

Substantia nigra area evaluated by neuromelanin-sensitive MRI as an imaging biomarker of disease progression in Parkinson's disease

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BACKGROUND

A specific T1-weighted magnetic resonance imaging (MRI) sequence has been shown to detect substantia nigra (SN) neuromelanin (NM) signal changes that accurately discriminate Parkinson's disease (PD) patients from controls, even in early disease stages. However, it is unclear what happens to these SN changes in later disease stages

OBJECTIVE

To investigate the pattern of SN-NM area loss and contrast ratio (CR) intensity changes in late-stage Parkinson's disease (LSPD) patients, compared to *de novo* PD patients and PD patients with a 2-5 year disease duration in order to evaluate NM changes throughout disease progression.

METHODS

❖ A comparative cross-sectional study was performed, analyzing SN-NM MRI signals in late stage PD patients (LSPD) (Schwab and England Activities of Daily Living Scale score <50 or Hoehn Yahr Stage [HY] >3), comparing them with other disease stages, i.e. *de novo* (untreated patients; disease duration < 6 months) and 2-5 year PD and controls.

❖ For all groups SN-NM signal area and contrast ratio (CR) values (Figure 1) for the internal and lateral SN regions were obtained with semi-automated methods.

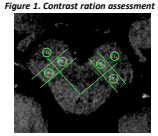


Figure 1. Representative CR assessment by means of circular regions of interest (ROIs) on an NM-sensitive T1-weighted MRI. CCR: crus cerebri right; CCL: crus cerebri left; SNIL: substantia nigra, left lateral region; SNIR: substantia nigra, right lateral region; SNIR: substantia nigra, right lateral region.

| Demographic & clinical data | Healthy subjects | De novo PD | 2-5 year PD | LSPD | P value |
|-----------------------------|---------------------|--------------------|---------------------|-----------------------|--|
| Number (female/male) | 10 (4/6) | 12 (7/5) | 9 (2/7) | 13 (7/6) | 0.3 |
| Age, yrs | 60 [55-69.2] | 62.5 [52.5 – 73.7] | 66 [63.5 – 71.2] | 78 [68.5-81.5] | a, f: 1; b: 0.8; c: 0.001; d: 0.003; e: 0.08; |
| HY | NA | 2 | 2 | 4 | d - e: <0.001 |
| LEDD | NA | 0 | 480 [325-810] | 1040 [725-1325] | e <0.01 |
| MDS-UPDRS part II | NA | 6.2 [3.5 – 10.6] | 10.1 [1.7 – 12.8] | 36 [30-40.5] | d - e: <0.001; f: 0.1 |
| MDS-UPDRS part III | NA | 32.3 [28.7 – 47] | 24.5 [13.4 – 43.1] | 51 [41-53.5] | f: 1; e: 0.02; d: 0.09; |
| Area [(mm) ²] | 40.63 [33.03-55.64] | 27.7 [17.13-360.4] | 22.65 [8.64- 46.84] | 18.68 [12.50 – 26.47] | a: 0.002; b, c <0.001; d: 0.005; e: 1; f: 0.8; |
| CR Internal region | 1.16 [1.11 – 1.19] | 1.15 [1.09 – 1.21] | 1.12 [1.05 – 1.16] | 1.12 [1.09 – 1.18] | 0.06 |
| CR Lateral region | 1.10 [1.02 – 1.12] | 1.06 [0.10 – 1.13] | 1.03 [0.99 – 1.08] | 1.04 [0.10 – 1.1] | b: 0.008; a,c:0.1; d,e,f: 1; |

Table 1. Demographic, clinical and neuromelanin assessment data of patients and controls. Values are presented as median [IQR: 25th – 75th percentile] if not otherwise specified. NA: not available; LEDD: levodopa equivalent daily dose. CR: contrast ratio. HY: Hoehn and Yahr rating scale; MDS-UPDRS: Movement disorders society Unified Parkinson's disease Rating Scale Comparisons: a) controls versus *de novo* PD; b) controls versus 2-5 yrs PD; c) controls versus LSPD; d) *de novo* PD versus LSPD; e) 2-5 yrs versus LSPD; f: *de novo* PD versus 2-5 yrs PD. Statistical significant results are in bold characters.

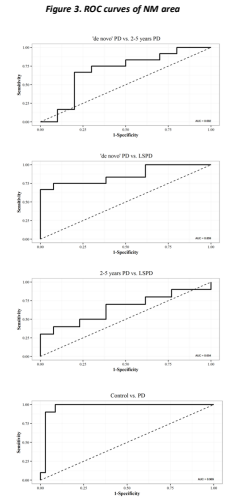


Figure 3. Receiver Operator Characteristics (ROC) curves of the NM area for: a) differentiating between *de novo* PD versus 2-5 year PD patients (A); b) *de novo* PD versus LSPD patients (B); c) 2-5 year PD versus LSPD patients (C); d) PD versus controls;

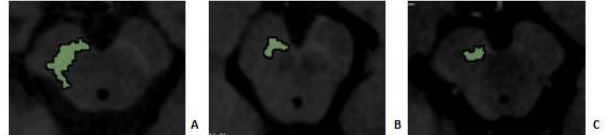


Figure 2. Neuromelanin (NM) area selection on NM sensitive magnetic resonance images of the SN of a healthy control (a), a *de novo* PD patient (b) and a LSPD patient (c).

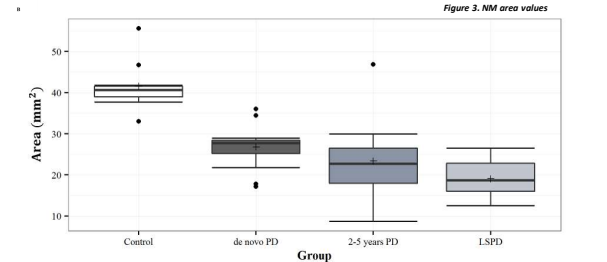


Figure 4. Median area values of the SN high intensity region on NM-sensitive MRI in *de novo* PD patients, 2-5 year PD patients, LSPD patients and controls

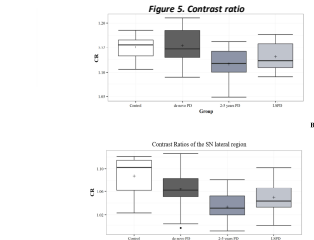


Figure 5. CR values in in *de novo* PD patients, 2-5 year PD patients, LSPD patients and controls for the SN internal region (A) and lateral region (B).

RESULTS

➤ **13 LSPD, 12 *de novo* patients with PD, 10 PD patients with a 2-5 year disease duration, and 10 controls** were included (Table 1).

➤ LSPD patients had a median disease duration of 14 years [IQR: 9-17]. They were significantly older compared to controls and *de novo* PD patients and had a worse HY stage and MDS-UPDRS part II compared to the *de novo* and 2-5 year PD groups.

➤ **NM signal area** was significantly decreased in *de novo* PD compared to LSPD (Figure 2 and 3) (*P*-value = 0.005; sensitivity: 75%; specificity 92% and AUC: 0.86) (Figure 4, Panel B).

➤ In the lateral SN region, a decrease in the CR was detected in all PD groups compared to controls; despite not reaching statistical significance, a slight increment was observed comparing LSPD to 2-5 year PD (Figure 5).

➤ **NM signal area significantly correlated with HY** ($R = -0.37$; $P < 0.05$) and **MDS-UPDRS part II** ($R = -0.4$; $P < 0.05$) while a weak correlation was found with MDS-UPDRS part III ($R = -0.26$; $P = 0.1$).

➤ A moderate correlation was found between age and CRI ($R = -0.42$; $P < 0.05$) and CRl ($R = -0.36$; $P < 0.05$). No correlations were found between HY, MDS-UPDRS part II, MDS-UPDRS part III, LEDD and CRI or CRl.

CONCLUSION

❖ In the present study, with semi-automated MRI measures, **we detected a stage-dependent progressive decrease in the SN-NM area of PD patients.**

❖ A marked SN-NM area decrease occurred in parallel with other markers of disease severity.

❖ Our findings suggest that NM-sensitive MRI could be used as a **potential biomarker for nigral degeneration and disease progression** in PD patients.

❖ CR values, although showing a tendency for a decrease with disease progression, presented a slight, albeit not significant, increase in the LSPD group; its interaction with therapeutic intervention and its modifications with disease progression needs further investigation.

❖ *This is the first study that observed SN-NM area modifications in a sample of LSPD patients, allowing an assessment of the modifications of NM signal in very late disease stage.*