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Longitudinal changes of cortical microstructure in Parkinson's disease assessed with T1 relaxometry

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ABSTRACT

Background: Histological evidence suggests that pathology in Parkinson's disease (PD) goes beyond nigrostriatal degeneration and also affects the cerebral cortex. Quantitative MRI (qMRI) techniques allow the assessment of changes in brain tissue composition. However, the development and pattern of disease-related cortical changes have not yet been demonstrated in PD with qMRI methods. The aim of this study was to investigate longitudinal cortical microstructural changes in PD with quantitative T1 relaxometry.
Methods: 13 patients with mild to moderate PD and 20 matched healthy subjects underwent high resolution T1 mapping at two time points with an interval of 6.4 years (healthy subjects: 6.5 years). Data from two healthy subjects had to be excluded due to MRI artifacts. Surface-based analysis of cortical T1 values was performed with the FreeSurfer toolbox.
Results: In PD patients, a widespread decrease of cortical T1 was detected during follow-up which affected large parts of the temporo-parietal and occipital cortices and also frontal areas. In contrast, age-related T1 decrease in the healthy control group was much less pronounced and only found in lateral frontal, parietal and temporal areas. Average cortical T1 values did not differ between the groups at baseline ($p = 0.17$), but were reduced in patients at follow-up ($p = 0.0004$). Annualized relative changes of cortical T1 were higher in patients vs. healthy subjects (patients: -0.72 ± 0.64%/year; healthy subjects: -0.17 ± 0.41%/year, $p = 0.007$).
Conclusions: In patients with PD, the development of widespread changes in cortical microstructure was observed as reflected by a reduction of cortical T1. The pattern of T1 decrease in PD patients exceeded the normal T1 decrease as found in physiological aging and showed considerable overlap with the pattern of cortical thinning demonstrated in previous PD studies. Therefore, cortical T1 might be a promising additional imaging marker for future longitudinal PD studies. The biological mechanisms underlying cortical T1 reductions remain to be further elucidated.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by the loss of dopaminergic cells in the substantia nigra (SN) (Hornykiewicz, 2006). However, it has become widely accepted that the prevailing pathology in the brainstem at early stages is later followed by a spreading deposition of α-synuclein across the cerebral cortex (Braak et al., 2003; McCann et al., 2016).

In fact, the involvement of the cerebral cortex in PD has been repeatedly confirmed by conventional magnetic resonance imaging (MRI) studies reporting multiple cortical abnormalities such as regional cortical thinning (Mak et al., 2015), gray matter (GM) volume decline (Jia et al., 2015), increased atrophy rate (Tessa et al., 2014) and a loss of cortical gyrification (Sterling et al., 2016). Conventional MRI techniques allow volumetric measurements, but still, they are based on mixed signal contrasts which renders the interpretation of the underlying microstructural tissue processes impossible (Tofts, 2003).

Abbreviations: BG, basal ganglia; GE, gradient echo; GM, gray matter; HY, Hoehn and Yahr; MRI, magnetic resonance imaging; PD, Parkinson's disease; qMRI, quantitative MRI; SN, substantia nigra; UPDRS III, motor part of the Unified Parkinson's disease rating scale.

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In contrast, quantitative MRI (qMRI) provides well-defined physical parameters, such as the relaxation times T1 and T2*, or the proton density, which are not affected by hardware-specific artifacts (Deoni, 2010). This allows taking insight into changes of tissue composition which might be specifically linked to certain neurobiological processes. For instance, the longitudinal relaxation time (T1) is considered to reflect microstructural tissue properties such as the water content (Fatouros et al., 1991; Gelman et al., 2001), macromolecular mass fraction (Rooney et al., 2007), degree of myelination (Lutti et al., 2014), ferritin (Brooks et al., 1998) and iron content (Gelman et al., 2001; Rooney et al., 2007).

In PD, previous qMRI studies mainly focused on mapping the transverse relaxation times T2 and T2*, aiming to assess the iron content in the SN and the basal ganglia (BG) (Du et al., 2011; Gorell et al., 1995; Martin et al., 2008). Iron accumulation in the SN is a key feature of PD (Dexter et al., 1991), possibly contributing to cell death via oxidative stress (Olanow, 2007), and is suggested to relate to disease progression (Ulla et al., 2013). Other studies applied quantitative T1 mapping techniques, intending to visualize PD-related damage within the SN and the brainstem (Baudrexel et al., 2010; Menke et al., 2010; Vymazal et al., 1999) reporting reduced (Baudrexel et al., 2010) or unchanged T1 (Menke et al., 2010; Vymazal et al., 1999) values.

Despite the increasing evidence for PD-related histopathological (Braak et al., 2003) and volumetric alterations in the cerebral cortex (Jia et al., 2015; Mak et al., 2015; Sterling et al., 2016; Tessa et al., 2014), only a few studies assessed cortical relaxation times in PD: one study reported no effect in T2* (Ulla et al., 2013), two studies focused on T2 values, reporting both regional T2 shortening (Mondino et al., 2002) and prolongation (Vymazal et al., 1999) in the prefrontal cortex. The only cross-sectional study using T1 relaxometry reported shortening of cortical T1 relaxation time in PD (Vymazal et al., 1999) which was attributed to the decrease of the cortical ferritin (Dexter et al., 1990).

To date, the development over time and distribution of disease-related microstructural changes across the cerebral cortex has not been shown so far in PD with qMRI methods. To compare physiological with PD related cortical T1 changes, we employed an established qMRI technique for quantitative T1 mapping (Preibisch and Deichmann, 2009) together with an advanced surface-based analysis of cortical GM to investigate cortical T1 changes in PD and their relation to cortical atrophy in a longitudinal study across six and a half years. According to the previous imaging (Gracien et al., 2016; Vymazal et al., 1999) and histopathological evidence (Dexter et al., 1990), we expected a more prominent T1 decrease in PD patients.

2. Methods

2.1. Participants

13 patients with early PD and 20 matched healthy subjects participated in the longitudinal study. Data from two healthy subjects had to be excluded due to MRI artifacts. All patients fulfilled the brain bank criteria for PD diagnosis (Hughes et al., 1992). Detailed medical history of each participant and scoring of the patients on the Hoehn and Yahr (HY) scale and Unified Parkinson's disease rating scale part III (UPDRS III) were performed by an experienced neurologist. Because of their normal neurological status, healthy subjects were not explicitly rated on the UPDRS III or on the HY scale. Exclusion criteria were: psychiatric diseases, drug abuse, uncontrolled arterial hypertension or diabetes mellitus and other neurological diseases.

Participants largely overlapped with those of two previous studies of our group (Baudrexel et al., 2010; Gracien et al., 2016). However, these studies had different goals and did not report longitudinal T1 changes in PD. All research procedures conformed to the Declaration of Helsinki and the study was approved by the Institutional Review Board. Written informed consent of all participants was obtained for each time point.

2.2. T1 mapping

MRI scans were performed at baseline and six and a half years later using a 3 Tesla whole body MR scanner (Trio, Siemens Medical Solutions, Erlangen, Germany; radio frequency (RF) transmission: body coil, RF reception: 8-channel phased-array head coil).

The calculation of quantitative parameter maps was performed with custom-built MATLAB scripts (The MathWorks Inc., Natick, MA, USA) according to (Preibisch and Deichmann, 2009). For T1 mapping, two RF-spoiled three-dimensional gradient echo (GE) data sets with flip angles (FA) of 4° and 18° were acquired (matrix size = $256 * 224 * 160$, isotropic spatial resolution = 1 mm, TR = 7.6 ms, TE = 2.4 ms, band width = 206 Hz/pixel, scan duration = 9:05 min). The respective contrast differences allowed for the voxel-wise T1 calculation as explained in (Deoni et al., 2005). Furthermore, T1 maps were corrected for inhomogeneities of the transmitted RF field amplitude B1 (duration of B1-mapping: 4:51 min), utilizing the method described by (Yarnykh, 2007), and for the effects of incomplete spoiling of transverse magnetization according to (Preibisch and Deichmann, 2009).

The scanner hardware did not change during the study. Furthermore, a custom-built MRI sequence developed in our lab was used for T1 mapping. In this way, it was possible to recompile the identical sequence code in the case of software upgrades, assuring identical data acquisition conditions and thus longitudinal data stability. The programs for data processing, in particular for calculating the T1 maps, were not changed during the study.

2.3. Analysis of T1 values and cortical thickness

Custom-built programs utilizing the FreeSurfer toolbox version 5.3.0 (Dale et al., 1999; Fischl et al., 1999) were used for further data processing and analysis. Cortical segmentation of the T1-weighted GE data sets acquired at FA = 18° was achieved with the "recon-all" stream implemented in FreeSurfer. Afterwards, to avoid partial voluming, T1 values in the middle of the cortex with a distance of at least 40% of the cortical thickness from surrounding tissues were extracted and their mean values were projected to the surface. Furthermore, cortical thickness was calculated and also saved in surface data sets. For the vertex-wise calculation of the annual percentage change of cortical T1 and of the cortical thickness, data were further processed using the longitudinal stream implemented in FreeSurfer (Reuter et al., 2012).

For statistical analysis of cortical T1, individual data sets were normalized and smoothed with a 5 mm Gaussian kernel. For between-group comparisons, surface based statistics were then conducted using an unpaired *t*-test design for baseline and follow-up T1 data and for the annual rate of T1 change. For longitudinal statistical comparisons of cortical T1, a paired *t*-test design was chosen. Analogous to the surface-based analysis of T1, between-group comparisons were also performed for baseline and follow-up cortical thickness data and for the annual rate of cortical thickness change. For all surface-based statistical tests, a vertex threshold of $p = 0.05$ was applied. Since we expected a decrease of cortical T1 and cortical thickness (Gracien et al., 2016; Mak et al., 2015; Vymazal et al., 1999), the respective one-sided tests were used. Corrections for multiple comparisons were carried out at cluster level using Monte Carlo simulations, maintaining only clusters with corrected *p* values $p \leq 0.01$.

In addition to the vertex-based analysis, between-group comparisons were performed for averaged values of cortical T1 and cortical thickness and their respective annualized percentage change rates. Analogous to the vertex-based analysis, we tested for a global decrease of cortical T1 and cortical thickness mean values over time by using the respective one-sided tests. Furthermore, the relation between rates of cortical T1 change and change in UPDRS III was explored using Spearman rank correlations.

For the evaluation of T1-changes in deep GM, masks of the caudate nucleus, putamen and thalamus, the structures which allowed for the

most robust automatic segmentation, were generated from the GE images acquired at FA = 18° using the FSL "FIRST" toolbox as described in (Patenaude et al., 2011). The resulting masks were eroded by a 3 × 3 × 3 mm kernel and coregistered to the T1 images for extraction of mean T1 values. As we had no clear expectation with respect to the direction of T1 changes in the BG (Vymazal et al., 1999), two-sided tests were used.

Before applying parametric tests, all data (cortical T1, deep GM T1, cortical thickness and respective relative changes per year) were tested for normality using Shapiro-Wilk tests. In case of non-normality, as happened to be the case for cortical thickness data, Mann-Whitney *U* tests were applied for evaluation of group differences. Otherwise, *t*-tests were used.

3. Results

3.1. Characteristics of PD patients and healthy subjects

Demographic data and clinical characteristics of all further analyzed subjects are displayed in Table 1. Age did not differ between groups ($p = 0.53$). Patients' history and clinical examination revealed no signs of overt dementia, although this was not formally tested.

3.2. T1 relaxometry

Maps displaying the average annual percentage change of cortical T1 for patients and healthy controls are presented in Fig. 1. Within-group comparisons showing clusters of significantly reduced T1 values over time are presented in Fig. 2.

In healthy control subjects, significant T1 reductions were found bilaterally in lateral frontal, temporal and inferior parietal areas. In contrast, T1 reductions in the patient group were much more widespread and bilaterally affected large parts of the entire neocortex, particularly marked in the temporal, parietal and occipital cortices. Over time, no significant increases in cortical T1 could be detected in both groups.

Fig. 3 demonstrates clusters indicating a higher annual rate of cortical T1 decrease in patients as compared to the healthy subjects. Increased rates of cortical T1 reduction were found in the occipital cortex, left precuneus, left dorsal cingulate, bilaterally in the temporal cortex (predominantly in the temporal poles and temporoparietal junction) and also in the frontal cortex including the left supplementary motor area, the left and right caudal middle frontal cortex and the right inferior frontal cortex.

Fig. 4 presents the results for the between-group comparison of cortical T1 values as measured at follow-up. The analysis revealed a widespread bilateral pattern of reduced T1 values affecting large parts of the temporal and occipital cortex. T1 reductions are further found in the superior and inferior parietal cortex excluding the central region, in the precuneus and posterior cingulate gyrus, and also in frontal regions (left superior frontal cortex, left caudal middle frontal cortex, right inferior frontal cortex). Please note the similarity with the pattern shown in Fig. 3. No significant increases of cortical T1 were found. Also, the comparison of baseline cortical T1 values revealed no significant differences between groups.

Average cortical T1 relaxation times (mean ± standard deviation) did not differ between the two groups at baseline (patients: 1669.8 ± 42.3 ms; healthy controls: 1685.0 ± 44.7 ms; $p = 0.17$) but were significantly reduced in patients at follow-up (patients: 1584.3 ± 63.7 ms; healthy controls: 1663.8 ± 41.8 ms; $p = 0.0004$). Annualized relative changes of cortical T1 decrease were larger in patients vs. healthy controls (patients: −0.72 ± 0.64%/year; healthy controls: −0.17 ± 0.41%/year, $p = 0.007$). Annualized relative changes of cortical T1 values and changes in UPDRS III scores were not correlated ($r = 0.22$, $p = 0.47$).

In the deep GM, T1 values did not differ significantly between groups at baseline (patients/healthy subjects: caudate nucleus 1356.9 ± 101.2/1408.1 ± 94.6 ms, putamen 1336.7 ± 51.1/1347.0 ± 81.8 ms, thalamus 1366.0 ± 101.7/1393.5 ± 91.0 ms; *p*-values ≥ 0.17). At follow-up, group comparisons only revealed a trend towards lower thalamic T1 values in patients vs. healthy controls (patients/healthy subjects: caudate nucleus 1428.1 ± 104.1/1468.0 ± 75.0 ms, putamen 1340.2 ± 89.7/1360.0 ± 63.2 ms, thalamus 1316.8 ± 85.5/1379.4 ± 84.8 ms; thalamus $p = 0.054$, *p*-values for the other regions ≥ 0.25). Also, no significant group differences were observed for the annualized percentage change rates of T1 in any deep GM region (*p*-values ≥ 0.34).

3.3. Cortical thickness analysis

Surface-based analysis did not reveal significant between-group differences in cortical thickness at baseline or follow-up. However, two small clusters indicating an increased rate of cortical thinning in patients vs. healthy controls were found in the left superior frontal and caudal middle frontal cortex (Supplementary Fig. 1).

Neither the average thickness values at baseline or follow-up differed between the two groups (baseline: patients: 2.36 ± 0.07 mm, healthy controls: 2.36 ± 0.08 mm, $p = 0.37$; follow-up: patients: 2.28 ± 0.13 mm, healthy controls: 2.30 ± 0.12 mm, $p = 0.30$), nor the average annualized percentage change of cortical thickness (patients: −0.53 ± 0.56%/year; healthy controls: −0.37 ± 0.46%/year; $p = 0.17$).

Table 1
Demographics and clinical group characteristics (values given as mean ± standard deviation).

Demographics and clinical group characteristics		
	Patients $n = 13$ (Baseline/follow-up)	Healthy controls $n = 18$ (Baseline/follow-up)
Age	62.6 ± 8.1/69.0 ± 8.1	64.4 ± 7.9/70.9 ± 7.9
Gender (F/M)	6/7	9/9
Scan interval	6.4 ± 0.2	6.5 ± 0.2
Disease duration	4.5 ± 2.7/10.9 ± 2.8	–
Hoehn and Yahr scale	1.2 ± 0.4/2.0 ± 0.6	–
Hoehn and Yahr range	1–2/1–3	–
UPDRS III total	16.8 ± 5.6/23.4 ± 4.3	–
UPDRS III change	6.5 ± 4.2	–

4. Discussion

The key finding of this study is the development of widespread bilateral changes in cortical microarchitecture in PD patients over a period of six and a half years, as reflected by the decrease in the longitudinal relaxation time T1. Cortical T1 decrease was most pronounced bilaterally in the temporo-parietal and occipital cortex but was also found in mesial frontal regions (e.g. supplementary motor cortex). The changes clearly extended beyond the physiological T1 decrease observed during healthy aging and were already observable at mild to moderate disease stages.

To the best of our knowledge, only one prior study used qMRI to assess PD related changes in cortical T1. In agreement with our findings, this study reported a decrease of T1 within a small region of interest (ROI) in the medial prefrontal cortex in PD patients vs. healthy control subjects (Vymazal et al., 1999). Mean disease duration was 9.7 ± 5.9 years and comparable to our patients at the time of the second measurement (10.9 ± 2.8 years). However, the result reported in the aforementioned study was based on the evaluation of a single arbitrary cortical ROI and might therefore not be representative for the whole cortical volume, given that histopathological changes in PD are heterogeneously distributed across the cortex (Braak et al., 2003; Ferrer, 2009). Furthermore, partial volume effects might have affected the evaluation of relaxation times from very small cortical ROIs. The methods

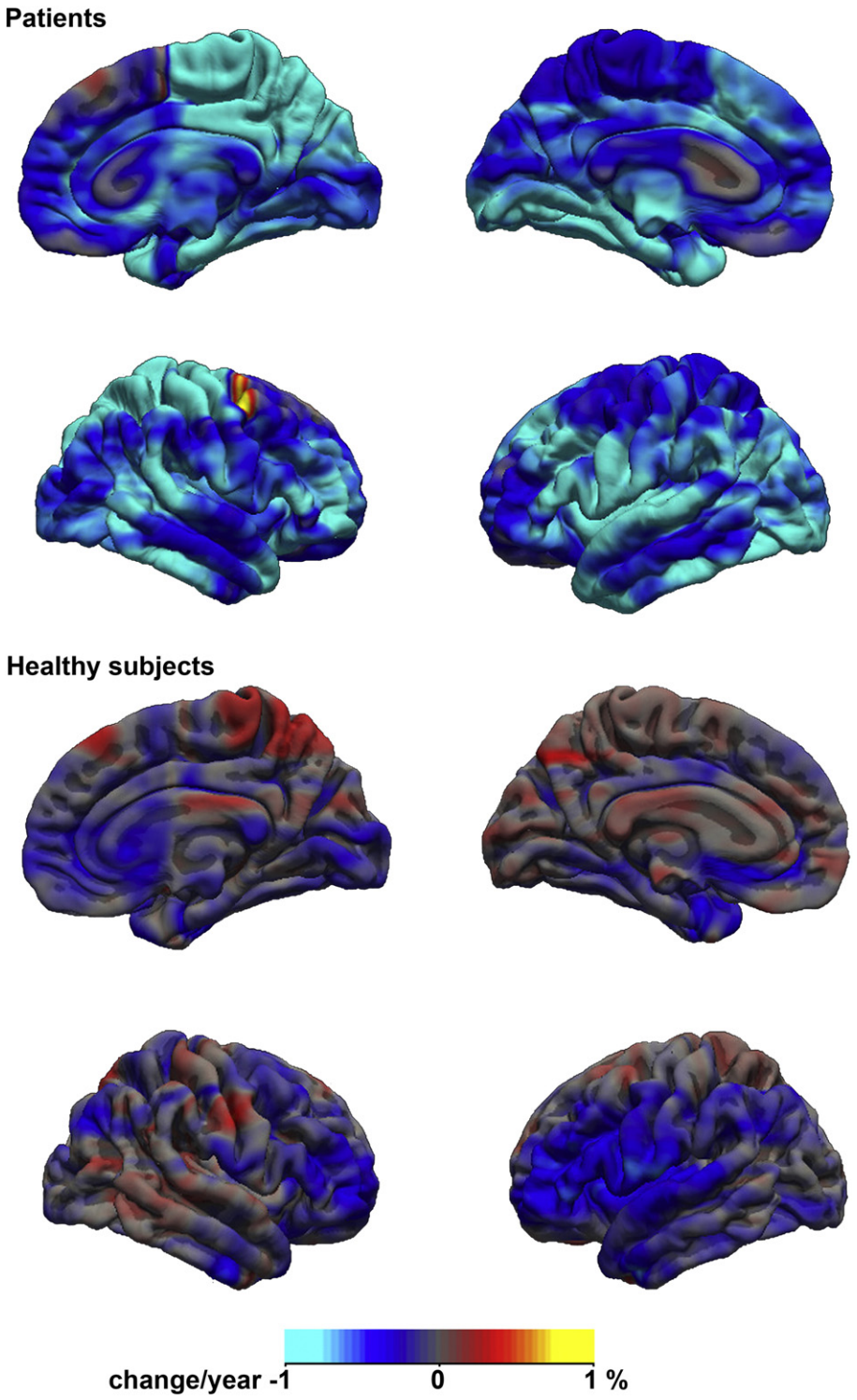

Fig. 1. Maps displaying the average annual percentage change of cortical T1 for patients with PD (top) and healthy control subjects (bottom).

applied in the current study are of advantage as an automated segmentation procedure was followed, all cortical regions were analyzed vertex-wise and cortical T1 values were read in the middle of the cortical layer to reduce partial volume effects.

4.1. Candidate mechanisms of cortical T1 shortening in PD

The question arises which microstructural processes may cause the observed T1 shortening in PD. T1 of a given brain voxel is determined by the physical properties of its underlying tissue and is mainly dependent on (i) the free water content, (ii) the iron content, and (iii) the total amount of tissue components and the concentrations and types of macromolecules (e.g. degree of myelination) (Fatouros et al., 1991; Gelman et al., 2001; Lutti et al., 2014; Rooney et al., 2007). With respect to physiological (healthy) aging in the senescence life period, a significant decrease of cortical T1 in temporal, parietal and lateral-frontal areas has been described in a recent MRI study performed by our group (Gracien et al., 2016). The T1 decrease was attributed to an age driven

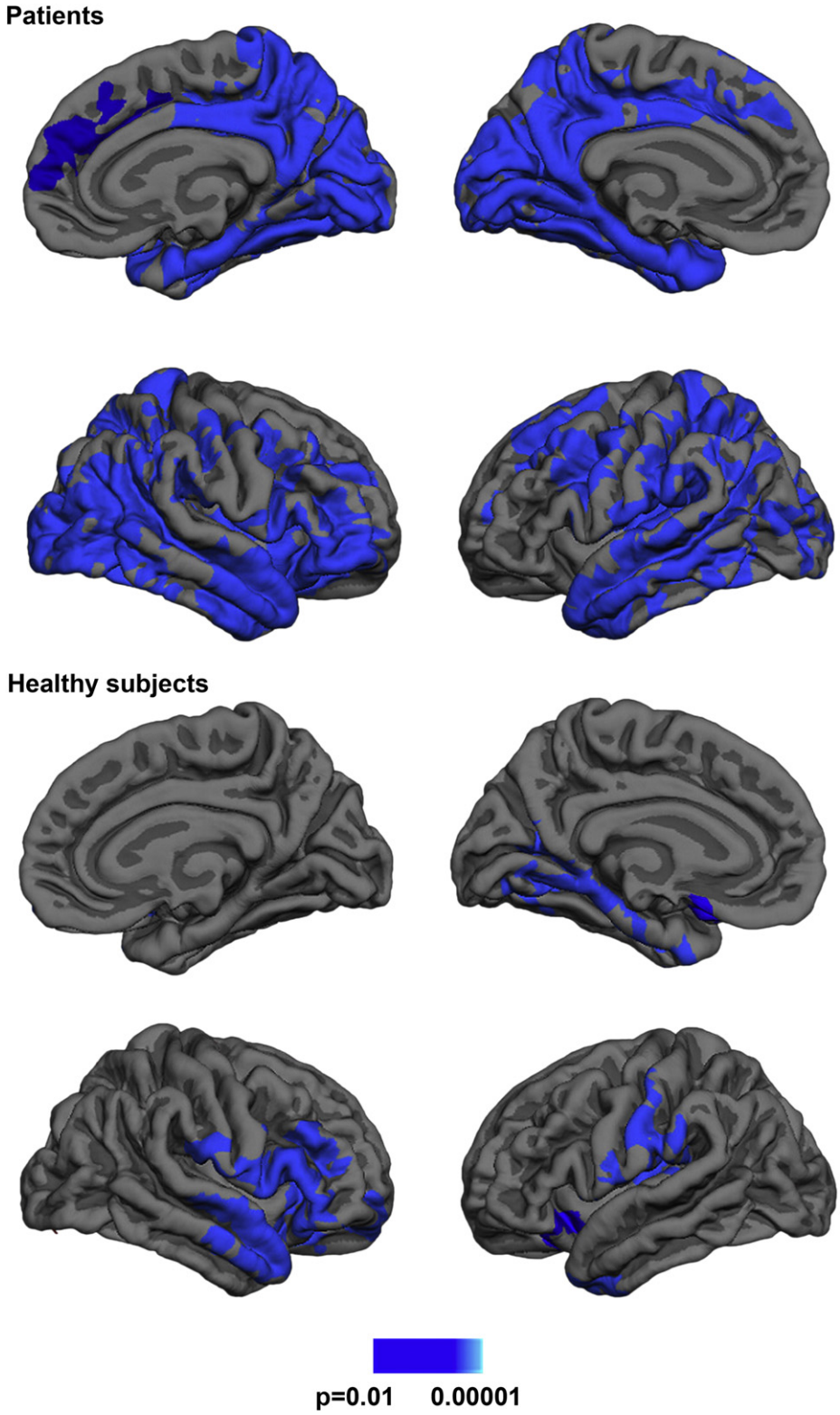

Fig. 2. Statistical maps of longitudinal within-group comparisons indicating areas displaying a significant decrease of cortical T1 values over time in patients with PD (top) and in healthy control subjects (bottom).

increase in cortical iron levels (Daugherty and Raz, 2015; Hallgren and Sourander, 1958) and to an decrease in free water content, as has been demonstrated with proton density mapping in a previous in vivo imaging study (Neeb et al., 2006).

With respect to PD, there is increasing evidence that cortical metabolic defects, in particular impaired mitochondrial function, oxidative stress, and abnormal phosphorylation of proteins at cortical synapses, are already present at early clinical stages (Ferrer et al., 2011; Ferrer, 2009). One of the significant sources of oxidative stress in PD is iron (Hare et al., 2013). The iron content has been shown to be increased in the SN in PD (Dexter et al., 1989) and to gradually elevate in the cortical tissue during aging in healthy subjects (Hallgren and Sourander,

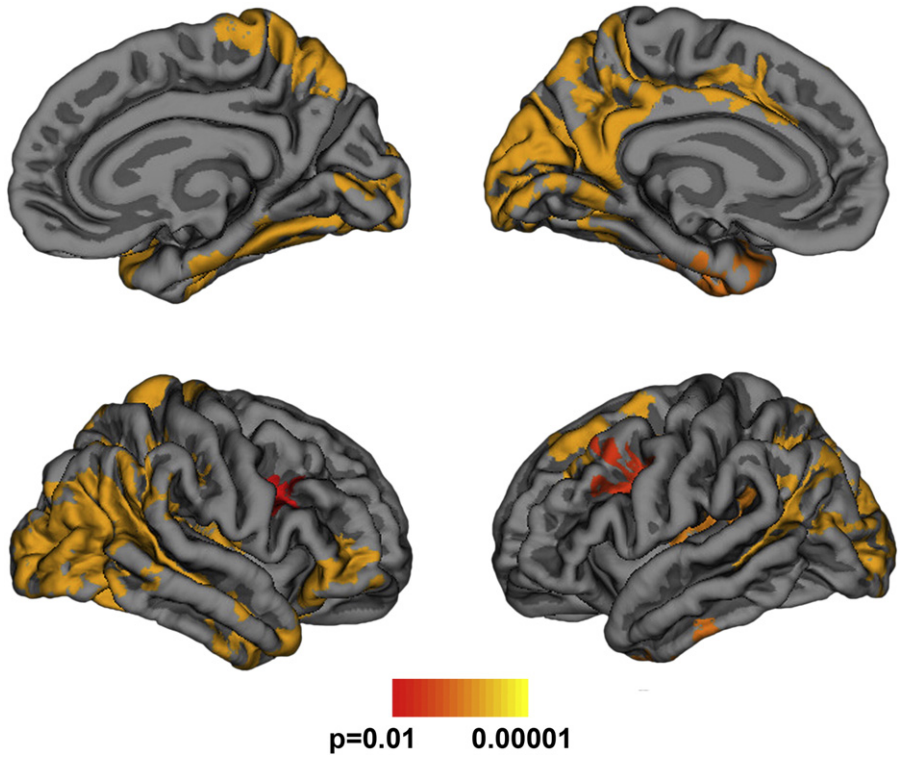

Fig. 3. Clusters indicating a higher annual rate of cortical T1 decrease in patients as compared to the healthy controls.

1958). However, the cortical T1 shortening observed in PD patients is unlikely to be due to a net iron accumulation since the total brain iron content is either normal (Dexter et al., 1989; Loeffler et al., 1995) or even lower than in the healthy population (Yu et al., 2013). Instead, as has been suggested by Vymazal et al. (1999), cortical T1 shortening may be linked to the decrease of the cortical ferritin levels (Brooks et al., 1998; Dexter et al., 1990; Vymazal et al., 1999). Ferritin is the most common iron storage protein in the brain (Stankiewicz et al., 2007).

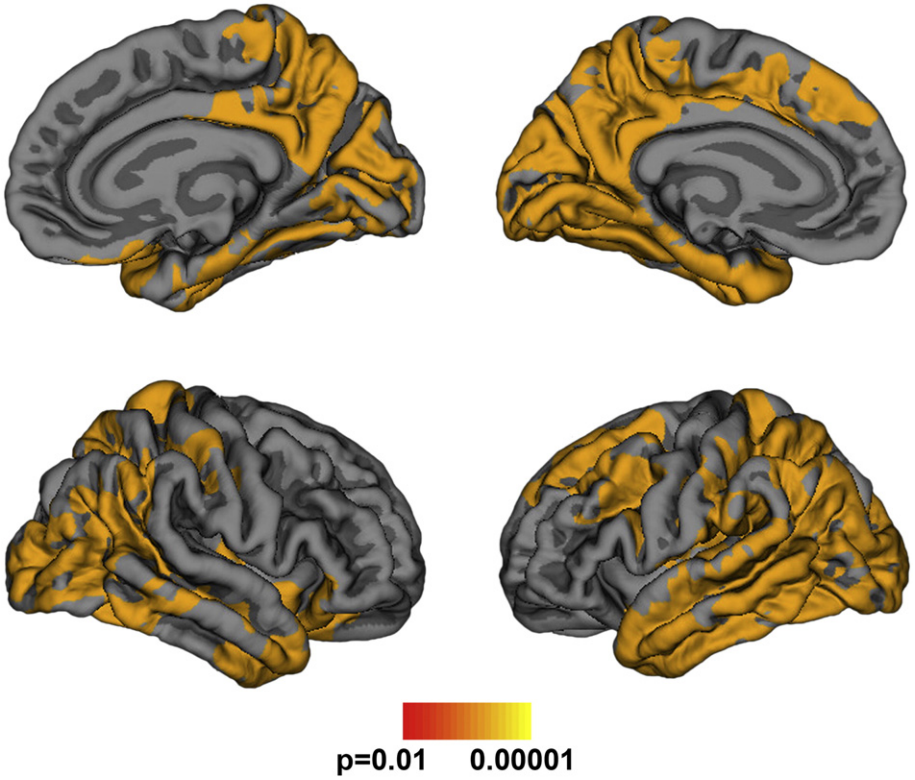

Fig. 4. Clusters indicating significantly lower cortical T1 values in patients as compared to the healthy controls at follow-up.

Stored (Fe^{3+}) iron particles are largely shielded from water molecules by a protein shell and have only little effect on T1 (Schenck, 2003; Schenck, 1995; Vymazal et al., 1992). In contrast, soluble (Fe^{2+}) iron ions exert a considerably stronger T1 reducing effect (Schenck, 2003). Decreased levels of cortical ferritin as observed in PD (Dexter et al., 1990) may result in a shift from bound iron towards more soluble iron and thus contribute to some extent to the observed decrease in T1.

The formation of Lewy bodies along with selective neural loss constitutes the histological hallmark of PD (Hughes et al., 1992; Jellinger, 2009) and could be another mechanism that possibly influences the T1 relaxation time by changing the cortical tissue composition. So far, most histopathological studies of the cortex in PD focused on the analysis of the distribution of Lewy bodies, which consist of densely aggregated α-synuclein and other proteins such as ubiquitin (Braak et al., 2003). Due to their properties as a solid-like object (Uversky and Eliezer, 2009), Lewy bodies may contribute to the shortening of cortical T1. However, since they only constitute a very small fraction of the cortical volume (Halliday et al., 2005), it is questionable, whether Lewy bodies indeed exert a significant T1 reducing effect. The histopathological observation, that Lewy bodies are predominantly observed in the neocortex of strongly affected patients (i.e. at the stages 5 and 6 according to (Braak et al., 2003) which corresponds to the stages III–V according to HY (Hoehn and Yahr, 1967)) further arguments against this hypothesis since the maximum HY stage in our follow-up cohort was III (Braak et al., 2003; Jellinger, 2009; Jellinger, 2006).

To our knowledge, only one histopathological study performed post-mortem counts of the number of cortical neurons in PD patients (MacDonald and Halliday, 2002). The study describes a moderate decline of pyramidal neurons within the supplementary motor cortex in patients vs. healthy controls, whereas other parts of the motor cortex are spared from neuronal loss. This finding fits into the view that neuronal loss is highly selective in PD and restricted to specific brain areas, not only at subcortical but also at cortical level. Similar to healthy aging (Freeman et al., 2008; Pakkenberg et al., 2003), total cortical neuronal loss in PD seems to be rather small, although this has not yet been systematically investigated for the whole cortex. Dendritic regression constitutes a major histological finding in healthy aging and is suggested to play a fundamental role in the pathophysiology of neurodegenerative dementias (Dickstein et al., 2007). However, whether regression of cortical neuropil is generally more prominent in PD than in age matched healthy controls has not yet been systematically investigated (Scheff et al., 2014; Zhan et al., 1993). To our knowledge, the same holds true for the loss of cortical myelin. On the other hand, it is meanwhile well accepted and also demonstrated by in vivo imaging, that PD is accompanied by ubiquitous (also cortical) microglia activation and proliferation mediating neuroinflammatory processes via the secretion of cytokines and reactive oxygen species (Gerhard et al., 2006; McGeer and McGeer, 2008).

The different cellular changes mentioned in the previous paragraph may either contribute to the T1 decrease (in case of a net increase in cortical cellular concentrations) or attenuate the T1 decrease (in case of a net decrease of cortical cellular concentrations). Since cortical water content was shown to be reduced in older healthy subjects in vivo (Neeb et al., 2006), we suggest that the cellular compartment in the PD affected cortex may indeed increase over time.

It has to be kept in mind that the observed T1 shortening may also be induced by processes in cortical tissue microarchitecture which have not been described so far, since histopathological evidence is still limited to explain the findings of this study (Dexter et al., 1992; Dexter et al., 1990; Ferrer, 2009; MacDonald and Halliday, 2002; McCann et al., 2016). For example, the microstructural overlap between Alzheimer and PD pathology such as amyloid plaques, neurofibrillary tangles and gliotic reactions at later PD stages may also contribute to the observed changes in T1 (Irwin et al., 2013). As different mechanisms might have synergistic or opposing effects on the T1 relaxation time, it is in general problematic to identify the underlying main process leading to cortical T1 changes. For this reason, studies combining multimodal qMRI techniques (i.e. T1 —, T2 —, T2*—, proton density mapping, magnetization transfer imaging, diffusion tensor imaging) with quantitative histopathological analyses are needed to disentangle the effects of biological processes on qMRI parameters such as T1.

Noteworthy, in contrast to the observed cortical T1 decrease, T1 did not change significantly in any deep GM region in PD. A possible explanation might be that microstructural changes that shorten GM T1 coexist with changes that predominantly occur in the deep GM and cause T1 prolongation such as microangiopathic lesions.

4.2. Relation to atrophy

Recent cross-sectional and longitudinal morphometric studies have unveiled a relatively consistent pattern of cortical thickness reductions and atrophy affecting the frontal and temporo-parietal cortices in patients with PD (Hanganu et al., 2014; Ibarretxe-Bilbao et al., 2012; Jia et al., 2015; Mak et al., 2015; Tessa et al., 2014; Uribe et al., 2016; Zarei et al., 2013). This specific pattern was shown to be related to overall disease progression (Ibarretxe-Bilbao et al., 2012; Zarei et al., 2013) and, probably to an even stronger degree, to the decline in cognitive functioning (Barker and Williams-Gray, 2014; Hanganu et al., 2014; Mak et al., 2015; Zarei et al., 2013). The pattern of T1 reductions as presented in Figs. 3 and 4 is principally in good agreement with these previous morphometric results. However, aside from a rather similar topography and amount of frontal T1 changes, temporo-parietal T1 reductions were more widespread and extended into the occipital cortex including the lateral occipital and primary visual cortex and the cuneus. In contrast to these profound occipital T1 changes, occipital atrophy has less consistently been described in the literature (Hanganu et al., 2014; Uribe et al., 2016). Similar to the atrophy in other regions, it has been linked to disease progression and to the cognitive status of patients. Using radio-tracer based imaging techniques, occipital hypometabolism and hypoperfusion has been shown to occur even in cognitively intact PD patients (Abe et al., 2003; Bohnen et al., 1999), suggesting a relatively early involvement of occipital areas during the course of the disease.

One possible reason for this more widespread pattern of cortical changes observed with T1 relaxometry as compared to the changes reported in recent cortical thickness or voxel-based morphometry studies might be the somewhat more advanced age (69.0 ± 8.1 years) and disease duration (10.9 ± 2.8 years) of patients at the time of the second measurement (for comparison: the range of average age was about 56–73 years and the range of average disease duration was about 3–11 years in (Hanganu et al., 2014; Ibarretxe-Bilbao et al., 2012; Jia et al., 2015; Mak et al., 2015; Tessa et al., 2014; Uribe et al., 2016; Zarei et al., 2013)). Age and disease duration likely constitute independent factors of disease progression in PD (Levy, 2007). Another possible explanation is that T1 as a marker for tissue microstructure might be more sensitive for the detection of cortical changes associated with PD as compared to cortical thickness measures. This hypothesis is also supported by the finding that, in contrast to the massive T1 changes, only minor changes in the rate of cortical thickness reduction were detected in this pilot study. This renders cortical T1 a promising additional imaging marker for the mapping of PD progression in future longitudinal studies. However, further investigations are definitely required to clarify the principal temporal and spatial-anatomical interrelations between the changes in cortical T1 and those in cortical thickness.

4.3. Limitations

One limitation of this work refers to the fact that we did not specifically assess the cognitive status of our patients, as this was not within our main research focus during the initiation of this study almost a decade ago. It therefore remains an open question to which extend the observed T1 reductions are driven by the development of MCI in some of the patients during the follow-up period. The prevalence of MCI in PD

is known to be dependent on age and disease duration and was reported to be around 20–40% in patients with similar disease duration (Aarsland et al., 2010) as in our study. However, we do not think that this compromises the principal findings of our study. First, the observation that T1 relaxometry can be used to detect cortical changes in PD is per se a novel finding. Second, only minor differences in the rate of cortical thinning were observed in patients vs. healthy controls. Therefore, it is unlikely that our cohort predominantly comprised patients with MCI or even dementia.

Another limitation refers to the relatively small sample size of our study cohort.

Accordingly, some alterations of cortical thickness or deep GM T1 values might have remained undetected, as they did not reach the level of significance applied in this study due to the lack of power. Sample bias and an increased false discovery rate are other problems inherent to small sample studies that potentially limit the generalizability of the results (Button et al., 2013; Friston, 2012). However, a clear strength of this study is the longitudinal design with a long observation interval of 6.4 years, which increases statistical power due to the larger individual effect sizes. In spite of the small sample size, this pilot study revealed a pattern of T1 reductions in distinct cortical areas which are known to be affected from atrophy in PD and, thus, underlines the potential of T1 relaxometry for the investigation of neurodegenerative diseases in larger studies. As previous studies which assessed cortical T2 and T2* values in PD showed either no effect in T2* (Ulla et al., 2013), T2 shortening (Mondino et al., 2002) or T2 prolongation (Vymazal et al., 1999), a multi-parametric qMRI approach including T1, T2 and T2* mapping along with the measurement of other quantitative MRI-parameters (e.g. proton density, magnetization transfer ratio) should be employed in future studies to better characterize the biological mechanisms underlying cortical T1 changes in PD.

4.4. Conclusion

It could be demonstrated that T1 relaxometry is capable to detect biologically meaningful patterns of cortical microstructural change associated with PD, rendering T1 a promising imaging marker for future studies of cortical pathology in PD. Further investigations are needed to better understand the mechanisms underlying the observed change in T1 and, also, to better characterize the relation between T1 change and cortical atrophy measures.

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