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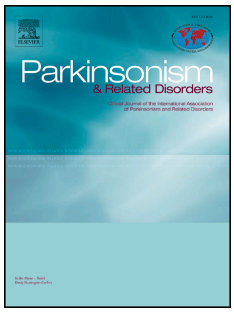

Seven tesla MRI of the substantia nigra in patients with rapid eye movement sleep behavior disorder

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Title page

Title

Seven tesla MRI of the substantia nigra in patients with Rapid Eye Movement Sleep Behaviour Disorder

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Abstract

Introduction: Susceptibility-weighted imaging of the substantia nigra (SN) both at 7 and 3 Tesla (T) has shown high accuracy in distinguishing patients with Parkinson's disease (PD) and healthy subjects (HS). Patients with rapid eye movement (REM) behavior disorder (RBD) can develop synucleinopathies, and such risk is higher with dopamine transporter single photon emission tomography (123I-FP-CIT SPECT) evidence of nigro-striatal dysfunction. We aimed at evaluating SN 7T magnetic resonance imaging (7T-MRI) in patients with RBD and determining the agreement between MRI and 123I-FP-CIT SPECT.

Methods: Fifteen patients with idiopathic RBD confirmed by polysomnography and a recent 123I-FP-CIT SPECT underwent a 7T MR by using three-dimensional gradient-recalled-echo multiecho susceptibility-weighted imaging of the SN; the findings were randomly presented with those of 14 HS and 28 patients with PD and blindly evaluated by an expert neuroradiologist, according to recently published criteria. MRI and SPECT results were also compared.

Results: Nine subjects with RBD had abnormal SPECT; among them, the findings of 7T-MRI were rated abnormal in eight. Out of six subjects with RBD with normal SPECT, the 7T-MRI findings of five were rated normal. The Cohen's kappa statistic value of agreement was 0.722.

Conclusion: Gradient-recalled-echo multiecho susceptibility-weighted imaging of the SN at 7T is abnormal in 60% of patients with RBD. The 7T-MRI and 123I-FP-CIT SPECT results showed good agreement. 7T-MRI of the SN could represent a safe marker for neurodegenerative disease in patients with RBD, however longitudinal study is warranted.

Introduction

Seven Tesla (7T) magnetic resonance imaging (MRI) of the substantia nigra (SN) using high-resolution three-dimensional susceptibility-weighted imaging (SWI) has been described previously, and its pathological correlates are well defined [1,2]. The loss of typical anatomy of the SN, particularly the loss of the hyperintense laminar or ovoid-shaped inner components, is reportedly able to differentiate patients with Parkinson's disease (PD) from healthy subjects (HS) with high accuracy in both 7T and 3T MRI [3] and a recent meta-analysis of the studies performed both with high and ultra-high fields MRI confirmed such results [4]. Furthermore, patients with Multiple System Atrophy (MSA), those with Progressive Supranuclear Palsy [4], and some patients with Corticobasal Syndrome show a comparable abnormal anatomy of the SN in both 7T and 3T MRI. Recently, the abnormal aspect of the SN in susceptibility-weighted imaging has been described in asymptomatic carriers of *LRRK2* mutations suggesting that such aspect might be an early marker of degenerative parkinsonism even before the onset of motor symptoms [5].

Owing to the physical properties of SWI sequences [6], and partially consistent with pathological data [1], the abnormal aspect observed in patients with PD and, presumably, even in patients with atypical parkinsonisms is probably due to iron accumulation.

Idiopathic rapid eye movement (REM) behavior disorder (iRBD) can precede the manifestation of neurodegenerative disorders with risk estimates of 17,7% at 5 years, 40,6% at 10 years and 52,4% at 12 years [7]. The risk of forthcoming conversion is higher in patients with dopamine transporter Single Photon Emission Tomography (123I-FP-CIT SPECT) evidence of nigro-striatal involvement and, although with some controversies and lower predictive values, with trans-cranial sonographic evidence of SN abnormality [8]. Although not specifically related to the pathogenesis of RBD, both methods identify SN abnormalities either directly (Sonography) or indirectly (SPECT) before the onset of motor symptoms.

The description of biomarkers that might detect patients with RBD with high risk of conversion could be the first step in selecting subjects in the pre-clinical PD state [9] for neuroprotective drug trials.

We aimed at evaluating the 7T-MRI anatomy of the SN in patients with RBD and determining its agreement with 123I-FP-CIT SPECT.

Methods

Patients

We enrolled patients with polysomnography-confirmed iRBD according to International Classification of Sleep Disorders 3 diagnostic criteria. We included only those subjects who

underwent 123I-FP-CIT SPECT within 3 months of the study, independently from the results of such examination. Criteria for exclusion were the presence of a clinical diagnosis of parkinsonism, dementia, and the presence of any contraindication to MRI. Patients with a history of head trauma, cerebrovascular disease, neurological conditions, other sleep disorders, or current/past treatment with a drug known to influence REM sleep were not included. All patients gave their informed consent for the enrollment and diagnostic procedures that adhered to an experimental protocol named "Seven Tesla MR imaging as preclinical biomarker in populations at risk for Parkinson disease" (RF-2013-02354829) approved and funded by Italian Ministry of Health and co-funded by Health-Service of Tuscany. The local competent ethics committee approved the study.

Two movement disorders specialists clinically evaluated (on the same day of the MRI procedure) all patients to exclude the diagnosis of parkinsonism. Unified Parkinson's Disease Rating Scale motor item (UPDRSIII) was performed to identify mild motor symptoms. Mini Mental State Examination (MMSE) was included in the clinical evaluation. The results of 123I-FP-CIT SCAN results were collected.

MRI protocol and analysis

All the enrolled patients underwent a 7T-MRI using a GE950MRI scanner (GE Healthcare Medical Systems, Milwaukee, WI, USA) equipped with a 2ch-tx/32ch-rx head coil (Nova Medical, Wilmington, MA USA). The MRI protocol included three-dimensional (3D) gradient-recalled-echo (GRE) multiecho susceptibility-weighted imaging (SWAN; GE Healthcare) sequence targeted to the midbrain with the following parameters: covered volume=160×160×21.6 mm^3, acquisition matrix=320×320×18, eight equally spaced echoes ranging between TE=5.6 ms and TE=41.5 ms, TR=55.7 ms, flip angle=8°, NEX=0.7, receiver-bandwidth=50 kHz, scan duration=4 min 2 s. The final images were the average of the data from individual echoes, reconstructed with voxel size=0.3125×0.3125×1.2 mm^3.

The SN anatomy was evaluated along the rostro-caudal axis at the level of the inferior third of the red nucleus (level I), and at the level of the superior cerebellar peduncle decussation (level II) where the signal changes are more informative for diagnosing PD [2].

An expert neuroradiologist (M.C.), blinded to the SPECT results and clinical diagnosis, performed the analysis. To guarantee a blind evaluation, the images previously obtained from 28 patients with PD [Male/Female (M/F), 17/11; age, 59.1±9.1 years; UPDRSIII score, 17.4±7.2; MMSE score, 29±1; disease duration, 2.1±1.6 years; values, mean± standard deviation (SD)], and 14 HS healthy subjects (M/F, 10/4; age, 57.6±7 years; values, mean±SD) were randomly presented to the examiner.

The criteria for SN abnormality were the loss of the hyperintense lateral spots at level I or the loss of the three-layered organization at level II at least on one side of the midbrain, according to previously published criteria [2]. Images were also rated for quality (motion and susceptibility artifacts) as either good or poor.

Statistics

Contingency tables (Fisher's exact probability tests) were used to calculate differences in the frequencies of categorical variables.

Between-groups comparison was performed using analysis of variance (ANOVA) test and Student's t-test or Mann Whitney U-test respectively for parametric and non-parametric variables. Statistical significance level was set at $p<0.05$.

MRI and SPECT results were cross-tabulated for the calculation of agreement and Cohen's kappa statistic (k). Agreement was evaluated as follows: $k<0.2$= low; k between 0.2 and 0.4=fair; between 0.41 and 0.61=moderate; k between 0.61 and 0.80=good; and $k>0.80$=excellent.

Results

We enrolled 15 patients (M/F, 12/3; age, 69.3±7.1 years; UPDRSIII score, 3.7±2.2; MMSE score, 28.8±1.1; disease duration, 6.3±4.1 years; values, mean±SD). Among-groups analysis of patients with RBD, PD and HS revealed a significant difference in age ($p<0.01$), whereas sex frequency did not show any significant difference among RBD, PD, and HS ($p>0.05$). Clinical and demographical data of patients with RBD are detailed in Table 1. Nine subjects with RBD showed abnormal 123I-FP-CIT SPECT findings. Figure 1 shows representative images of a patient with normal 3D GRE multiecho susceptibility-weighted imaging MR of the SN at the level of the superior cerebellar peduncles decussation (left side) and the inferior third of the red nucleus (right side) showing the laminar and ovoidal hyperintensity respectively (Figure 1A) and normal 123I-FP-CIT SPECT (Figure 1B). The figure also shows representative images of a patient with RBD showing homogeneously hypointense SN in 3D GRE multiecho susceptibility-weighted imaging MR of the SN (Figure 1C) and bilateral reduced radiotracer uptake (Figure 1D).

Regarding image quality analysis, 14 images were rated as good, and one was rated as poor.

The 7T-MR images from 9 patients with RBD (60%) were rated as "abnormal". Eight out of nine patients with RBD with abnormal MRI showed bilateral abnormal SN.

The 7T-MR images from 27 subjects with PD and one HS were rated as "abnormal." Fisher's exact test revealed that MRI outcome significantly differed between groups (HS vs. PD $p<0.0001$; RBD vs. HS $p=0.0052$; RBD vs. PD $p=0.0045$).

The agreement between MRI and SPECT methods was good (k=0.722) when the whole sample was considered and excellent (k=0.851) when the analysis was limited to high quality images.

When comparing patients with RBD with normal MRI and those with abnormal MRI, no statistically significant difference emerged in age (p=0.066), sex (p=0.108), RBD duration (p=0.573), UPDRSIII score (p=0.491), and MMSE score (p=0.116).

Discussion

Our data support the involvement of the SN at least in some patients with RBD, revealing that, in 7T-3D GRE multiecho susceptibility-weighted imaging, the SN has abnormal anatomy in 60% of patients with iRBD and without signs of parkinsonism and in 89% of those with RBD with evidence of 123I-FP CIT SPECT abnormality.

Recently, SN abnormality has been reported in 3T-SWI imaging in about 2/3rd of patients with RBD not investigated for dopaminergic dysfunction [10]. Moreover, our data are in line with both 123I-FP-CIT SPECT and sonographic studies showing evidence of nigral and nigro-striatal degeneration in at least 60% of patients with RBD [8]. It is reasonable to speculate that the abnormal aspect of the SN in patients with RBD is due to an increase in the iron content in the pars compacta ventralis. Relaxometry of the SN in RBD population [11] does not support such iron content increase; however, the R2* value was measured in the whole SN. Therefore, the difference restricted to the pars compacta ventralis could have been missed. It is possible that iRBD population includes two different RBD subgroups: one with evidence of SN abnormality and nigro-striatal degeneration, and the other with normal anatomy and function of the nigro-striatal pathway thus reducing the sensitivity of relaxation measurement in revealing the iron content increase in the whole group of RBD patients.

On the other hand it is possible that RBD with abnormal SN are in a more advanced disease stage, albeit our and previous data [8] did not detected disease duration differences between groups with normal or abnormal SN or nigro-striatal degeneration. We are aware that the small sample included in our study does not allow firm conclusions about the relationship between SN degeneration and RBD duration and that the only retrospective collection of data about RBD duration could have biased this result.

Interestingly, although in a premotor state, most (8 out of 9) of subjects with RBD and abnormal MRI showed bilateral SN abnormality thus suggesting the development of parkinsonism even in the early motor stage. In fact RBD could be the pre-motor phase of MSA or Dementia with Lewy Bodies (DLB) other than PD. Atypical parkinsonisms have shown abnormal SN both at 7T and 3T, particularly MSA parkinsonism [4]. Longitudinal observation will unveil if patients with abnormal

SN will develop parkinsonism or not and if they will develop PD, MSA or DLB.

The disagreement between SPECT and 7T-MRI in RBD could be related to a suboptimal sensitivity and specificity of the MRI of the SN. However, it should be taken into account that, here, the patient with normal SPECT and abnormal MRI had an MR image of poor quality, and this could have biased the correct reading. Moreover, since the two imaging methods explore different components of the nigral neurons, the patient with normal MRI and abnormal SPECT could be interpreted according to the recent synaptopathy hypothesis. This hypothesis suggests that the neurodegenerative process starts in the dopaminergic synapses in PD and spreads back to the nigral neurons [12]. The disagreement between SPECT and 7T-MRI was previously reported and also similarly interpreted in asymptomatic *LRKK2* carriers [5]. An alternative explanation could be related to the accepted view that in the early and premotor phases of PD, dopamine transporter is downregulated as a compensatory phenomenon. In such cases, it is reasonable that despite a preserved nigral iron content, there could be a functional rearrangement at the synaptic level. Similar results indicating a disagreement between the altered presynaptic dopaminergic functional marker and the preservation of normal MRI SN aspect have been also reported in patients with PD [4].

The major limitations of this study are the small number of enrolled patients and the lack of a longitudinal evaluation of RBD. Moreover, the percentage of patients with RBD with abnormal SN could be influenced by a selection bias since the patients with RBD referring to a sleep center probably had severe sleep disorder. Moreover the difference in age between patients with RBD and patients with PD and HS used to blindly evaluate MRI image, could have biased our results, however previous data [2] suggest that SN abnormality in 3D GRE multiecho susceptibility-weighted imaging is an age-independent phenomen. Furthermore the implementation of the MRI protocol with neuromelanin imaging would have provided more information on dopaminergic neurons preservation and SN visualization, particularly considering the complex relationship between iron and neuromelanin [13]. A longitudinal study involving subjects with RBD is in progress; this study aims to establish the role of SN-MRI abnormality in evaluating the risk of progression from RBD to the motor phase of synucleinopathy and the mutual relationship of nigral anatomical changes with dopamine transporter presynaptic expression. However, the high agreement between MRI and SPECT results suggest that 7T-MRI of the SN could represent a non-invasive tool in the prediction of the highest rate of conversion from RBD to synucleinopathy. We believe that the use of SWI-MRI at even lower magnetic field could emerge as a possible marker of neurodegeneration in patients with RBD.

Authors' Roles

1) the conception and design of the study, (A) or acquisition of data (B), or analysis and interpretation (C) of data,
(2) drafting the article (A)or revising it critically (B)for important intellectual content,
(3) final approval of the version to be submitted.

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Conflicts of Interest: none.

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Figure Caption:

Figure 1: Example of RBD patients MRI and SPECT results

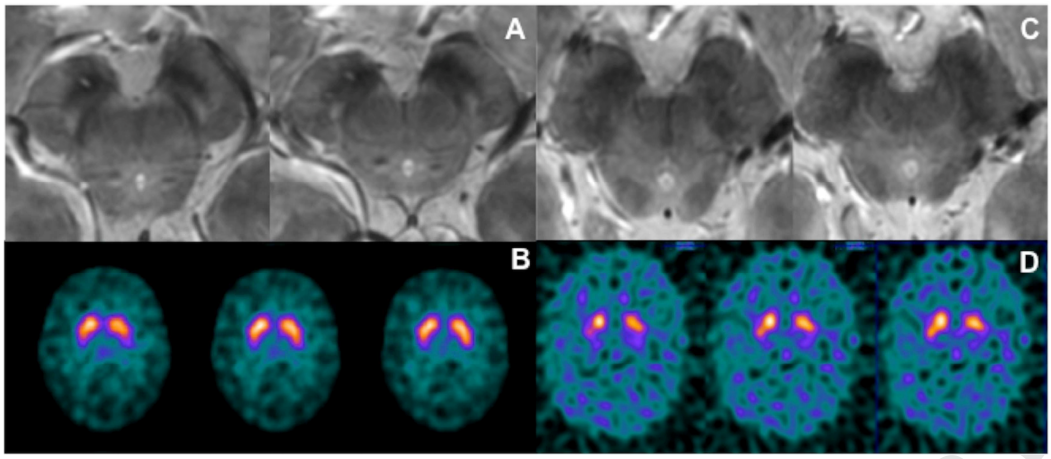
MRI and SPECT images of patients with RBD with either normal (A-B) or abnormal findings (C-D). A, C: 7T 3D GRE multiecho susceptibility-weighted imaging MR of the SN; B, D: 123I-FP-CIT SPECT.

MRI, Magnetic Resonance Imaging; SPECT, RBD, REM (Rapid Eye Movement) Behavior Disorder; GRE, gradient-recalled-echo; SN: Substantia Nigra; FP-CIT,

Table 1: individual clinical, demographic, MRI and SPECT data of RBD patients.

Age	Sex	RBD Duration (ys)	UPDRS III	MMSE	MRI Quality	MRI Right side		MRI Left side		MRI Diagnosis	SPECT Diagnosis
						LevI	LevII	LevI	LevII		
71	M	6	4	30	Good	A	A	N	A	A	A
75	M	2	3	29	Poor	A	A	A	A	A	N
70	M	4	3	29	Good	A	A	A	A	A	A
71	M	11	4	27	Good	A	A	A	A	A	A
69	M	7	0	27	Good	A	A	A	A	A	A
82	M	15	6	27	Good	A	A	A	A	A	A
72	M	2	4	29	Good	A	A	N	N	A	A
66	M	4	5	30	Good	A	A	A	A	A	A
72	F	10	6	28	Good	A	A	A	A	A	A
68	M	5	1	29	Good	N	N	N	N	N	N
68	M	13	3	29	Good	N	N	N	N	N	N
73	F	3	4	29	Good	N	N	N	N	N	N
49	M	5	0	30	Good	N	N	N	N	N	N
71	F	3	7	29	Good	N	N	N	N	N	A
62	F	4	5	30	Good	N	N	N	N	N	N

A: abnormal, LevI: level I, inferior third of the Red Nucleus; LevII: level II, Superior Cerebellar Peduncle Decussation; N: normal; MMSE: Mini Mental State Examination; RBD: REM Behaviour Disorder; SPECT: Single Photon Emission Tomography; UPDRS III: Unified Parkinson's Disease Rating Scale motor item



Highlights:

- MRI of the substantia nigra is abnormal in a substantial proportion of patients with iRBD despite no signs of parkinsonism
- MRI of the substantia nigra and 123I-FPCIT-SPECT results are highly consistent
- Substantia nigra MRI could provide insights about the risk of motor conversion