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T2-relaxometry predicts outcome of DBS in idiopathic Parkinson's disease

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ABSTRACT

Introduction: Deep brain stimulation (DBS) nowadays is a well-established treatment of motor symptoms in Parkinson's disease. The subthalamic nucleus (STN) is a common target for DBS, because motor improvements have been shown to be superior to best medical therapy, if DBS electrodes have been appropriately positioned. DBS target identification can be assisted by MRI beyond structural imaging by spatially resolved measurement of T2-relaxation times (T2r).

Aim: We pose the question, whether T2r of the STN is linked to the severity of the disease and whether outcome of DBS may be correlated to an asymmetric manifestation of the disease. Further, we investigated if abnormal T2r in the STN may be predictive for outcome of DBS.

Methods: Twelve patients underwent preoperative MR imaging including a multi echo relaxometry sequence (3 Tesla, Siemens Medical Systems, Erlangen, Germany) ahead of DBS. T2r were determined for STN, substantia nigra (SN), red nucleus (RN) and centrum semiovale (CSO). Unified Parkinson's disease Rating Scale (UPDRS) scores were tested before and after DBS. Patients' T2r and deduced values representing left-right asymmetry of measurements were correlated with UPDRS scores and measures for outcome of DBS. Furthermore, patients' T2r were compared with T2r measurements in 12 healthy controls (HC).

Results: Patients' T2r for SN (mean 45.4 ms ± 4.4 ms) and STN (mean 56.4 ms ± 3.8 ms) were significantly shorter than T2r in HCs for SN (mean 60.7 ± 4.6) and STN (mean 66.1 ms ± 4.0 ms). While no mean T2r asymmetry was found in the SN, patients' mean T2r for STN showed a weakened left-right correlation (Pearson correlation coefficient 0.19 versus 0.72 in HC) indicating asymmetric degeneration. T2r asymmetry was not linked to the more severely affected hemisphere.

The respective lower T2r within the left or right target region was significantly correlated to the outcome in terms of UPDRS III improvement in "off" state (Pearson correlation 0.82 corresponding to $p \ll 0.01$). Patients with T2r of STN lower than 50 ms showed no response to DBS in the UPDRS.

The maximum T2r for SN correlated to the improvement between UPDRS "off" minus and "on" (Dopamine response) but failed to predict DBS outcome.

Conclusions: The lower boundaries of T2r in the STN predict motor outcome in DBS. T2r asymmetry in the STN is not associated with increased clinical symptoms, but with response to therapy. Thus, patients with very low T2r may be inappropriate candidates for DBS.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease affecting the human nervous system on a multisystem level. The motor symptoms are considered to derive from a loss of dopaminergic projection neurons in the substantia nigra (SN) and accumulation of iron deposits in the SN. DBS is nowadays a well established therapy not only for advanced PD with fluctuating motor symptoms and dyskinesia (Deuschl et al., 2006), but has been proven to be superior to medical therapy at early stages of PD ahead of disabling motor complications (Schuepbach et al., 2013a). In younger patients the subthalamic nucleus (STN) is the target of choice to improve motor symptoms. Most often STN is targeted bilaterally (Moro et al., 1999). The globus pallidus

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internus (GP) is another effective target for treatment of the levodopa-responsive symptoms and motor fluctuations (Benabid et al., 2009; Follett et al., 2010; Odekerken et al., 2013; Okun et al., 2009; Weaver et al., 2009). Unilateral versus bilateral approaches to DBS both emerged to be efficacious to improve motor dysfunction (Shemisa et al., 2011), yet it remains an open question as how to appropriately determine unilateral approaches for a subset of patients. Patients with marked asymmetry of motor symptoms may benefit from unilateral DBS, if the target nucleus can be properly identified.

The rationale for MRI in PD is traditionally anchored in the exclusion of atypical Parkinson syndromes.

Current diagnostic methods for Parkinsonism include in some extent 18F-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) as well as dopaminergic receptor imaging by PET or single photon emission CT (SPECT). 18F-fluorodopa PET, 11C-dihydrotetrabenazine PET, FDG-PET and 123I-beta-carbomethoxy-3beta-(4-iodophenyl)tropane (DAT)-SPECT have been used to detect the loss of dopaminergic presynaptic terminals in the putamen originating from the SN pars compacta in PD patients (Ravina et al., 2005). Neuromelanin imaging at 3T MRI offers another aspect of changes within PD (Castellanos et al., 2015; Keita et al., 2016). Furthermore transcranial ultrasonographic imaging of the midbrain is discussed as a possible method for early assessment of degeneration of SN. (Bouwmans et al., 2013; Li et al., 2016).

Methods to assist diagnosis of PD with MRI are now evolving, encompassing quantitative iron assessment and neuromelanin sensitive MRI (Baudrexel et al., 2010; Ohtsuka et al., 2014). In research setting, arterial spin labeling and functional MRI using connectivity analysis have found profound differences between PD and HC (Detre et al., 2009; Robinson et al., 2009). To our knowledge, no previous MRI study aimed at a prediction of DBS outcome, except of a seminal study (Watanabe et al., 2012) that correlated T2r in STN to neurophysiological parameters, disease duration and laterality.

The degeneration of SN in PD involves iron accumulation, which can be assessed by T2 and T2* relaxometry. These values, correlated with micro structural characteristics of tissues, provide absolute, tissue specific, field strength and machine independent T2 values and are highly sensitive to e.g. iron content (Carneiro et al., 2006). In this study, we investigated whether a decrease of T2 relaxation times in the subthalamic nucleus (STN) can be used as surrogate marker for target selection in DBS. Our assumption was that i) an asymmetric clinical presentation is reflected by asymmetric degeneration within the basal ganglia loops, which could possibly be detected by T2r changes compared to HC and that ii) an asymmetric degeneration may affect the motor outcome of DBS. Patients with a high asymmetric index in motor function have profited of unilateral DBS in means of improvement of ipsi- and contralateral UPDRS, so that only few patients required a second DBS (Houtan et al., 2010). The T2r values could predict the degree of degeneration requiring bilateral or only unilateral DBS. Furthermore a severe degeneration within the basal ganglia loop, as seen by T2r values could predict a poor response to DBS and affect future patient eligibility.

The neuroradiological assumption is to see, if the iron content as seen by T2r values asymmetrically or symmetrically correlates with PD symptoms and/or DBS outcome.

2. Subjects and methods

Fourteen DBS patients (9 men, 5 women) with the standard neurological preoperative work-up of determining levodopa-responsive PD with motor complications and without contraindications underwent preoperative imaging including T2 relaxometry. Inclusion criteria to this study were DBS implantation, completed imaging protocol and pre- and post-operative UPDRS assessment. Two male subjects had to be excluded because of motion artifacts in the imaging. Mean age of evaluated patients (7 men, 5 women) was 63,25 years (range 44–80, median 62.5, SD 10.89) and all patients were right handed.

Twelve right handed controls (HC healthy controls) were examined (6 men, 6 women, age range 20–41, age average 28.5, age median 27, age SD 6.5). Exclusion criteria were, according to individual medical history, neurological diseases other than PD, drug abuse or neurologic disorders in 1st or 2nd line relatives.

The UPDRS scores I, II and III were assessed by a specialized paramedic of the Movement Disorder Center of our Institution's Neurological Department. UPDRS I ("cognitive") was determined during "on"-state while UPDRS II ("daily living") and UPDRS III ("motor") were determined in "on" as well as in "off" state. In addition the UPDRS III scores were determined separately for left and right sided symptoms yielding the according left and right UPDRS III subscores. All scores were determined 3 to 6 weeks preoperatively as well as 12 to 26 weeks postoperatively. DBS outcome was assessed by analyzing the differences of respective preoperative and postoperative UPDRS scores.

Patients and controls were examined at the 3 Tesla scanners (Siemens Magnetom Trio and Siemens Magnetom Verio; Siemens Medical Solutions, Erlangen, Germany) of our institution. T2r MRI data were acquired with identical multi-contrast spin echo (SE) sequences on both of the similar scanners. The multi-echo, fast spin echo sequence used the following parameters: 28 coronal contiguous 2 mm slices, FOV 220 mm, acquisition matrix 128×128, TR = 2000 ms and multiple TE ranging from 12 ms to 96 ms in steps of 12 ms. Acquisition time for the T2 data was 6.16 min. The total scan time for the entire imaging protocol was 38 min.

STN (left and right), SN (left and right) and for comparison RN (left and right) and CSO (right only) were chosen as regions of interest (ROI). The free hand ROIs were placed manually using an image at TE = 72 ms where the STN showed best contrast in a coronal plane on the T2 weighted image. The ROIs were chosen to cover the centers of the nuclei with the resulting signal being the average of the intensity values covered by the chosen ROIs. The ROI was positioned in the middle of the selected structure to avoid miscalculation due to partial volume of the surrounding tissue. Additional ROIs were positioned into the SN. For reference values ROIs were placed into NR bilaterally and into right CSO. Schaltenbrand and Wahren's Anatomic Atlas (1977) and Salamon's Neuroanatomy and Neurovasculature Web-Atlas Resource (2013) were used as the anatomic reference for manual ROI placements.

The absolute T2r were calculated from the T2 signal decay from the multi echo sequence. UPDRS III, i.e. the motor part of the UPDRS, was chosen for the clinical correlation as the standard clinical assessment scale for the severity of disease. Measured signal intensities for each TE were averaged for every selected region of interest (ROI). Signal decay time (T2) was calculated for each selected region of interest (ROI) as decay constant according to a robust least-squares fit of a mono exponential decay according to Formula 1:

$$Signal(\mathrm{TE}) = const * exp\left(-\frac{\mathrm{TE}}{\mathrm{T2}}\right) \quad (1)$$

The fitting algorithm for each ROI was applied to the 7 measurements from TE = 24 ms to TE = 96 ms. Measurements at TE = 12 ms were omitted to avoid non-exponential components of the signal at very short TE (Jones, 2003). Furthermore the formula assumes the constant including the factor $(1-\exp(-\frac{\mathrm{TR}}{\mathrm{T1}}))$ being independent from TE. According to the 7 ROIs the calculations resulted in a set of 7 T2 values for every patient and control. As the tissue specific T2r values are calculated from the decay curves regardless of absolute signal intensities the measurements are independent of the actual 3T scanner used.

For statistical workup, the measured T2r values for left side and right side were supplemented by the T2r mean, max and min values as well as the difference between left and right T2r values (all values in ms). Also the UPDRS scores were supplemented in a similar manner by difference scores (difference pre-operative minus post-operative,

difference "on"-state minus "off"-state). Pearson correlations of the resulting sets of T2r values and UPDRS scores were determined and analyzed for patients and HC. Furthermore for patients and HC possible correlations of T2r values with sex or age were tested.

3. Results

3.1. UPDRS pre- and post-operative

Patients averaged preoperative and postoperative total UPDRS I, II and III scores in "off"-state and in "on"-state are shown in Table 1. The designation "on" and "off" refers to dopaminergic medication. The DBS itself, after implantation, was always switched on.

Difference scores (Δ_UPDRS) were calculated as respective difference of preoperative UPDRS scores minus postoperative UPDRS scores and were interpreted as outcome. Positive Δ_UPDRS scores represent positive outcome of DBS.

The averaged preoperative UPDRS scores reflected the inclusion criteria for DBS and thus showed the comparatively smallest standard deviation. The positive averaged Δ_UPDRS scores represented the overall positive outcome of DBS. The higher standard deviation of the postoperative UPDRS scores and in particular the high standard deviation of the Δ_UPDRS scores with relative standard deviations above 100% indicated a highly variable outcome of DBS.

The differences in pre- and postoperative UPDRS scores (Δ_UPDRS) according to groups I–III are shown in Table 2. The UPDRS improvements were mostly due to improved motor (UPDRS III) performance during "off"-state as represented by Δ_UPDRS_III_off. The comparatively high standard deviation again reflects the variability in response to therapy.

3.2. T2 relaxation times in patients and controls

Table 3 compares mean and difference of left and right T2r values of the ROIs for HC und patients. T2r for NR (mean left and right side) showed a non significant decrease in patients (60.39 ± 4.27 ms) compared to HC (64.82 ± 5.16 ms). T2r for CSO indicated a non significant increase in patients (84.98 ± 3.31 ms) compared to HC (78.67 ± 1.79 ms).

Patients and HC significantly differed in measured T2r (mean left and right side) for STN and SN. Patient's T2r of STN (56.46 ± 3.81 ms) showed a decrease of almost 3 standard deviations in comparison to HC (66.10 ± 3.99 ms). Patient's T2r of SN (45.41 ± 4.42 ms) showed a significant decrease of >3 standard deviations in comparison to HC (60.72 ± 4.65 ms).

The calculated left to right differences of T2r showed an increased left to right difference as well as an increased variability of left to right differences of T2r of STN for patients (STN_dif 0.91 ± 6.52 ms) in comparison to HC (0.47 ± 3.51 ms) implicating occurrences of unilateral alterations as shown in Table 3.

The unilateral UPDRS III scores showed a slight but insignificant emphasis of left sided symptoms. Consequently, despite the significant decrease of STN T2r in patients, the Pearson correlations of left and right STN T2r with left and right UPDRS III showed no significant relation.

To illustrate differences in T2r values in controls and patients and asymmetric T2r the measurements are shown as two-dimensional diagrams with the measured T2r in the right hemisphere on the horizontal axis and the measured T2r in the left hemisphere on the vertical axis.

Fig. 1 illustrates T2r differences in controls vs. patients for the SN (left vs. right). For subjects with higher T2r in both groups there was a slight tendency to show higher T2r on the right side as visualized by the lines of best fit with a slope below 45°. Nevertheless for both groups the left and right values were highly correlated (Pearson Correlation $r = 0.76$ for controls and $r = 0.61$ for patients) indicating good parity.

Furthermore, the data showed a significant correlation of the difference in preoperative UPDRS III scores in "off" vs. "on" state with the minimum right or left SN T2r value (Pearson correlation 0.74), i.e. the higher the remaining minimal SN T2r value, the higher the effect of dopaminergic medication. No significant T2r differences were detected between controls and patients in the RN. Left and right T2r were highly correlated (Pearson Correlation 0.77 for volunteers and 0.61 for patients) indicating good parity.

Fig. 2 shows T2r of the STN in patients vs. controls. In controls left and right T2r were highly correlated (Pearson Correlation $r = 0.72$). In patients, in contrast, the left to right correlation was almost lost (Pearson Correlation $r = 0.19$) indicating predominantly unilateral alteration of the STN. Five patients had T2r in the range of healthy controls (>60 ms for STN_right), whereas only one single patient had T2r values >60 ms in STN_left.

Patients and controls differ in terms of decreased STN T2r (<58 ms) either uni- or bilaterally. While varying lateralization naturally weakens any correlation for mean T2r of STN the figure suggests correlations if at least one of left or right STN showed decreased T2r i.e. correlations with the minimum of left or right T2r.

Neither correlations of T2r and UPDRS to sex or age for patients nor correlations of T2r to sex or age for HC showed any significance.

3.3. Correlation of T2 relaxation times with UPDRS and outcome

Fig. 3 shows Δ_UPDRS_III_off vs. STN_min indicating that STN_min i.e. the minimum T2r value measured for STN right or left is highly correlated to the outcome of DBS in terms of UPDRS III improvement in "off" state. The Pearson correlation of STN_min to Δ_UPDRS_III_off is $r = 0.82$ corresponding to a $p < 0.01$.

Patients with pronounced asymmetry (T2 left STN minus T2 right STN) revealed the most prominent improvement of the UPDRS III.

Table 1
Total UPDRS and differences preoperative minus postoperative in on and off state.

	Mean	Std. Dev.	Relative Std. Dev.
UPDRS_off_pre	51.92	9.84	19.0%
UPDRS_off_post	36.25	15.47	42.7%
Δ_UPDRS_off	15.67	19.05	121.6%
UPDRS_on_pre	25.00	7.91	31.6%
UPDRS_on_post	20.67	11.26	54.5%
Δ_UPDRS_on	4.33	11.40	263.3%

Table 2
UPDRS differences preoperative minus postoperative.

	Mean	Std. Dev.
Δ_UPDRS_I	−0.42	1.31
Δ_UPDRS_II_off	3.83	5.15
Δ_UPDRS_II_on	2.75	3.98
Δ_UPDRS_III_off	12.25	14.50
Δ_UPDRS_III_on	2.00	8.91

Table 3
Left and right side mean and difference T2r in ms for controls and patients. STN_dif means T2 value in left STN minus T2r in the right STN NR_dif and SN_dif were derived accordingly.

	Controls		Patients	
	Mean	Std. Dev.	Mean	Std. Dev.
STN_mean	66.10	3.99	56.46	3.81
STN_dif	0.47	3.51	0.91	6.52
SN_mean	60.72	4.65	45.41	4.42
SN_dif	2.15	3.54	1.17	4.37
NR_mean	64.82	5.16	60.39	4.27
NR_dif	−0.21	3.79	0.50	4.22
CSO	78.67	1.79	84.98	3.31

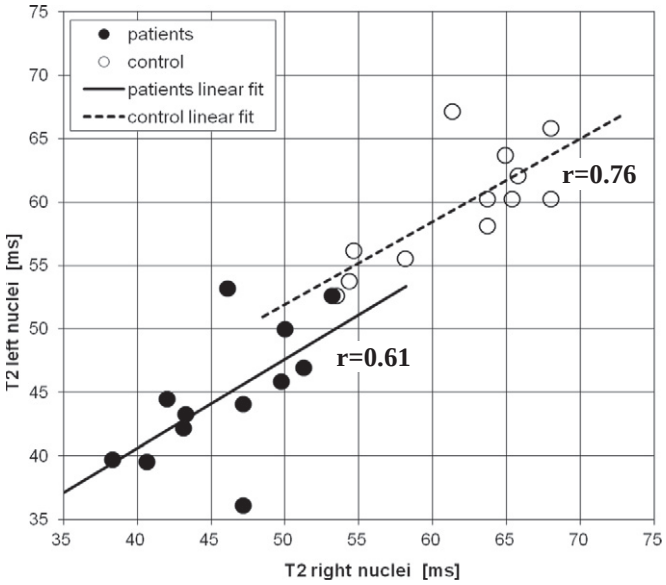

Fig. 1. Left and right SN T2r in patients and controls.

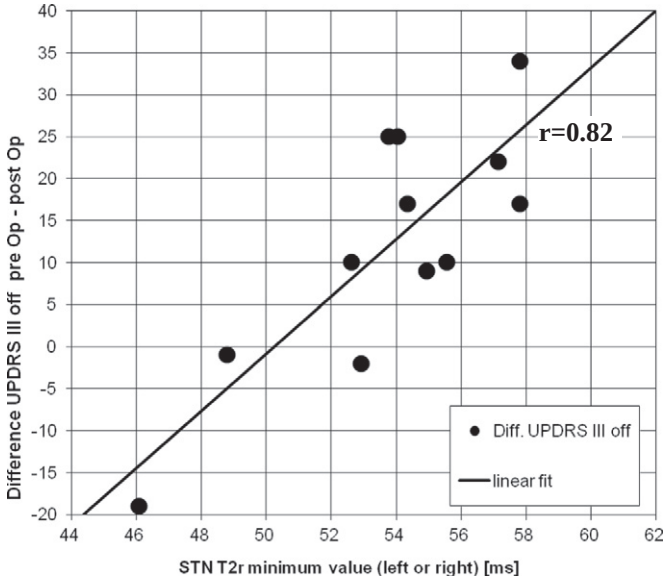

Fig. 3. Dependency of DBS outcome as determined by Δ_UPDRS_III_off on minimal T2r of STN.

Patients with a negative UPDRS outcome were revisited, their data confirmed and medical records reexamined. Patients with a negative UPDRS apparently seemed to deteriorate with rapidly progressive levodopa-resistant axial symptoms. The one patient with considerably negative outcome developed dementia.

4. Discussion

This study aimed to investigate whether decreases in the T2r in the STN and SN are predictive for motor outcome in PD. Two points stand out from our study:

1) T2r changes in the SN and in STN differentiate PD patients from HC. This finding confirms previous studies (Martin et al., 2008; Sian-Hülsmann et al., 2011) and has been confirmed by transcranial sonography (Berg, 2009). Several MRI methods are on trial for initial diagnosing PD (Ohtsuka et al., 2014). T2r is not the only MRI marker for distinction of PD and HC, e.g. resting state functional MRI, R2*, mean diffusivity and fractional anisotropy have also been found to have significant differences within the basal ganglia (Planetta et al., 2014; Prodoehl et al., 2014; Tir et al., 2014). Our findings implicate, that T2-relaxometry of STN and SN should be further evaluated to test if it offers the potential to differentiate early PD from HC and secondary Parkinson syndromes.

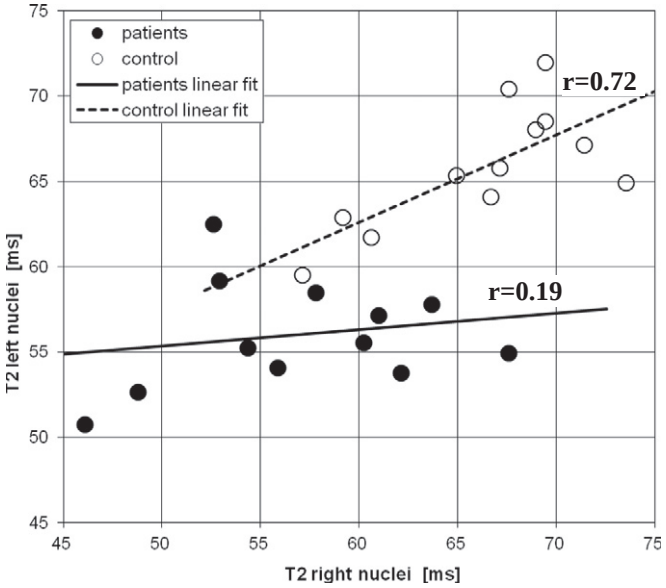

Fig. 2. Left and right STN T2r in patients and controls.

2) STN asymmetry and T2r minimum values were associated with better outcome of DBS in our patients. Lower T2r values may be reflected clinically by more severe motor impairment and thus a greater potential for improvement with DBS. It may be implicated that information gleaned from preoperative MRI may have a prognostic value and may be implemented as a potential surrogate marker for the prediction of successful DBS. Clues from our study may further implicate whether dissatisfaction with STN DBS in long term management (Farris and Giroux, 2013) can be predicted based on MRI findings. Patients with an unfavorable outcome in our cohort had worsening of levodopa-resistant axial symptoms, which are not expected to be improved by STN DBS. T2r values may be an indicator for this development.

While patients tend to show an unilateral decrease of STN T2r the laterality of symptoms was not reflected by the asymmetry of STN T2r. Lateralized manifestations of motor symptoms are characteristic for idiopathic PD (van der Hoorn et al., 2012) which, however, is invariably a bilateral disorder. During the progression of the disease laterality is usually preserved to some degree. This has until date not been correlated to intrinsic unilateral or side dominant changes within the brain on MRI. The dopaminergic innervation of the striatum is known to reflect the asymmetry of symptoms during onset and progression of PD (Marek et al., 1996). However, there is evidence to suggest that components of the basal ganglia loops are functionally connected across hemispheres (de Solages et al., 2010). This supports the observation that DBS outcome was best when at least one STN had near to normal T2r, independent of the most affected side of symptoms. Though, in context of DBS with targeting the basal ganglia, the degree of affection and laterality may impact clinical outcome (Kingsbury et al., 2010). Patients may also profit more of DBS during an earlier stage (Deuschl et al., 2013; Schuepbach et al., 2013b).

Iron depositions in the nuclei causing microstructural changes in tissue are the main factor affecting the T2r. The concept of individually regarding left and right minimum and maximum values alongside the mean T2r values takes lateralization of iron depositions into account. At which point the increasing iron content in SN or STN correlates to a clinically manifest PD is under examination. Previous studies indicated

that there is no change in SN iron content in incidental Lewy Body Disease or in pre-manifest PD, while others have found conflicting results (De Reuck et al., 2014). These findings may reflect different subgroups of PD, corresponding to the variation in motor symptoms exhibited in the disorder (Riederer and Sian-Hülsmann, 2012; Sian-Hülsmann et al., 2011). Increasing iron content in the SN in progression of PD has been described (Aquino et al., 2014a). The overall iron content in the STN did not seem to affect the outcome as neurodegeneration typically affects the SN but not the STN. Interestingly, T2r in the STN as a structural parameter nevertheless seems to correlate with clinical findings. While the mean values of STN T2r left and right provided no additional value, the minimum values of were correlated to DBS outcome with respect to UPDRS III. Very low minimum STN T2r predicted negative DBS outcome. More detailed, patients and controls differed in terms of decreased STN T2r(<58 ms) either uni- or bilaterally. The clinical data confirmed the UPDRS improvement in all but three patients, in whom levodopa-resistant axial signs worsened after neurosurgery, as has been reported in earlier studies (Benabid et al., 2009). Alternative Targets have also been considered, mainly GPi, with no relevant differences in results of UPDRS improvement (Okun et al., 2009). The latter may offer an alternative target, if the STN T2 values are very low and considered predictive for a negative outcome.

The effect of a left dominant hemisphere on DBS has been considered (Shemisa et al., 2011). The DBS performed on the dominant side was not proven to have a more beneficial effect than the non-dominant side.

Our observations on the T2 values of SN are congruent with literature (Du et al., 2012). Noteworthy is the correlation of SN minimum T2r values to the levodopa motor response (UPDRS III “off” vs. “on”). This has not been described before and should be investigated further.

A limitation of this study is the small number of patients affecting the power to detect differences. However, the correlations we report are highly significant. Our controls were recruited from a distinctly younger age group, which may result in a bias, even if no correlations with age were found. A study with age matched HC (Aquino et al., 2014b) found less pronounced T2r differences between patients and HC.

Though the initial assumption that the asymmetric iron content could correlate with asymmetric clinical disease could not be proved, the data suggest that the outcome of DBS may correlate to the maximum iron content in either of the STN. Further evaluation is needed to ensure which patients possibly have to be excluded from DBS.

5. Conclusion

The minimum T2r values of the left or right STN may be a predictive factor for motor improvement after STN-DBS.

The lateralization of the T2 values does not correlate with the more symptomatic side, but seems to indicate that the STN closest to normal values dictates the outcome. This may represent the imaging correlate to the hypothesized existence of a dominant STN.

The SN T2r values are reduced in PD patients compared to HC. Low minimal remaining SN T2r values may indicate a reduced efficacy of dopaminergic medication. Further studies are needed to evaluate the prognostic predictive value of very low minimum STN T2 values for rapid progression of treatment-resistant signs of PD after DBS and therefore unfavorable outcome.

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Conflict of interest

None.

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