MRI visual analysis of Neuromelanin and Nigrosome-1 for the assessment of Striatonigral disfunction in Huntington's Disease

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INTRODUCTION

- Huntington's Disease (HD) neuropathological hallmark is the progressive bilateral degeneration of the striatum[1], but nigrostriatal dopaminergic neuron degeneration and loss of Substantia Nigra (SN) and *Locus Coeruleus* (LC) neurons, as well as disruption of iron homeostasis, have also been reported[2-5].
- The physiopathology behind this neurodegeneration is still unclear.
- Recently developed magnetic resonance imaging (MRI) biomarkers, such as neuromelanin-sensitive MRI (NM-MRI)[6,7] and Nigrosome-1 (N1) visualization[8,9] on susceptibility-weighted imaging (SWI), permit *in vivo* evaluation of changes in NM containing neurons of the SN and LC and in iron deposition.
- The **aim** of this study was to use these novel MRI methods to further clarify SN and LC involvement in HD, assessing striatonigral disfunction through the visual analysis of MR NM and N1 images for the first time in HD.

MATERIALS & METHODS

Study design: Cross-sectional comparative study analyzing NM and N1 in HD patients and healthy controls (HC).

Setting: Centro Hospitalar Universitário de Lisboa Norte (CHULN), Lisbon, Portugal.

Participants:

HD patients, recruited from the Movement Disorders Outpatient Clinic at CHULN.

Healthy subjects recruited from hospital staff, with no signs or history of a neurodegenerative disorder.

Primary outcomes:

1. Area and signal intensity of the SN NM on NM-MRI using visual inspection (rated as normal/reduced)
2. Area and signal intensity of the LC NM on NM-MRI using visual inspection (rated as normal/ reduced)
3. Presence of the N1 on SWI, using visual inspection (rated as present/absent)

Secondary Outcome:

Area of SN NM on NM-MRI using semi-automatic segmentation (median area in mm^2)

Analytics: Fisher's exact test was used to compare visual analysis ratings between groups. Mann-Whitney U Test was used to compare SN NM area obtained using semi-automatic segmentation between groups.

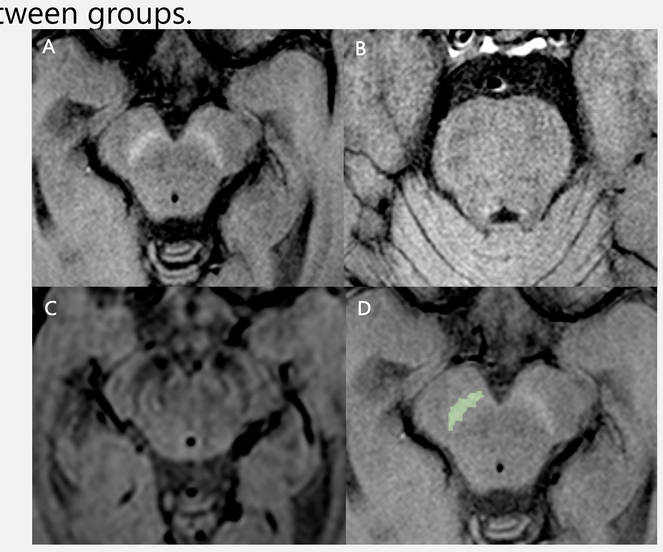

Fig. 1 NM-MRI images at the level of the SN (A) and at the level of the LC (B), showing normal NM area and signal intensity. SWI image (C) at the level of the SN, showing normal bilateral N-1 hyperintensity. NM-MRI with semi-automatic segmentation of the SN is shown in D. All imaging data were acquired using a 3.0 Tesla Philips Achieva MR scanner.

RESULTS

Twelve HD patients and 13 HC were included, as detailed in Table 1.
The acquired MR images allowed a clear identification of the SN and LC in all subjects, which were therefore included in the analysis.
SWI images were only available for 7 HD patients and 11 HC.

Table 1 Demographic and clinical characteristics of the study groups.

	Patients (n=12)	Controls (n=13)	p-value
Age (years)[1]	60.0 [45.0, 65.5]	69.0 [66.0, 76.0]	0.01*
Gender (%female)	5 (38.5%)	7 (58.3%)	0.33**
Age at first motor symptoms (years)[1]	48.5 [38.8, 59.3]	n/a	n/a
Disease duration (years)[1]	7.5 [1, 12]	n/a	n/a
TMS- UHDRS[1]	26 [9.5, 39]	n/a	n/a
TFC[1]	10 [7.25, 13]	n/a	n/a

[1] Median [Interquartile range]
TMS- UHDRS- Total Motor Score Unified Huntington's Rating Scale; TFC-Total functional capacity; n/a- not applicable.
* Mann-Whitney U-test. ** Fisher's exact test

1. Substantia Nigra Analysis

SN NM signal intensity was found to be reduced in HD patients (p= 0.011).
Visual and semi-quantitative analysis of the SN-NM area did not show significant differences between the groups.

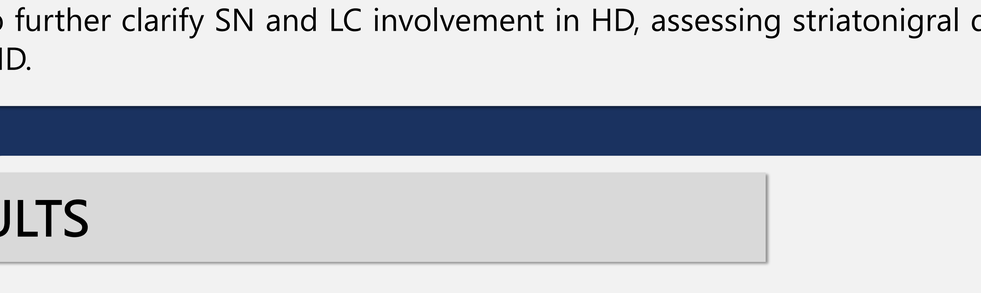

Fig. 2 SN NM-MRI visual analysis revealed SN NM reduction in 7/12 HD patients, compared to 4/13 in HC (p= 0.238). SN NM signal intensity was reduced in 7/12 HD patients, compared to 1/13 in HC (p= 0.011). Global analysis of the SN NM (area and signal intensity) showed its reduction in 10/12 HD patients, compared to 5/13 HC (p= 0.041).

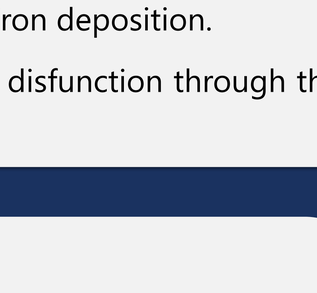

Fig.3 Semi-quantitative analysis of the SN-NM area revealed a median area of 32.0 [26.4, 38.3] in HC and a median area of 29.8 [27.4, 36.3] in HD patients, with a p value of 0.74

2. *Locus Coeruleus* visual Analysis

LC NM was found to be consistently reduced in HD.

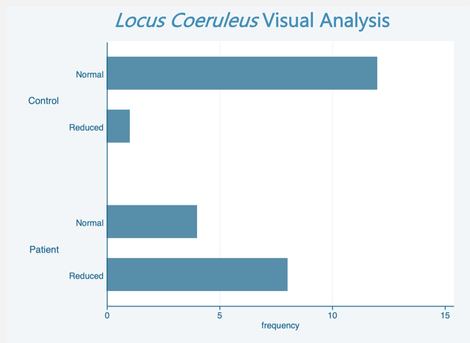

Fig.4 LC visual analysis. LC NM was reduced in 8/12 HD patients compared to 1/13 controls (p= 0.004).

3. Nigrosome-1 visual Analysis

No significant differences were found in the analysis of N1.

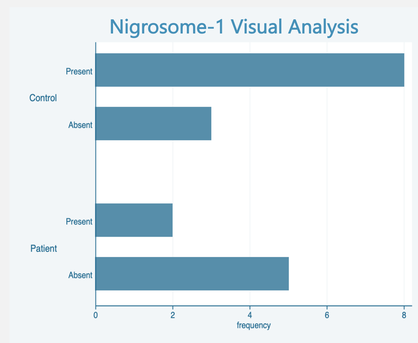

Fig .5 N1 visual analysis. N1 was absent in 5/7 HD patients and in 3/11 HC (p=0.145).

CONCLUSION

Our findings support the involvement of SN and LC in the pathophysiology of HD and strengthen the notion of NM-MRI as a noninvasive proxy measure of nigrostriatal function in the human brain. NM-sensitive imaging seems particularly promising to further study the physiopathology of HD and possible correlation between motor and non-motor symptoms and imaging findings.

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