Sleep dysfunction in Parkinson's disease is linked to reduced serotonergic function

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OBJECTIVE

We used positron emission tomography (PET) with [^{11}C]DASB, a marker of serotonin transporter (SERT) availability, to investigate whether sleep dysfunction in Parkinson's disease (PD) is associated with serotonergic dysfunction in brain regions modulating sleep.

BACKGROUND

Sleep disturbances are common in PD, significantly affecting patient's quality of life (1). The serotonergic system plays a critical role in the regulation of sleep and arousal. There is compelling evidence from preclinical, *post-mortem* and human imaging studies for the role of serotonergic dysfunction in PD (2-5).

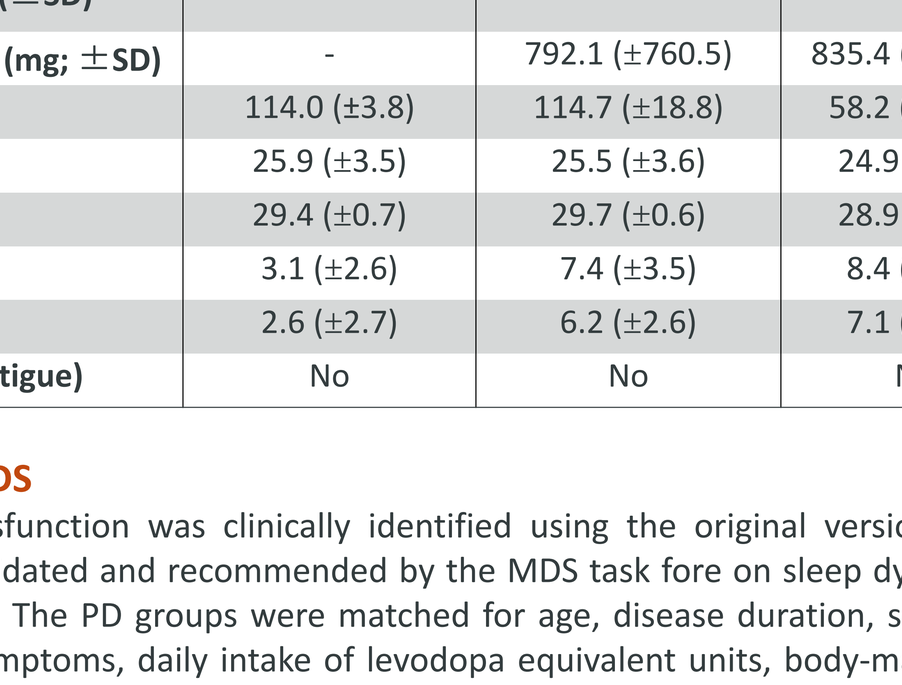
Table 1 Clinical characteristics of Parkinson's disease patients with and without sleep dysfunction and healthy controls.

	Healthy Controls	PD without sleep dysfunction	PD with sleep dysfunction
No	12	14	14
Age (years; ±SD)	63.4 (±7.1)	67.4 (±4.2)	65.9 (±8.8)
Disease duration (years; ±SD)	-	8.1 (±3.6)	8.7 (±3.1)
UPDRS-III	-	38.6 (±11.7)	44.1 (±9.7)
H&Y OFF (±SD)	-	2.4 (±1.0)	3.1 (±0.6)
Daily LED (mg; ±SD)	-	792.1 (±760.5)	835.4 (±315.4)
PDSS	114.0 (±3.8)	114.7 (±18.8)	58.2 (±17.2)
BMI	25.9 (±3.5)	25.5 (±3.6)	24.9 (±4.2)
MMSE	29.4 (±0.7)	29.7 (±0.6)	28.9 (±1.9)
BDI-II	3.1 (±2.6)	7.4 (±3.5)	8.4 (±3.1)
HRSD	2.6 (±2.7)	6.2 (±2.6)	7.1 (±2.3)
NMSS (Fatigue)	No	No	No

METHODS

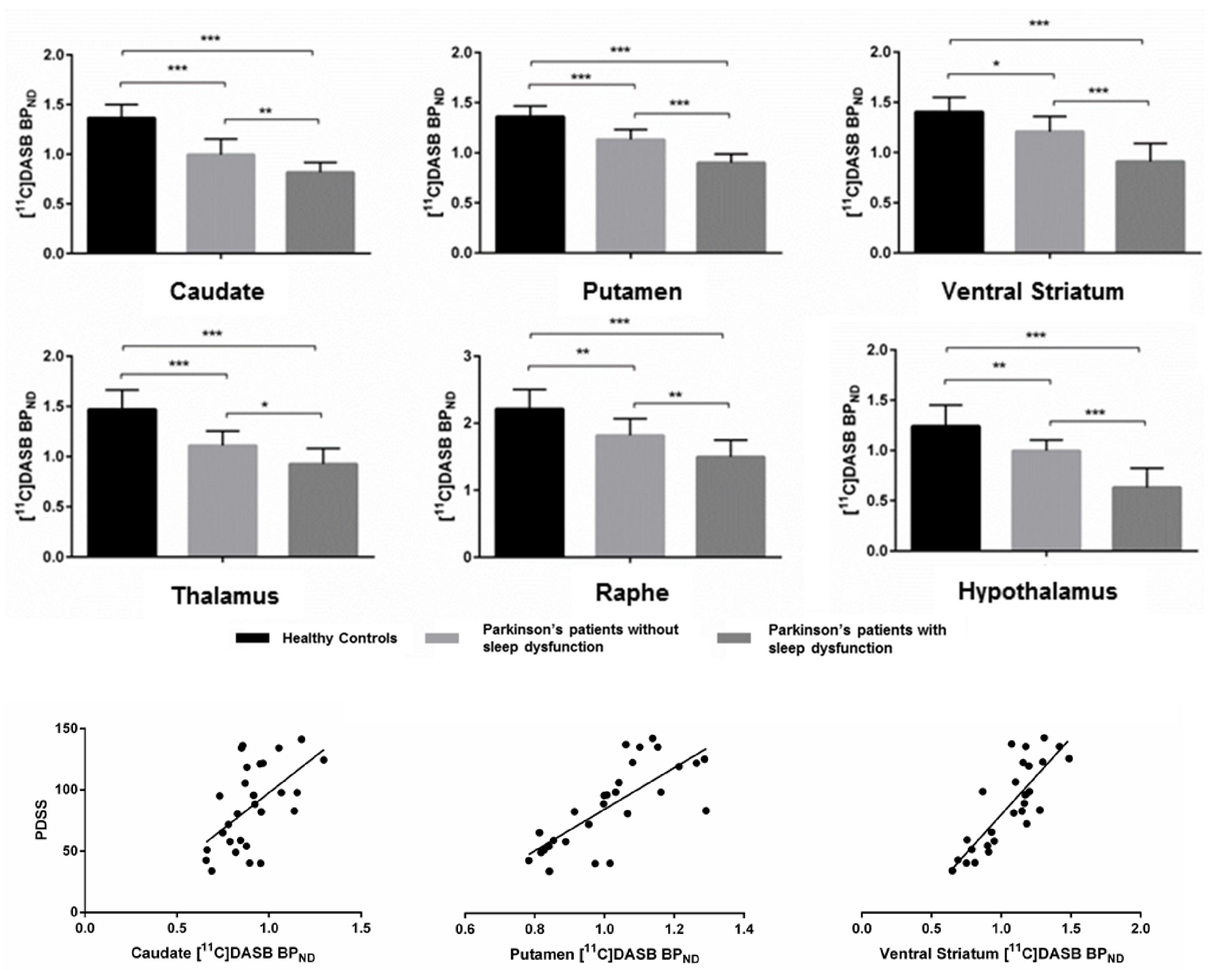
Sleep dysfunction was clinically identified using the original version of the PDSS, validated and recommended by the MDS task fore on sleep dysfunction in PD (6). The PD groups were matched for age, disease duration, severity of motor symptoms, daily intake of levodopa equivalent units, body-mass-index, depression and fatigue levels (Table 1). [^{11}C]DASB non-displaceable binding (BP_{ND}) was calculated in regions with known role in the regulation of sleep and arousal.

Figure 1 Loss of [^{11}C]DASB BP_{ND} in Parkinson's patients with sleep dysfunction.



[^{11}C]DASB PET images co-registered and fused with 1.5T MRI images showing basal ganglia and brain stem regions. Colour bar reflects [^{11}C]DASB BP_{ND}

Figure 2 Regional [^{11}C]DASB BP_{ND} loss in Parkinson's patients with sleep dysfunction correlates with impaired sleep scores



RESULTS

We found 14-25% loss of [^{11}C]DASB binding in PD patients without sleep dysfunction and 32-49% loss of [^{11}C]DASB binding in Parkinson's patients with sleep dysfunction, compared to healthy controls. PD patients with sleep dysfunction had lower [^{11}C]DASB binding in the caudate (p=0.004; effect size d=1.33), putamen (p<0.001; effect size d=2.32), ventral striatum (p<0.001; effect size d=1.99), thalamus (p=0.017; effect size d=1.22), hypothalamus (p<0.001; effect size d=2.34) and raphe nuclei (p=0.009; effect size d=1.27) compared to Parkinson's patients without sleep dysfunction. Higher severity of sleep symptoms correlated with lower [^{11}C]DASB binding in the caudate (r=0.77; p<0.001), putamen (r=0.84; p<0.001), ventral striatum (r=0.86; p<0.001), thalamus (r=0.79; p<0.001), hypothalamus (r=0.90; p<0.001) and raphe nuclei (r=0.83; p<0.001). There were no volumetric differences in any regions of interest between the groups of PD patients and healthy controls.

CONCLUSION

Our findings demonstrate that sleep dysfunction in PD is associated with reduced serotonergic function in midbrain raphe, basal ganglia and the hypothalamus. Strategies to increase serotonin levels in the brain could be a promising approach to treat sleep dysfunction in Parkinson's patients, and may also have relevance in other neurodegenerative disorders.

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