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Does structural neuroimaging reveal a disturbance of iron metabolism in Parkinson's disease? Implications from MRI and TCS studies

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Abstract A central role of iron in the pathogenesis of Parkinson's disease (PD) has been discussed for many years. Numerous studies using magnetic resonance imaging and transcranial sonography have been performed to detect alterations in tissue iron content of the substantia nigra. This manuscript reviews the findings of this still controversial issue and indicates that specific abnormalities that are suggested to be related to a disturbance of iron homeostasis may play an early role in the pathogenesis of PD.

Keywords Parkinson's disease · Substantia nigra · Magnetic resonance imaging · Transcranial sonography

Introduction

Histopathological and biochemical findings of increased iron levels in the substantia nigra (SN) of patients with Parkinson's disease (PD) (Riederer et al. 1988; Sofic et al. 1988; Dexter et al. 1993; Gerlach et al. 1994) have led to numerous efforts to visualize these changes for diagnostic reasons and to better understand pathophysiology of the disease. The aim of this review is to present an overview about statements on iron content of the SN obtained by two different methods MRI and TCS, respectively.

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Magnetic resonance imaging

The SN of normal adult brain contains an elevated concentration of iron relative to other brain regions. Non-heme iron within brain tissue is mainly stored in the form of ferritin; however, in the SN neuromelanin is mainly involved. Changes in iron metabolism and storage are discussed to contribute to elevated SN iron levels in PD.

Quantification of the iron content in vivo using magnetic resonance imaging (MRI) is desirable but not readily possible. Only the measurement of physical variables of protons like the transversal relaxation times T2, T2ρ, T2*, and T2′ is possible which describe relaxation processes responsible for the decay of transversal magnetisation and may allow some indirect conclusion about the iron content in the investigated tissue. Because iron is highly paramagnetic, it is reasoned that water in close proximity to an iron deposit experiences local magnetic field gradients that reduce the T2 and T2* relaxation times (Solomon 1955) with $1/T2^* = 1/T2 + 1/T2'$. The relaxation time T2 is tissue specific, whereas T2′ is a term which includes all individual contributions from macroscopic and microscopic magnetic field inhomogeneities. Therefore, the T2* relaxation time is composed of intrinsic T2 relaxation time and all individual macroscopic and microscopic magnetic field inhomogeneities which lead to decay of the transversal macroscopic magnetisation.

For the estimation of T2 relaxation time usually a spin-echo pulse sequence with several different echo times will be used. This means that following the excitation pulse transversal macroscopic magnetisation will be generated

which immediately starts to dephase with T2*. Thereby any information about T2 will be obscured. However, after the refocusing pulse in the spin-echo pulse sequence, the dephased transversal macroscopic magnetisation starts to rephase. When the first delay (TE/2) between the excitation pulse and the refocusing pulse has the same time as the second delay (TE/2) between the refocusing pulse and the data acquisition than all effects of magnetic field inhomogeneities are refocused (and T2′ will be zero) and the signal decrease is caused exclusively by T2 relaxation. By performing several experiments in which the echo time TE is varied, the corresponding signal intensities can be fitted to an exponential curve according to $I(TE) = I(0) * e^{-TE/T2}$ to obtain the relaxation time T2. However, the T2 relaxation time is not very sensitive for small changes and the method is limited by the generation of stimulated echos. This error can mostly be recognized when the signal intensity of the second echo is higher than of the first echo. Then the estimated T2 relaxation time is biased by T1 contributions.

For the estimation of T2* relaxation time usually a gradient-echo pulse sequence with several different echo times is used. However, in the case of a gradient-echo pulse sequence, the refocusing pulse is missing and the generated transversal macroscopic magnetisation will not be refocused. Therefore, all effects of magnetic field inhomogeneities contribute to signal decay ($1/T2^* = 1/T2 + 1/T2'$) which can also be measured by performing several experiments in which the echo time TE is varied. The signal intensities can be fitted in the same way to an exponential curve according to $I(TE) = I(0) * e^{-TE/T2^*}$ to obtain the relaxation time T2*. Now in opposite to T2, all individual effects which cause various macroscopic and microscopic magnetic field inhomogeneities contribute to T2* relaxation time. Therefore, T2* is neither tissue specific nor specific only for changes in free or stored iron levels and depends strongly from measurement parameters like slice thickness, voxel size and local shim quality. Additionally, for the curve fitting a monoexponential decay is assumed but not really fulfilled.

Therefore, these physical variables T2 and T2* of protons is affected by disturbances like global and local magnetic field inhomogeneities and tissue water diffusion in the presence of paramagnetic substances which have to be considered in the interpretation of results. So far it is unknown whether quantitative measurement of susceptibility changes is possible because the reasons for phase changes are not known. Some reasons for the phase contrast are blood deoxyhemoglobin, tissue myelin content, tissue iron content, chemical exchange processes between free water and macromolecules, and fiber orientation (Vymazal et al. (1996) and Haacke et al. (2005)).

In addition to the statement above, we want to refer to the review paper of Brass et al. (2006) which discusses the role of iron and its detection by MRI in various neurological disorders. It reviews the basic biochemical properties of iron and its influence on MRI signal and summarizes the sensitivity and specificity of MRI techniques in detecting iron.

In the following, we present a MEDLINE search for literature relating to differences in the iron levels in the SN between PD patients and normal controls. Results are summarized in Table 1. In brief, the search for possible differences in SN iron levels between PD patients and controls started more than 20 years ago. Using a multi-echo spin-echo pulse sequence for calculating T2 relaxation times, several groups obtained various results. Alternatively, for calculating T2* relaxation times a multi-echo gradient-echo pulse sequence was used by several groups. With this method, more consistent results were obtained in the region of the SN in PD patients compared to controls. However, the interpretation of the T2* values is ambiguous because there are many other sources for magnetic field inhomogeneities, unrelated to brain iron levels (see above and Schuff 2009). Another group (Michaeli et al. 2007; Nestrasil et al. 2010) calculated the adiabatic relaxation time $T2\rho$ within the SN which appears to be sensitive to iron deposition using a special pulse sequence with adiabatic radio frequency pulses. Susceptibility-weighted imaging (SWI) (Haacke et al. 2009) is the newest and frequently applied method that exploits the susceptibility differences between tissues and uses the phase image to detect these differences. The magnitude and phase data are combined to produce an enhanced contrast magnitude image which is sensitive to venous blood, hemorrhage and iron storage. Using such a SWI sequence, some groups also obtained different results in the region of the SN in PD patients as compared to controls.

Considering the data (Table 1), the published results about differences in T2 and T2* relaxation times as well as in phase images are inconsistent. It is worth noting that it is difficult to compare MRI results because parameters such as image resolution and slice thickness varied between the studies. Furthermore, different regions have been assigned to be the SN. Moreover, the effects of simultaneous changes in iron content and cell loss on relaxation times in the SN of PD patients are not clear yet. Michaeli et al. (2007) and Nestrasil et al. (2010) found in addition to the reduced $T2\rho$ values increased $T1\rho$ values in PD patients, which appear to reflect the neuronal loss in the SN. Baudrexel et al. (2010) performed also supplementary a T1-mapping and found a T1 decrease which was interpreted as selective neuronal loss. Péran et al. (2010) and Du et al. (2011) performed additional DTI measurements and revealed significantly lower FA values in the SN of PD patients. However, consequences for T2 and T2* measurements as well as phase changes of these differences are still unknown.

Table 1 Overview about MEDLINE search for literature relating to differences in the MRI iron levels in the SN between PD patients and normal controls

Used method	Studied by	Number of patients	Number of controls	Magnetic field strength	Results (…in the SN of PD patients compared to controls)
T2 measurements (or R2 = 1/T2)	(Braffman et al. 1989)	21	24	1.5 T	No significant difference in T2 values
	(Rutledge et al. 1993)	12	30	1.5 T	Slightly reduced T2 values
	(Antonini et al. 1993)	30	33	1.5 T	Reduced T2 values
	(Ordidge et al. 1994)	7	7	3 T	No difference in T2 values in 4 PD patients and significantly elevated T2 values in 3 PD patients
	(Savoiardo et al. 1994)	–	–	1.5 T	Minimal alterations in T2 values
	(Ryvlin et al. 1995)	45	45	2 T	Significantly reduced T2 values in the SNc
	(Gorell et al. 1995)	13	10	3 T	Reduced R2 values
	(Vymazal et al. 1999)	23	18	1.5 T	Non-significant reduced T2 values
	(Mondino et al. 2002)	25	27	1.5 T	No significant difference in T2 values between both groups
	(Atasoy et al. 2004)	20	16	1.5 T	Reduced T2 values
	(Kosta et al. 2006)	40	40	1.5 T	Significantly reduced T2 values within the SNc
	(Bartzokis et al. 1999)	14	14	0.5 T and 1.5 T	Earlier–onset PD patients had significant increases in field-dependent R2 increase, while later-onset PD subjects had significantly decreased field-dependent R2 increase
T2* measurements (or R2* = 1/T2*)	(Braffman et al. 1989)	21	24	1.5 T	No significant difference in T2* values
	(Ordidge et al. 1994)	7	7	3 T	Slightly reduced T2* and significantly increased R2′ values
	(Gorell et al. 1995)	13	9	3 T	Increased R2* and R2′ values
	(Graham et al. 2000)	25	14	1.5 T	Increased R2* and R2′ values
	(Wallis et al. 2008)	70	10	3 T	Increased R2′ values
	(Martin et al. 2008)	26	13	3 T	Significantly increased R2* values in the SNc but reduced R2* values in the SNr
	(Baudrexel et al. 2010)	20	20	3 T	Reduced T2* values
	(Péran et al. 2010)	30	22	3 T	Significantly increased R2* values
	(Du et al. 2011)	16	16	3 T	Increased R2* values
T1ρ and T2ρ measurements	(Michaeli et al. 2007)	8	8	4 T	Significantly reduced T2ρ values
	(Nestrasil et al. 2010)	9	10	4 T	Reduced T2ρ values
SWI measurements	(Zhang et al. 2009)	42	30	1.5 T	Significantly lower phase radians
	(Schuff 2009)	9	16	3 T	Huge variability in the phase shift between subjects
	(Zhang et al. 2010)	40	26	1.5 T	Significantly increased phase shift values
	(Huang et al. 2010)	30	19	3 T	Significantly different mean phase values
	(Gupta et al. 2010)	11	11	1.5 T	No significant increased phase shift values
	(Jin et al. 2011)	45	45	3 T	Significantly reduced average phase values
	(Wang et al. 2012)	16	44	1.5 T	Significant difference in phase shifts
	(Lotfipour et al. 2012)	9	11	7 T	Increased susceptibility values only in the SNc but not for the whole SN; effect in the SNc was lost when age was controlled

Transcranial sonography

In the last years, transcranial sonography (TCS) has been established as a valuable supplementary tool in the diagnosis of PD. Depicting the normally hypoechogenic mesencephalic brainstem through the temporal bone window, an area of increased echogenicity (SN hyperechogenicity – SN+) can be visualized in about 90 % of PD patients, which is measured planimetrically to determine the size (Berg et al. 2008). Although the method is—similar to all sonographic methods—depending on the skill of the investigator, it is easy and cost effective applicability and the rapidness with which it can be performed has meanwhile lead to its application all over the world. Several findings (i) stress the hypotheses that increased iron levels contribute to this sonographic abnormality and (ii) indicate that—if it is indeed iron that is responsible for the change in echo signal—iron accumulation is a very early process in the pathogenesis of PD.

(i-a) Echogenicity of the SN of 3–4 months old Wistar rats unilaterally injected with different concentrations of iron, ferritin, 6-hydroxydopamin, a combination of 6-hydroxydopamin and desferrioxamine, and zinc was compared to the non-injected contralateral side after 1 week. Comparison revealed a dose dependent increase of area of SN echogenicity following injection of iron or of 6-hydroxydopamin (Berg et al. 1999b). A smaller effect on SN echogenicity was found for increasing concentrations of zinc, which is also known to contribute to the release of iron.

(i-b) The same effect of iron on tissue echogenicity was found in a post mortem study. Ultrasound examination of 60 brains immediately after autopsy and relation of the area of hyperechogenicity to histological and biochemical investigations revealed a significant association of increasing area of SN echogenicity and increasing iron levels (Berg et al. 1999a; Berg et al. 2002; Zecca et al. 2005), which was not found for copper, zinc, manganese and calcium. Moreover, the echogenic area of the SN correlated significantly positively with H- and L-ferritin concentration (Zecca et al. 2005), whereas multivariate analysis revealed a significant negative correlation between echogenicity and neuromelanin content of the SN. Patients included in this study did not suffer from PD during life time. However, these results mirror typical findings reported from PD brains: Loss of neuromelanin and increase of iron in the substantia nigra. Comparison with three PD brains confirmed the positive association of SN echogenicity and iron content as well as the negative correlation of SN echogenicity and neuromelanin content. Additionally in the SN of individuals with and without PD, an association of iron and increased microglia activation was detected, which may—at least in part—be influenced by the large amount of iron bound to ferritin in the migrating activated microglia (Connor et al. 1994).

(i-c) In vivo, the positive correlation of area of SN echogenicity and iron content in patients with PD as well as subjects with SN hyperechogenicity could be confirmed using MRI (Behnke et al. 2009), which may, even if the predication regarding iron content using MRI is not consistent (see above) support the idea that iron does play a role in the enhanced echo signal. According to these studies, it is very likely that indeed increased iron content as well as microglia activation is at least in part the reasons for enhanced SN echogenicity. However, it cannot be ruled out that other factors playing a role in the pathogenesis of PD may additionally contribute to this echo feature.

(ii) the area of SN+ is not related to the stages of the disease and does not seem to change during the disease process (Berg et al. 2005) thus the ultrasound feature is helpful in the early differential diagnosis of the disease (Gaenslen et al. 2008). Moreover, several studies could show an association of SN hyperechogenicity in yet healthy individuals with risk and premotor markers for PD (for review see Berg 2011). Importantly in some of them functional neuroimaging revealed a subclinical affection of the presynaptic dopaminergic system, indicating imminent PD (Iranzo et al. 2010). Recently, it was shown in a large prospective study of 1,847 individuals that healthy individuals with SN+ have a more than 17fold increased risk to develop PD during life time (Berg et al. 2011). This stresses the potential of SN+ as risk factor for PD and implicates that if indeed iron contributes to the ultrasound signal iron accumulation occurs early in the disease process.

Percentage of healthy subjects with SN+ (in general about 10 %) exceeds the prevalence of PD which is age

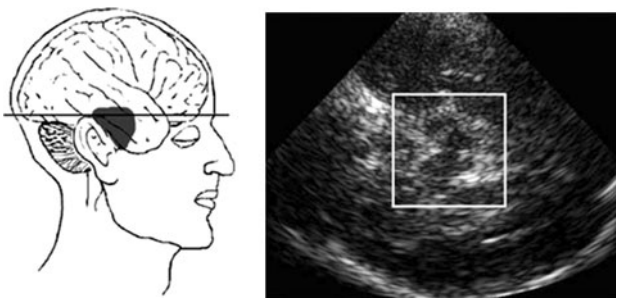

Fig. 1 Mesencepahlic scanning plane in which transcranial sonography for the depiction of the substantia nigra (SN) is performed. *Left* the grey zone in front of the ear marks the area of the temporal bone window at which the ultrasound probe is located. The scanning plane is marked with a line. *Right* ultrasound image in the mesencephalic scanning plane. The hypoechogenic mesencephalic brainstem is highlighted with a *square*. The *arrow* marks the area of hyperechogenicity at the anatomical site of the SN ipsilateral to the insonating probe

depending, ranging from 1.5 % in the group of 55 years old to 3.5 % in the group of 75 years old (De Rijk et al. 1997). It is therefore obvious, that not all subjects with SN+ will develop PD during life-time. Still, the molecular constellation of higher levels of iron, changes in L-ferritin and H-ferritin levels and reduced neuromelanin concentration revealed by the postmortem studies may describe a noxious cellular milieu promoting the generation of oxyradicals and cell damage.

The cause for iron accumulation is still a matter of debate. However, if indices that iron contributes to SN+ are correct, the facts that first degree relatives of PD patients have a higher prevalence of SN+ (Ruprecht-Dörfler et al. 2003) and that monogenetic forms of PD, in which iron contributes to the pathophysiological cascades (Berg 2007) are also associated with SN+—even in clinically unaffected mutation carriers—support the role of iron in PD pathogenesis and its visualization by TCS (Fig. 1).

Taken together, structural neuroimaging data are inconclusive to support a role of iron in the pathogenesis of PD. While TCS supports this hypothesis, numerous MRI studies do not show differences in parameters interpreted as being related to tissue iron content. The questions whether methodological, technical or pathophysiologial issues contribute to these inconsistencies needs to be further investigated.

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