# Non-motor symptom burden is associated with thalamic atrophy in Parkinson's disease

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## OBJECTIVE

To investigate whether non-motor symptom burden is associated with cortical and subcortical morphological changes in Parkinson's disease (PD) patients.

## BACKGROUND

Non-motor symptoms have been recognized as an important component of Parkinson's disease (PD). They occur in almost 100% of the PD patients and can precede the onset of motor symptoms (1). Sleep disturbances, depression, gastrointestinal and urinary dysfunction, fatigue and cognitive impairment are often unresponsive to dopamine replacement therapy and greatly affect the quality of life of PD patients (2). Previous Magnetic Resonance (MR) imaging studies have investigated cortical and subcortical changes in PD patients showing different patterns of cortical thinning at different stages of the disease (3-5). The neuroanatomical correlates of non-motor symptoms in PD remain still unclear.

**Table 1 Clinical characteristics of Parkinson's disease patients with mild to moderate and severe non-motor symptoms burden.**

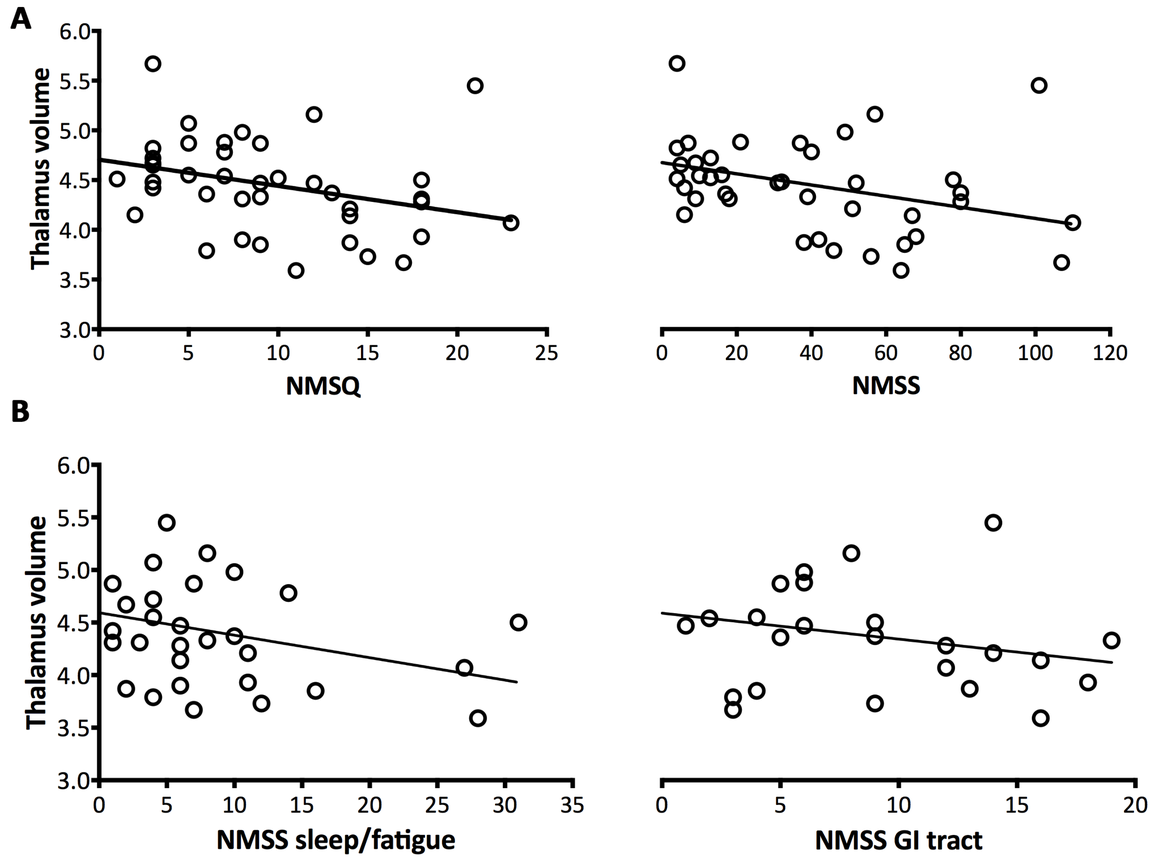
| | PD mild to moderate NMS burden (NMSS= 0-40) | PD severe NMS burden (NMSS ≥ 41) |
|---|---|---|
| **No (%)** | 23 (56.1%) | 18 (43.9%) |
| **Gender (M, %)** | 15 (65.2%) | 9 (50%) |
| **Age (years; ±SD)** | 60.8 (±8.9) | 68.1 (±8.3)* |
| **Disease duration[a] (months)** | 53.5 (±60.4) | 110.8 (±73.8)* |
| **Daily LED (mg; ±SD)** | 266.3 (±438.3) | 1109.3 (±1219.6)* |
| **H&Y OFF (±SD)** | 1.6 (±0.8) | 2.6 (±1.2)* |
| **MMSE (±SD)** | 28.3 (±1.6) | 29.2 (±1.3) |
| **PDQ-39 (±SD)** | 16.4 (±16.1) | 48.2 (±24.4)*** |

[a]From time of first appearance of Parkinson's disease motor symptoms. H&Y= Hoehn & Yahr; LED = levodopa equivalent dose; MMSE= Mini Mental Status Examination; NMSS= Non-motor Symptoms Scale; PDQ-39 = 39-item Parkinson's Disease Questionnaire; UPDRS-III= Unified Parkinson's Disease Rating Scale part III. *P<0.05; ***P<0.001.

## METHODS

We studied 41 non-demented PD patients (24M, mean age: 64.0±9.3 years). Non-motor symptoms burden was assessed using the Non-Motor Symptoms Questionnaire (NMSQ) and Non-Motor Symptoms Scale (NMSS). PD patients were divided into two groups according to the non-motor symptoms burden as assessed by the NMSS: 1) PD patients with mild to moderate (NMSS levels 0-2, NMSS scores: 0-40; No=23) and 2) severe (NMSS levels 3 and 4, NMSS scores: ≥41; No=18) non-motor symptoms burden (Table 1). Cortical thickness and subcortical nuclei volume analyses were carried out using the automated surface-based analysis package Free-Surfer (version 5.3.0). Reconstructed data sets were visually inspected for accuracy, and segmentation errors were corrected. All individual volumes were normalized for intracranial volume (ICV) automatically generated by FreeSurfer. Since no laterality was observed and for minimizing the number of comparisons, average hemispheric CTh and subcortical nuclei values were processed in the statistical analysis.

**Figure 1 Correlations between thalamic atrophy and non-motor symptoms in Parkinson's disease patients.**




Loss of thalamic volume correlated with **(A)** higher NMSQ ($r$=−0.42, $P$=0.042) and NMSS ($r$=−0.47, $P$=0.014) total scores; **(B)** higher NMSS domain 2 sleep/fatigue ($r$=−0.36, $P$=0.042) and NMSS domain 6 gastrointestinal tract ($r$=−0.36, $P$=0.042) subscores.

## RESULTS

Thalamic atrophy was associated with worse NMSQ ($r$=−0.42, $P$=0.042) and NMSS ($r$=−0.47, $P$=0.014) total scores. The non-motor symptoms that drove this correlation were sleep/fatigue ($r$=−0.36, $P$=0.042) and gastrointestinal tract dysfunction ($r$=−0.36, $P$=0.042). When the PD patients were divided into two groups, We found significant differences in subcortical nuclei volumes between the groups of PD patients with mild to moderate and severe non-motor symptoms ($P$=0.045). PD patients with severe non-motor symptoms burden had significant loss of thalamic volume compared to the group with mild to moderate non-motor symptoms burden ($P$=0.048). Since PD patients with severe non-motor symptoms burden had longer disease duration and were on higher daily LED, we repeated the multivariate analysis adding disease duration and daily LED as covariate and this did not influence the results. No significant differences in cortical thickness were found between the two groups (all $P$>0.10).

## CONCLUSION

Our findings indicate that greater non-motor symptoms burden is associated with thalamic atrophy in PD patients and in specific sleep/fatigue disorders and gastro-intestinal dysfunction were the non-motor symptoms, which drive this correlation. When we divided our cohort of PD patients into two groups according to the severity of non-motor symptoms, we found that PD patients with severe non-motor symptoms burden had 9% significant loss of thalamic volume compared to those with mild to moderate non-motor-symptoms burden. Thalamus plays an important role in processing sensory information including visceral afferent from the gastrointestinal tract and in regulating states of sleep and wakefulness.

## REFERENCES

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