring of rest tremor score is separated into amplitude and constancy and this could potentially complicate the use of rest tremor scores from the two scales in the correlation analysis. We reviewed all rest tremor scores in the PD⁻ (n = 11) evaluated with the MDS-UPDRS-III and found that two PD patients may have been scored differently with the UPDRS and MDS-UPDRS scales, due to higher constancy score compared to the amplitude score. We then performed a correlation analysis where these patients were excluded, which did not alter the results. We therefore concluded that scores of rest tremor in this pooled cohort of PD patients is not confounded by the use of two different scales. This is also in line with the original validation study of the MDS-UPDRS scale, where all parts of MDS-UPDRS and UPDRS scales were compared (Goetz et al., 2008). PD patients were scanned either in...
an ON or OFF state, but we failed to find any significant treatment effect on scan findings for the group. To further support this, we performed a sub-analysis of the PD patients who were scanned in the OFF state. In this analysis, similar significant differences were found between PD- and PD+ and between both PD+ and PD0 compared to HC. Moreover, both the ON and OFF patients were reasonably distributed between the two groups.

7. Conclusion

We have shown that noradrenaline transporter binding, that may reflect density of noradrenergic neurons and terminals, are relatively more preserved in PD+ compared to PD0. However, both groups had significantly less noradrenaline terminal function compared to HC apart from the LC and the thalamus of PD- cases. The loss of noradrenergic innervation in the thalami of PD+ cases is in line with earlier in-vitro studies and could potentially act to suppress tremor generation and influence the variable efficacy of levodopa medication when tremor is present.

Financial support

Funded by the Lundbeck Foundation (grant number 6970), Denmark; the Danish Council for Independent Research, Medical Sciences, (grant number 0602-02700), Denmark; the Danish Association of Parkinson’s Disease (Parkinson-foreningen), Denmark; the Else Kröner-Fresenius-Stiftung; the Swiss National Science Foundation (grant number P2SKP3_161812), Switzerland; and the Hildergard Hensler-Stiftung (grant number 2019_EKES.02), Switzerland.

Author statement


Declaration of Competing Interest

The authors declare no conflicts of interests with regards to this manuscript.

References

