Lack of MRI evidence for increased iron in the substantia nigra of PD brains at 7T

E. F. Cox[1], K. Gontu[2], A. Peters[1], A. Schaefer[1], N. Bajaj[2], P. A. Gowland[1], and D. P. Auer[3]

[1]Sir Peter Mansfield MR Centre, Univerisity of Nottingham, Nottingham, United Kingdom, [2]Neurology, Nottingham University Hospital, Nottingham, United Kingdom, [3]Academic Radiology, University of Nottingham, Nottingham, UK, United Kingdom

Background:

Parkinson's disease is a common neurodegenerative disorder leading to progressive motor and nonmotor symptoms related to subcortical neuronal cell loss. The underlying pathophysiology is not well understood and a role of iron and free oxygen radicals is debated.1 There is stong post mortem evidence of increased total iron in the substantia nigra in PD brains with an indication of regional specificity for the pars compacta 2,3. There is a long standing interest in developing biomarkers of cerebral iron, and the iron sensitivity of the MRI signal makes it a suitable candidate. A number of studies reported increased iron in the substantia nigra of PD using different MRI measures (T2, T2*, T2', field dependent relaxivity index, FDRI)4-9. There are however unresolved controversies regarding the respective sensitivities and T2 abnormalities were least consistent. Using ferritin sensitive FDRI, Bartzokis6 showed increased iron only in patients with early-onset PD, with reduced iron in patients with late-onset disease. Findings in the basal ganglia are even less consistent claiming both elevated and reduced iron storage. Ultrahigh-field MRI is expected to provide a more reliable and sensitive assessment of brain iron stores.

Aim: To assess T2 and T2* in the substantia nigra and other subcortical nuclei in patients with Parkinson's disease using a gradient echo-spin echo (GESE) sequence at 7T, assuming that T2 and T2' are good markers of paramagnetic iron.

Method: 5 patients with Parkinson disease (PD, mean age 57.4, range 34-81), 2 with multisystem atrophy (MSA, mean age 68) and 5 matched controls (mean age 52.2, range 33-66) were included. All subjects gave written informed consent; the study was approved by the local Ethics Committee. For scanning a gradient echo spin echo sequence was used on a Philips Achieva 7T MRI scanner. The sequence and fitting is described in more detail elsewhere12. In brief, it consists of a series of gradient echoes superimposed on a spin echo (SE) repeated N times for each phase encoding step. The signal obtained at each gradient echo10 is fitted using the Powell algorithm11 to give T2 and T2'. The sequence is insensitive to RF pulse errors since errors in either of the pulse flip angles will cause equal attenuation of all the echoes, leading to a simple reduction in SNR. It is also insensitive to T1 saturation (weighting) since the time between the refocusing pulse and next 90o pulse is kept constant. The sequence parameters were 1x1x3 mm voxel size, TR=2s, =1.43ms, M=25, total time=3mins; 3T: □□=1.43ms, M=31, total time=3mins. Regions of interest were manually drawn using ANALZE software for the substantia nigra with one ROI including the total SN including the pars reticulata (SNT), and a more refined ROI in the laterodorsal SN centered on the pars compacta (ldSN), the dorsolateral putamen (dPUT), medial globus pallidus (Pall), red nuclei (RN) and reference WM (WM).

Results: Patients with PD did not show reduced T2, T2* or T2' values in any of the selected ROIs. This is in contradiction to previous reports at lower field suggesting enhanced transverse relaxivity due to increased paramagnetic iron. Of note, PD patients showed a trend for higher putamenal T2 values in PD ($p<0.1$, table).

Individual comparison of relaxation times in the two MSA patients showed variability between the two for the putamen and apparently lower T2* in the red nuclei.

All values in ms	SNT	ldSN	dPUT	Pall	RN	WM
T2: Controls	24.0 +/-2.6	34.0 +/- 2.8	30.0 +/- 5.0	32.7 +/-10.6	29.3 +/-3.8	61.2 +/-41.2
T2: PD	27.6 +/-5.4	33.7 +/- 2.9	**37.1 +/- 6.7**	36.5 +/-11.6	28.6 +/-2.6	62.2 +/-45.9
T2: MSA	28.0 +/-5.7	37.7 +/-4.7	33.5 +/- 7.6	26.9	29.8 +/-7.4	56.0
T2*: Controls	18.7 +/-3.4	23.3 +/-4.4	23.3 +/- 5.7	20.9 +/-8.0	19.2 +/-1.8	30.0 +/-4.1
T2*: PD	17.1 +/-1.6	20.6 +/-1.5	25.5 +/-5.0	27.2 +/-10.0	19.1 +/-2.1	26.2 +/-5.0
T2*: MSA	22.8 +/- 3.9	23.5 +/-0.5	59.7 +/-31.9	20.8	15.3 +/-0.4	28.0
T2': Controls	34.9 +/-16.3	68.3 +/-27.4	68.3 +/-26.5	49.5 +/-14.4	46.4 +/-15.4	109.3 +/-89.0
T2': PD	36.1 +/-12.9	54.6 +/-7.7	73.9 +/-26.7	50.7 +/-22.2	37.8 +/-12.9	71.4 +/-28.1
T2': MSA	49.0 +/-7.1	59.4 +/-14.8	90.2 +/-41.7	38.0	50.8 +/-15.9	35.0

Discussion:

Contrary to our hypothesis we were unable to detect alterations in T2, T2* or T2' in the substantia nigra of patients with PD at 7T. Given the high sensitivity of ultrahigh-field for iron, the findings were unexpected. They accord however with a lack of altered FDRI in patients with late-onset disease6. Increased iron as seen post mortem and in transcranial sonography13 in PD brains may not translate proportionately into enhanced relaxivity as previously assumed. It has been recognised that inferences about the effect of tissue iron on relaxation times is problematic because of two critical assumptions (i) that tissue iron is mainly stored as ferritin and (ii) that iron concentration is the dominant factor governing relaxation behaviour. Both assumptions may be wrong in PD brains. Reduced nigral ferritin levels were reported in PD3. The second assumption is unlikely to be true in brain diseases with altered tissue water. In fact, a MRI study at 11.7T of a genetic rodent model of iron overload concords well with our findings: no T2 reduction was observed in the substantia nigra despite histologic evidence of increased ferric iron and ferritin. Histogram analysis in that study suggested a bimodal T2 distribution with some pixels showing T2 elevation offseting the effects from iron increase. T2 increase was felt to be associated with increased free fluid.14 Similar vacuolisations may be present in PD brains and in fact are the most likely cause of the observed T2 increase in the putamen that was also previously noted.8

In conclusion, despite increased iron sensitivity of ultra high-field MRI, no increase of iron was detected in the substantia nigra of PD patients. If we do not challenge the compelling post mortem evidence of increased iron, the data support the notion that iron concentrations cannot be directly inferred from relaxation time measurments of diseased tissue even at ultrahigh-field. Direct validation studies on post mortem material is warranted.

References

1. Jellinger K, Drugs Aging 14:115-140, 1999, 2. Sofic E. et al., J Neural Transm 74: 199-205, 1988 3. Dexter D et al., Brain 114: 1953-1975, 1991, 4 Antonini A et al., Neurology 43: 697-700, 1993, 5. Gorell JM Neurology 45: 1138-43, 1995, 6 Bartzokis G et al., MRI 17:213-22, 1999, 7 Ryvlin P et al., Arch Neurol 52:583-8, 1995, 8 Graham JM et al., Brain 123:2423-31, 2000, 9 Vymazal J et al., Radiology 211:489-95, 10, Miszkiel KA et al. MRI. 15, 1113-1119 (1997), 11. Press WH et al. Num. Rec. in C (2nd Ed.). 12. Cox E et al., submitted (ISMRM08) 13 Berg D et al., Neurotox Res 1:1-13, 1996, 14. Grabill et al., Brain Res 971:95-106, 2003.