Magnetic Resonance Imaging at 7T enables the diagnosis of Parkinson’s disease

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Aims and objectives

The pathological basis of dopaminergic degeneration in Parkinson’s Disease (PD) is neuronal depletion in the pars compacta of substantia nigra (SNpc) (1). At present there is no established MRI marker for the diagnosis of PD on an individual basis (2). T1- and T2-weighted Spin-Echo (SE), GRE sequences as well as Segmented-Inversion-Recovery (IR) ratio imaging (3) failed to visualize the normal anatomy of the Substantia Nigra (SN) and they are not enough sensitive to detect the morphological changes due to the nigrostriatal denervation in PD (4). More encouraging evidences result from relaxometry (5), DTI (6) and neuromelanin imaging (7) for addressing SN neuronal depletion.

Ultra High Field (UHF) MRI could be used to increase the spatial resolution by exploiting the higher Signal-to-Noise Ratio and to refine targeted MR images onto brain structures involved in a specific pathologic process (8).

The purpose of this contribution was twofold: 1) to evaluate the normal anatomy of the SN by means of UHF-MR; 2) to define the accuracy of UHF-MR targeted imaging in distinguishing PD patients from healthy subjects (HS).

Methods and materials

A target imaging of the SN was set up on a 7T scanner (MR 950 GE Healthcare) equipped with a 2ch-transmit/32ch-receive head coil (Nova Medical).

SN anatomy

The normal UHF-MR anatomy of SN was investigated ex-vivo in a formalin fixed gross specimen from a cadaver and in-vivo in 8 HS (Mean age: 40.1ys). Ex-vivo MRI acquisition consisted of a SE-PD sequence targeted to the midbrain: TR=1200 ms, TE=20 ms, NEX=2, FA90°, Thickness=1 mm, spacing=1.5 mm, receiver-bandwidth=65.1 KHz, FOV=10 cm (in plane resolution=190 µm).

The in vivo MR protocol for the HS included 3D "SWAN" multi-echo GRE acquisitions (TR=55.7ms, TEs=5.57ms, 10.7ms, 15.84ms, 20.97ms, 26.1ms, 31.23ms, 36.36ms, 41.5ms, thickness=1.2mm, FOV=16cm, in plane resolution=312µm). Prescriptions were pseudo-axial, perpendicular to the floor of the fourth ventricle.

Two observers were invited to define the anatomical correlates of signal partitions within the SN by comparing UHF-MR images and neuroanatomical atlas (9).

Diagnostic power
In order to define the diagnostic role of UHF-MR in PD, the aforementioned in vivo MR protocol including SWAN sequence was applied in a population of 9 HS (55.5±9 ys) and 15 early stage PD patients (57±9 ys) (Hoehn and Yahr Staging range 1-2). Using a custom software implemented in MatLab the data obtained from each echo of the SWAN images was used to produce T2* maps by exponential curve fitting.

Two blinded observers evaluated UHF-MR images of patients and controls annotating deviation from normal anatomy of the SN. Sensitivity and specificity in diagnosing PD was calculated.

On the basis of the SN anatomy revealed in HS, ROIs were manually drawn in different components identified within the SN with SWAN images as represented in Figure 1. ROIs were superimposed onto relaxation maps and T2* was measured in the SN of PD patients and HS. Comparison between groups was performed with ANOVA test, corrected for multiple comparisons.

**Images for this section:**

![Image](image_url)

**Fig. 1:** Schematic depiction of ROIs at the level of superior cerebellar pedicles decussation (LEV 2) and at the level of the inferior third of the red nucleus (LEV 1). ROIs were drawn on SWAN images and were co-registered and superimposed to the T2* relaxation maps. At level2 three layers of different signal intensity were detectable in SN of HS (central image). They were bordered and named from posterior to anterior LEV 2_1, LEV2_2 and LEV2_3. At level1 (right image) two ROIs were placed in the lateral oval shaped hyperintense area (LEV1_LAT) and in the medial hypointense area (LEV1_MED) of the SN. In the SN of PD patients the normal anatomy was lost and ROIs were drawn at level2 by separating the homogeneous hypointense band of SN in three layers of equal thickness. At level1 two oval shaped ROIs were drawn along the SN axis.
Results

SN anatomy

In Figure 2 we show in detail the SN anatomy at UHF. The two observers described a ventral low signal layer, an intermediate high signal tier and a dorsal low signal stratum.

In vivo imaging of the SN in HS was differently described at the inferior third of the Red Nucleus (Level 1) and at the level of Superior Cerebellar Pedicles Decussation (SCPD) (Level 2). As shown in Figure 3 at level 1 a homogeneous hypointense region is observed medially, while a small oval hyperintense area is appreciable laterally between two hypointense layers. At level (2) a trilaminar organization characterized by a central hyperintense layer between two hypointense tiers is visible.

Diagnostic power

The loss of the oval hyperintense area at level 1 or the loss of trilaminar organization at level 2 within the SN was considered as abnormal (Figure 3). An abnormal SN was revealed in all patients with PD by both readers, while SN was considered normal in all HS for reader 1 and in 8 out of 9 HS for reader 2. The UHF SWAN images allow to discriminate between PD patients and HC with 100% sensitivity and 88% specificity.

The loss of normal anatomy of the SN in PD with respect to HS is showed with 3D surfacing of signal intensity reported in Figure 4.

ROIs for measuring T2* were placed within the SN as represented in Figure 1: at level 1 a ROI (LEV1_LAT) in the lateral part corresponding to the oval shaped hyperintense area, and a ROI (LEV1_MED) in the medial part of SN. At level 2 three ROIs of the same thickness (respectively LEV2_1, LEV2_2 and LEV2_3) were placed within SN from back to front and corresponding to the three layers of different signal intensity detectable in SN of HS.

T2* mean values in each ROI are represented in Figure 5 and detailed in Table 1. Between-group comparison revealed the shortening of T2* both at LEV2_2 and LEV1_LAT when evaluating SN contralateral to the most clinically affected side and a significant reduction of T2* at LEV1_LAT and with trend towards reduction at LEV2_2 when evaluating the side of SN homolateral to the clinically most affected side.

Images for this section:
Fig. 2: Ex-vivo Proton Density image revealing a tri layered representation of SN. 
a: crux cerebri; b: SN pars reticulata (pr); c: ventral component of the SNpc; 
d: dorsal component of SNpc; e: brachium conjunctivum.
**Fig. 3:** In the upper row: SWAN images obtained at level 1 (right; left SN) and at level 2 (left; right SN) are fuse in a single midbrain picture. At level 1 an oval area of signal hyperintensity is detected in the lateral part of the SN. At level 2 is appreciable the thin hyperintense band between the two hypointense layers. In the lower row the midbrain image of two PD patients. The SN anatomy was considered abnormal for the loss of the signal hyperintensity at both level 1 and 2.

**Fig. 4:** The pattern of signal intensity distribution within the SN is shown for three representative HS (left) and three representative PD patients (right). In red circles is highlighted the "hill and valley pattern": the hyperintense signal of the intermediate part of SN is a "hill" in HC and its disappearance in PD forms a "valley" in patients.
Fig. 5: Histogram of T2* mean values in each ROIs both in HS and PD patients. For HS a mean value was obtained between right and left SNs. In PD group, right and left SN ROIs were considered irrespectively to their anatomical location by averaging the T2* values of the SN contralateral to the most clinically affected side (SN_PDcontralateral), as well as for the homolateral side (SN_PDhomolateral). *p<0.05 comparing PD patients with HS; §p=0.07 comparing PD patients with HS.
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<tr>
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<tr>
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Table 1
Conclusion

The internal anatomy of the SN has been classified on the basis of the distribution of neurons(1). Within the SNc, two tiers of pigmented neurons are identified: the dorsal (SNcd) and ventral (SNcv) tiers, oriented antero-medially along the course of the mesencephalon.

We believe that the forefront hypointense tier at UHF-MRI corresponds to the pars reticularis of the SN while the posterior and intermediate tiers correspond respectively to the dorsal and the ventral components of the SNc.

UHF-MR is capable of revealing at visual inspection the loss of the three layered organization and of the lateral bright spot of SN in PD patients. Such sign allowed us to discriminate PD subjects from HS with high sensitivity and specificity.

The UHF high resolution imaging of the SN allows to detect a shorter $T2^*$ in the SNcv in PD, suggesting an increased level of iron in this region as the determinant of the homogeneous hypointense signal previously observed in the SN of PD patients (10).

Personal information

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References