Several very rare forms of dementia are associated with characteristic focal atrophy predominantly of the frontal and/or temporal lobes and currently lack imaging solutions to monitor disease. Magnetic resonance fingerprinting (MRF) is a recently developed technique providing quantitative relaxivity maps and images with various tissue contrasts out of a single sequence acquisition. This pilot study explores the utility of MRF-based T1 and T2 mapping to discover focal differences in relaxation times between patients with frontotemporal lobe degenerative dementia and healthy controls. 8 patients and 30 healthy controls underwent a 3 T MRI including an axial 2D spoiled gradient echo MRF sequence. T1 and T2 relaxation maps were generated based on an extended phase graphs algorithm-founded dictionary involving inner product pattern matching. A region of interest (ROI)-based analysis of T1 and T2 relaxation times was performed with FSL and ITK-SNAP. Depending on the brain region analyzed, T1 relaxation times were up to 10.28% longer in patients than in controls reaching significant differences in cortical gray matter ($P = .047$) and global white matter ($P = .023$) as well as in both hippocampi ($P = .001$ left; $P = .027$ right). T2 relaxation times were similarly longer in the hippocampus by up to 19.18% in patients compared with controls. The clinically most affected patient had the most control-deviant relaxation times. There was a strong correlation of T1 relaxation time in the amygdala with duration of the clinically manifest disease (Spearman Rho = .94; $P = .001$) and of T1 relaxation times in the left hippocampus with disease severity (Rho = .90, $P = .002$). In conclusion, MRF-based relaxometry is a promising and time-saving new MRI tool to study focal cerebral alterations and identify patients with frontotemporal lobe degeneration. To validate the results of this pilot study, MRF is worth further exploration as a diagnostic tool in neurodegenerative diseases.
1 | INTRODUCTION

The early diagnosis of dementia and delineation of subtypes remain a great challenge for diagnostic neuroradiology.

Frontotemporal dementia (FTD) used to be an umbrella term for clinical syndromes comprising progressive behavioral disturbances and language deficits due to focal neurodegeneration in parts of the frontal and temporal lobes (FTLD). Current classifications differentiate the behavioral variant of frontotemporal dementia (bvFTD) and three subtypes of primary progressive aphasia (PPA) specified as agrammatic variant (avPPA), semantic variant (svPPA) and logopenic variant (lvPPA) (Figure 1). The underlying histopathology is variable and includes different forms of tauopathies, TDP43-proteinopathies and atypical Alzheimer dementia (AD) pathology – the latter being associated with lvPPA ("atypical AD"). The much rarer prevalence of these syndromes compared to typical AD is a challenge and often leads to diagnostic delays.

Despite a current lack of cure, it is crucial to identify patients with dementia and patterns of frontotemporal atrophy correctly at the earliest possible moment, not only to provide optimized medical and supportive care, but also to gain deeper insight into the complex course of disease.

Clinical neuropsychological testing is the diagnostic key for bvFTD and PPA types, whereas neuroimaging is mainly used to rule out differential diagnoses and comorbidities. A majority of MRI studies dealing with differential diagnoses of these dementia forms focused on focal atrophy analyzing volumetric data or morphometric patterns. More recent studies showed alterations in functional connectivity with diffusion tensor imaging (DTI) and in brain activity with arterial spin labeling (ASL) or with BOLD imaging. Changes in neuronal connectivity observed by DTI stresses the involvement of white matter structures. Mendes et al. identified focal microhemorrhages in their cohort of FTD patients with unique focal prevalence for each sub-diagnosis.

As shown in patients with multiple sclerosis, T1 and T2 relaxometry, or mapping, detect structural tissue changes very sensitively at very early stages of the disease. These findings make frontotemporal spectrum dementias suitable for T1- and T2-relaxometric mapping analyses. The biochemical composition of a tissue, its isotropy, and its perfusion affect its T1 and T2 relaxation times as measured by MRI. Diagnostic relaxation mapping applications were already successfully implemented in Huntington's disease and AD.
T1 and T2 maps can also be generated with a recent innovation in MRI: The MR fingerprinting technique (MRF). MRF is an approach to acquire data including quantitative relaxation time maps and multiple synthetic tissue contrast weightings from a single sequence acquisition. Synthetic reconstruction of MR images in multiple weightings and quantitative mapping are feasible based on raw data from one sequence acquisition. The pseudo-random variations of flip angles, repetition times and k-space sampling yield a unique signal evolution for each voxel. This signal evolution is like a “fingerprint” for the corresponding tissue. As in criminalistics, the fingerprint is compared with fingerprints of multiple different tissues and the match with one of these fingerprints brings the diagnosis. The dictionary of these fingerprints is based on simulated signal evolutions including the range of all expected tissue relaxation parameter values. Due to the ability to obtain multiple images with different contrast weighing and parameter maps from a single sequence, MRF is potentially very timesaving in terms of acquisition, which means greater comfort especially for vulnerable patients with dementia.

This pilot study assesses whether MRF-based T1 and T2 mapping can identify focal alterations of T1 and T2 relaxation times in bvFTD/PPA patients compared to healthy controls and whether there is a correlation between relaxation times and the duration of the clinically manifest disease as well as disease severity.

2 | EXPERIMENTAL

2.1 | Study overview

This MRI study is in accordance with the ethical guidelines set for research on humans as defined by the Declaration of Helsinki and was performed with permission of the institutional ethics committee involving written informed consent of all participants or where necessary the patients’ legal guardians. Gestural consent and conclusive action regarding MRI study participation were obligatory for all patients. All 8 patients had received their diagnosis previous to study participation and were monitored by the University Hospital Bonn memory clinic. Last clinical assessment was on the day of study inclusion. Dual cerebral pathology as well as contraindications for 3 Tesla MRI were exclusion criteria. Accidental MR findings of brain pathology such as stroke resulted in secondary study exclusion of both patients and controls. 30 age-matched healthy controls between 55 and 80 years were recruited locally and received the same MR protocol as the FTD patients. Post-processing of MRF data was performed with custom-made software tools. T1 and T2 relaxation times between patients and controls as well as between subgroups of patients were compared.

2.2 | Clinical assessment

Diagnosis was based on the current clinical criteria by Rascovsky et al. for bvFTD and Gorno-Tempini et al. for PPA as well as 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in the majority of cases. Cerebrospinal fluid protein analyses were retrieved from hospital files.

Disease severity at the time of the study MRI was rated on a clinical dementia rating (CDR) scale modified for bvFTD/PPA patients (including a scale for behavioral disturbances and language impairment in addition to the five scales of the conventional CDR) by a clinician blinded to the MRI fingerprinting data (K.F.). The sum of boxes was a global measure for overall disease severity. Healthy controls needed to be without a history of any neurological disease or severe head trauma. On the day of the MRI, all controls underwent a minimal mental state examination (MMSE) to exclude obvious cases of cognitive impairment. A score of 28 and higher (out of 30) was defined as normal.

2.3 | MRI protocol

All participants were scanned with the same 3 Tesla MRI (Achieva TX, Philips Healthcare, Best, The Netherlands) using an 8-channel head coil. The scan protocol consisted of:

A 3D T1-weighted TFE sequence (repetition time/echo time (TR/TE) 7.8/3.6 ms; field of view (FOV) 256x256x130 mm; voxel size 1 mm³; 170 slices; 4 min. 26 s acquisition time), a B1 map (TR/TE 24/2.1 ms; FOV 240x240x60 mm; voxel size 2.5x2.5x5 mm; 12 slices; 2 min. acquisition time) and an axial multi-slice 2D MRF sequence (TR/TE 15/3.5 ms; FOV 240x240x60 mm; voxel size 1x1x5 mm; 12 slices; 3 min 12 s acquisition time; two spiral interleaves/slice, acquisition window 7.0 ms, acceleration factor 15). The MRF sequence completely covered the temporal and limbic lobes, insula, deep gray matter (GM) and in part frontal, parietal and occipital lobes. The spoiled gradient echo MRF sequence started with an adiabatic inversion pulse followed by an optimized flip angle sequence (0 to 60⁰) with read-outs over 500 time-points (Figure 2).
2.4 | T1 and T2 map reconstruction

MRF reconstruction was dictionary-based using the extended phase graphs (EPG) algorithm for dictionary generation including slice profile of the radio frequency pulse in the computations.\(^{27}\) T1 was sampled in 10-ms steps between 10 ms and 2000 ms, T2 was sampled in 1-ms steps between 10 ms and 200 ms, and in 10-ms steps between 210 ms and 600 ms. The dictionary also included a variation of B1 relative to its nominal value between 0.75 and 1.25 with a step size of 0.01. MRF-based T1- and T2-relaxometric maps were obtained by inner product pattern matching between the observed signal response of each voxel and the simulated signal evolutions of the dictionary (Figure 3). The matching was performed on the complex signals obtained after gridding and phase sensitive coil combination.\(^{28}\) B1 maps were used to correct both the T1- and T2-relaxometric maps for field inhomogeneity, by restricting the dictionary for MRF matching to the measured B1 value for each voxel. Further synthetic T1- and T2-weighted sequences were generated (Figure 3).

2.5 | Structural analysis

FSL 5.0 (Oxford, UK) was used to segment 3D structural data and to co-register the relaxation maps in order to extract relaxation times from the following segments/regions of interest (ROI): cortical GM, the normal-appearing white matter (NAWM), the white matter affected by periventricular leucomatous/leucomatous (where applicable) and global white matter (WM) as a sum of NAWM and leucomatous WM; Figure 4) all obtained from segmentation with FAST (part of FSL)\(^{29}\). For the definition of ROIs hard segmentations from FSL FAST, which deliver robust segmentations of each ROI – CSF, white and grey matter (WM, GM) – were used.

In order to minimize CSF contamination, the quantitative MRF maps were resampled by nearest neighbor interpolation into a 1 mm isotropic space for segmentation and afterwards down sampled into the original acquisition resolution with 5 mm slice thickness. The hippocampus, amygdala, and three deep GM structures (putamen, pallidum and caudate) were obtained from identical segmentation with FIRST (part of FSL; Figure 4). ITK-SNAP 3.6.0 was used for visualization, control of segmentation quality and segmental parameter extraction.\(^{30,31}\) A neuroradiologist corrected mismatching ROI manually on a pixel-by-pixel basis in ITK-SNAP to minimize CSF contamination of ROI or WM lesions, falsely contributing to GM. Corrections were visually controlled in all three dimensions. Main criteria were partial or complete extension of pixels into adjacent structures, or completely false identification of structures. In case of insufficient matching between region of interest and anatomical structure the structure disqualified for further analysis.

Additional skull volume-corrected brain volumetry was based on the 3D T1-weighted dataset and used to verify the visually assessed (V.K.) asymmetric atrophy of symmetric brain structures to define a more atrophy-affected hemisphere (MAH) and a less atrophy-affected hemisphere (LAH).

2.6 | Statistics

Descriptive statistics involved age and sex distributions between patients and controls, which were further analyzed by an independent sample t-test and Fisher exact tests respectively. Due to the fact that the control group size exceeded the patient group size random control subgroup validation testing was performed to rule out systematic effects of the sample size on these parameters. Descriptive statistics were extended for patient diagnostic subgroups (lvPPA, svPPA, bvFTD, FTDCrn (non-classified)). Inter-group sex ratio and leucomatous prevalence differences were statistically evaluated with Fisher exact tests. Independent sample t-tests were applied to compare T1 and T2 relaxation times between patients and controls. The latter analyses were performed twice: First, comparing ROI sorted by hemispherical side (e.g. structure left patient hemisphere with structure left control hemisphere), and second, with ROI classified by the more severely atrophy-affected hemisphere in the patients (MAH). The comparative healthy control regions of interest remained the left hemisphere for the patients’ MAH and the right hemisphere for the patients’ LAH regions of interest. Disease duration and severity of disease were correlated to T1 and T2 relaxation times (Spearman Rho).
FIGURE 3  Patient image reconstruction. Axial views of the 3D T1-weighted (3D T1w) anatomic sequence, MRF-based reconstructed synthetic T1-weighted, T2-weighted images (rec T1w, rec T2w) as well as the quantitative T1 and T2 maps with corresponding relaxation time scales in all 8 FTD patients. Patients with a right hemisphere being the more atrophy-affected hemisphere (MAH) are marked in white boxes. Note that some deliberate ceiling effect can be observed in the CSF region of the virtual T1 maps due to a limitation of T1 relaxation to 2000 ms.
3 | RESULTS

3.1 | Study participants

Of 31 control volunteers, one was rejected for analysis due to multiple older infarcts diagnosed during the study MRI.

Clinical and demographic data of the patients (5 women, 3 men) is presented in Table 1. All were right-handed assuming left-hemispherial language dominance. Mean patient age was 65.8 ± 6.8 years. Healthy controls (n = 30; 15 women, 15 men; MMSE mean ± standard deviation 29.53 ± 0.72 and patients did not differ significantly in age (66.3 ± 4.9 years; P = .52) or sex distribution (P = .69). There was no evidence for a systematic effect of the unequal sample size concerning the results based on random control subgroup analyses. Five patients were diagnosed with a form of PPA (3 lvPPA and 2 svPPA). There were two bvFTD patients. The patient diagnosed with "FTD, non-classified" (FTDnc), had a complex clinical syndrome combining bvFTD features and marked left sided apraxia and hemi-neglect due to a histologically proven tauopathy predominantly affecting the right hemisphere. Due to the rare classification of this patient it was decided to split statistical analyses either accepting or excluding the patient into the remaining group of 7. Six patients showed a left hemispherically dominant atrophy (MAH left, LAH right), while in two the right hemisphere was identified as the MAH. Leucariosis could be detected in six patients (75.0%) and six controls (20.0%) marking a significant difference in prevalence (P = .01).

3.2 | ROI-based relaxometry in patients and controls

Comparing the diagnostic subgroups, T1 and T2 relaxation times of the clinically most affected patient (with a not further specified tauopathy with frontotemporal lobe degeneration, FTDnc) showed the largest discrepancy from controls especially in T2 relaxometry, while lvPPA patients' relaxation times were most discrepant to controls when exclusively comparing the spectrum of PPA/bvFTD patients (Table 2). Because of the identification of the FTDnc as a both clinical and relaxometric outlier, all subsequent analyses were performed twice (with, n = 8, and without, n = 7, the FTDnc patient).
TABLE 1  Frontotemporal spectrum dementia patient overview

| Patient | Sex | Age (in years) | Duration of symptoms (in years) | Sub-group | More atrophy-affected hemisphere | Pathology according to CSF | FDG-PET | Severity score of communication impairment by sum of boxes |
|---------|-----|---------------|-------------------------------|-----------|---------------------------------|-----------------------------|---------|----------------------------------------------------------|
| 1       | F   | 76            | 3                             | lvPPA     | Left                            | AD                          | left frontotemporal hypometabolism | 7.5     |
| 2       | F   | 76            | 8                             | lvPPA     | Left                            | AD                          | left-dominated frontotemporal hypometabolism | 7.5     |
| 3       | M   | 61            | 6                             | svPPA     | Left                            | Non-AD                      | left-dominated frontotemporal hypometabolism | 9.5     |
| 4       | M   | 66            | 5                             | bvFTD     | Left                            | Non-AD                      | -                                  | 9       |
| 5       | M   | 62            | 6                             | lvPPA     | Left                            | AD                          | left parietal hypometabolism | 5       |
| 6       | F   | 55            | 9                             | FTDnc     | Right                           | Non-AD                      | right frontotemporal and parietal hypometabolism | 19      |
| 7       | F   | 63            | 2                             | bvFTD     | Left                            | Non-AD                      | left-dominated frontal hypometabolism | 14      |
| 8       | F   | 67            | 1                             | svPPA     | Right                           | AD                          | -                                  | 4.5     |

Patients’ cerebrospinal fluid (CSF) was analyzed for phosphotau (pTau) protein and amyloid beta 42 (Aβ42). An Alzheimer typical protein constellation (indicated as AD in the table) was defined as a Aβ42/pTau ratio smaller than 7.5. The disease severity score was built on the sum of boxes of the clinical dementia rating (CDR) scale. lvPPA: logopenic variant progressive aphasia, bvFTD: behavioral variant frontotemporal dementia, svPPA: semantic variant progressive aphasia, FTDnc: non-classified tauopathic frontotemporal dementia.

TABLE 2  Relaxation times in GM and NAWM of diagnostic subgroup and controls (in ms)

| T1 relaxometry | lvPPA (n = 3) | svPPA (n = 2) | bvFTD (n = 2) | FTDnc (n = 1) | Controls (n = 30) |
|----------------|--------------|--------------|--------------|---------------|-------------------|
| Patient        | 1533.53      | 1479.92      | 1446.81      | 1713.85       | N/A               |
| Individual GM  | 1635.21      | 1442.63      | 1495.56      |               |                   |
| Mean GM        | 1537.92 ± 95.12 | 1461.28 ± 26.37 | 1471.19 ± 34.47 | 1713.85 | 1438.63 ± 40.29   |
| Patient        | 1163.83      | 1017.78      | 1026.14      | 1192.58       | N/A               |
| Individual WM  | 1221.42      | 1056.98      | 1218.28      |               |                   |
| Mean NAWM      | 1134.83 ± 104.17 | 1037.38 ± 27.71 | 1122.21 ± 135.86 | 1192.58 | 1016.46 ± 62.90   |

| T2 relaxometry | lvPPA (n = 3) | svPPA (n = 2) | bvFTD (n = 2) | FTDnc (n = 1) | Controls (n = 30) |
|----------------|--------------|--------------|--------------|---------------|-------------------|
| Patient        | 78.86        | 62.11        | 65.45        | 50.73         | N/A               |
| Individual GM  | 76.44        | 63.98        | 64.90        |               |                   |
| Mean GM        | 73.31 ± 7.61 | 65.04 ± 1.32 | 65.18 ± 0.39 | 50.73         | 61.38 ± 10.19     |
| Patient        | 60.22        | 43.89        | 48.95        | 43.60         | N/A               |
| Individual WM  | 53.18        | 48.44        | 49.41        |               |                   |
| Mean NAWM      | 53.49 ± 6.58 | 46.17 ± 3.22 | 49.18 ± 0.32 | 43.60         | 45.47 ± 6.82      |

Caption: All relaxation times are stated in ms with standard deviation where applicable. Note that while relaxation times in all patient groups are longer than in controls in T1 and T2 relaxometry, the FTDnc patient showed a clearly shorter T2 relaxation time than the controls especially in GM (bold). bvFTD: behavioral variant frontotemporal dementia, FTDnc: non-classified tauopathic frontotemporal dementia. GM: gray matter, lvPPA: logopenic variant progressive aphasia, NAWM: normal appearing white matter, svPPA: semantic variant progressive aphasia.

Frontotemporal spectrum dementia patients (n = 8) showed significantly longer T1 relaxation times in cortical GM (P = .047), NAWM (P = .020) and global WM (P = .023; Figure 5) than healthy controls (n = 30). The T1 relaxation time in patients was significantly prolonged in both hippocampi indifferent of the predominantly atrophic side (MAH) (left hippocampus: P = .001; right hippocampus: P = .027, n = 8; Figure 5). Group differences regarding these P-values changed to P = .07 (GM), P = .05 (NAWM) and P = .056 (global WM) after exclusion of the FTDnc patient and P = .001 (left hippocampus) as well as P = .04 (right hippocampus; n = 7). When comparing relaxation times in hippocampi of FTD patients to those of controls under consideration of the MAH rather than by left–right division, absolute differences between patients and controls became more evident on the MAH (Table 3), while the hippocampus of the LAH showed T1 relaxation times closer to the controls (MAH hippocampus:...
This persisted after exclusion of the FTDnc patient ($P = .0001$ and $P = .10$ respectively; $n = 7$). Notably, relative differences between patients and controls were small (Table 3) and T1 relaxation times of deep GM structures were not significantly different between patients and controls. Also, a trend towards longer relaxation times of right-hemispherical structures in comparison to left-hemispherical structures was identified (e.g. hippocampi in FTD patients right versus left: $+34.89$ ms ($+2.17\%$); hippocampi in controls: $+43.37$ ms ($+2.98\%$; $n = 8$)).

Regional T2 relaxometric differences between FTD patients and controls were limited (Table 3). While T2 relaxation times were by tendency also longer in FTD patients for most regions, only relaxation times in the right hippocampus ($P = .025$) and amygdala ($P = .019$) showed relaxometric differences at a 5% significance level ($n = 8$; Figure 5), which remained significant after exclusion of the FTDnc patient ($P = .015$ and $P = .023$ respectively; $n = 7$). When comparing hippocampal and amygdalal T2 relaxation times of the more and respectively less atrophy-affected hemisphere with those of controls, these only differed significantly in the hippocampus of the more atrophy-affected hemisphere ($P = .003$; $n = 8$; Figure 5). This persisted after exclusion of the FTDnc patient ($P = .005$). Neither cortical GM or WM, nor deep GM structure T2 relaxation times differed significantly between FTD patients and controls. Relatively stronger than for T1 maps, longer relaxation times were observed in right-hemispheric structures compared to left-hemispheric structures again also for MRF-based T2-mapping (e.g. right versus left: hippocampi in patients: $+5.95$ ms ($+10.49\%$); hippocampi in controls: $+3.19$ ms ($+6.25\%$)).

### 3.3 Correlation of relaxation times with clinical parameters

A strong correlation between longer disease duration and longer T1 relaxation times in the left amygdala was observed (Rho = .92, $P = .001$; Figure 6). It persisted after disqualification of the FTDnc patient as an outlier (Rho = .88, $P = .008$) and also when both amygdalae were considered as one ROI (Rho = .94; $P = .001$). When separating for more and less atrophy-affected hemispheres T1 relaxometric values of the amygdala of the LAH were significantly correlated with longer T1 relaxation times (amygdala of the LAH: Rho = .814; $P = .014$), which remained significant after removal of the outlier (Rho = .811; $P = .027$).
There was a weak to moderate correlation between shorter T2 relaxation times in the left putamen and longer disease duration (left putamen: Rho = −.74; P = .035) that gained strength when separating by more and less affected hemispheres (putamen of the MAH: Rho = .84, P = .009), but did not persist after removal of values for the FTDnc outlier (Rho = −.63; P = .144).

A strong correlation between longer T1 relaxation times in the left hippocampus and disease severity (Rho = .90, P = .002; Figure 6) was observed which remained significant after outlier discrimination (Rho = .85, P = .016).

For the left pallidum a negative correlation was identified between disease severity and T2 relaxation time (Rho = −.72, P = .045), that turned stronger when separating for the MAH and LAH (MAH: Rho = −.96, P = .001; Figure 6) and remained strong when excluding the FTDnc outlier value (MAH: Rho = −.94; P = .002). A modest negative correlation was observed between severity and the T2 relaxation times in the amygdala of the MAH (MAH side: Rho = −.73; P = .04), which did not persist after exclusion of the FTDnc patient (MAH side: Rho = −.16; P = .159).

4 | DISCUSSION

In this pilot study, we could show that MRF-based T1 and T2 mapping are suitable to identify patients diagnosed with dementias involving frontotemporal lobe degeneration. Patients had longer T1 relaxation times than controls in the hippocampi but also in the cortical gray matter.

| TABLE 3 | Absolute relaxation times and their difference in percent between patients and controls in structures with significant differences between patients (n = 8) and controls (n = 30) |
|----------|----------------------------------------------------------------------------------|
| **T1 relaxometry** |                                                                                       |
| Structure                        | Difference of relaxation times in % FTD vs. control | P-value | Group | Relaxation time (in ms) |
| GM                                | 5.94%                                                                                   | .047    | Patient | 1524.07 ± 100.05 |
|                                   |                                                                                       |         | Control | 1438.63 ± 40.29 |
| NAWM                              | 9.65%                                                                                   | .020    | Patient | 1114.53 ± 92.80 |
|                                   |                                                                                       |         | Control | 1016.46 ± 62.90 |
| Global WM                         | 10.12%                                                                                  | .023    | Patient | 1119.51 ± 99.71 |
|                                   |                                                                                       |         | Control | 1016.61 ± 63.00 |
| Left hippocampus                  | 7.22%                                                                                   | .001    | Patient | 1606.93 ± 70.26 |
|                                   |                                                                                       |         | Control | 1498.74 ± 68.09 |
| Right hippocampus                 | 6.47%                                                                                   | .027    | Patient | 1641.83 ± 156.13 |
|                                   |                                                                                       |         | Control | 1542.10 ± 93.57 |
| More affected hippocampus         | 10.28%                                                                                  | .0001   | Patient | 1652.83 ± 129.40 |
|                                   |                                                                                       |         | Control | 1498.73 ± 68.09 |
| Less affected hippocampus         | 3.49%                                                                                   | .167    | Patient | 1595.93 ± 106.84 |
|                                   |                                                                                       |         | Control | 1542.10 ± 93.59 |
| **T2 relaxometry**                |                                                                                       |         |         | |
| Left hippocampus                  | 11.03%                                                                                  | .117    | Patient | 56.69 ± 11.51 |
|                                   |                                                                                       |         | Control | 51.05 ± 8.05 |
| Right hippocampus                 | 15.47%                                                                                  | .025    | Patient | 62.63 ± 7.86 |
|                                   |                                                                                       |         | Control | 54.24 ± 9.24 |
| Left amygdala                     | 1.83%                                                                                   | .741    | Patient | 52.96 ± 9.72 |
|                                   |                                                                                       |         | Control | 53.94 ± 6.77 |
| Right amygdala                    | 13.48%                                                                                  | .019    | Patient | 67.55 ± 7.38 |
|                                   |                                                                                       |         | Control | 59.54 ± 7.84 |
| More affected hippocampus         | 19.18%                                                                                  | .003    | Patient | 60.84 ± 6.73 |
|                                   |                                                                                       |         | Control | 51.05 ± 8.05 |
| Less affected hippocampus         | 7.81%                                                                                   | .297    | Patient | 58.47 ± 12.88 |
|                                   |                                                                                       |         | Control | 54.24 ± 9.24 |
| More affected amygdala            | 6.34%                                                                                   | .822    | Patient | 57.36 ± 7.79 |
|                                   |                                                                                       |         | Control | 53.94 ± 6.77 |
| Less affected amygdala            | 3.90%                                                                                   | .533    | Patient | 61.88 ± 13.86 |
|                                   |                                                                                       |         | Control | 59.54 ± 7.84 |

**Caption:** Regions of interest with significant differences between patients and controls are labeled in **bold italic** font. The contralateral structure is used for comparison. FTD: frontotemporal dementia; GM: gray matter, NAWM: normal-appearing white matter, WM: white matter. The percentages are created by division of the larger value by the smaller of each structure (A/B-1 times 100).
as well as in white matter, while relaxation times of deep gray matter brain structures (putamen, pallidum and caudate) were consistently not different between both groups. Uni-hemispheric stronger differences in relaxation times between patients and controls reflected the characteristic asymmetric atrophy in frontotemporal dementias. Finally, we found correlations between disease severity and duration with T1 and T2 relaxation times. Although a very small sample size for each subgroup substantially reduces the significance of subgroup analyses, the differences in relaxation times between these subgroups was noticeable and needs further investigation of the rare dementia spectrum.

Indications and demand for neuroimaging in dementia patients will increase due to the rising incidence of dementia in the aging population, but non-invasive MRI techniques are currently not sufficiently explored in terms of quantitative measurements beyond volumetry. Conventional T1 and T2 mapping techniques are based on measurement series with one variable parameter (flip angle or inversion time to map T1 and TE to map T2). The signal changes generated in the measurement series are a function of the respective relaxation time, whereas MRF provides a

**FIGURE 6** Correlation of relaxation times with duration of clinical symptoms and severity in frontotemporal dementia spectrum patients \((n = 8)\). A: The duration of clinical symptoms correlated well with longer mean T1 relaxation times of the amygdalae. B: A significant correlation of longer T1 relaxation times in the left hippocampus with higher clinical severity scores was observed. C: A higher clinical severity score was significantly correlated with shorter T2 relaxation times in the pallidum of the more atrophy-affected hemisphere (MAH pallidum)
AD patients could already be discriminated from healthy controls with standard mapping techniques. The relatively small differences between relaxation times of patients and controls even in significantly differing regions such as the hippocampus are in the range of differences identified by Haris et al. (all less than 10%).

Another aim was to elucidate whether one can find a representation of volumetric asymmetry also in the degree of relaxometric differences and therefore sorted regional relaxometric values by more and less atrophy-affected hemispheres (MAH/LAH). In six patients, this was the left hemisphere and in 2 it was the right. Right-sided temporal atrophy in FTD is considered an independent entity by some authors with a unique clinical course and imaging features. However, the MRF-based maps showed systematically higher relaxation times of the right hemisphere, which are not relevant when comparing the same structure between patients and controls. This systematic difference can nevertheless become a distorting factor when analyzing for the more atrophy-affected hemisphere, as then the group consists of 6 left and 2 right hemispherical structures. In T1 maps this difference is small (~2%) compared to the difference between patients and controls (up to ~7%). This explains why the MAH/LAH analysis of T1 relaxation times in the hippocampi could unveil that the hippocampi of the MAH also have a larger T1 relaxation time difference than controls.

A systematical inhomogeneity of the relaxation times in MRF-based T1 and T2 maps is most likely explained by the limited accuracy of the B1 map correction. The MRF reconstruction of this study is the most commonly applied direct dictionary matching to highly undersampled data. Recent works show that iterative reconstruction methods can further improve the precision of MRF parameter maps and allow acquisition with shorter MRF sequences.

This pilot study included eight patients split into four different diagnostic subgroups. One patient (FTDnc) not only showed a far longer course of disease than the others, but was also clinically more severely affected than the others. Her T1 and especially T2 relaxation times were furthermore discordant with trends observed in the seven other individuals and revealed outlier values (Table 2). Due to this outlier effect, it was necessary to perform all analyses both with and without disqualification of this patient, which led to differences especially regarding the correlations with clinical data. Nevertheless, it was feasible to identify relaxation times in the hippocampi of patients as significantly differing from controls both with T1 and T2 mapping. Another structure with longer relaxation times was the amygdala in T2 mapping. Both regions have already been identified as substantially atrophy-affected in patients with frontotemporal dementia types. Relaxometry here most likely reflects the biochemical changes that in part have already been identified by other techniques. T1 relaxation times in cortical GM and WM were significantly longer in patients or at least very close to after reduction of the outlier patient, which reflects that frontotemporal dementia forms affect both the GM and the WM as can be demonstrated by cortical atrophy and reduced connectivity. In this context it is noteworthy that deep GM structures did not reveal any differences between patients and controls, which could have been expected differently from volumetric studies in patients with frontotemporal dementia forms.

However, although being a small pilot, this study also attempted to explore whether substantial differences in relaxation times exist in patients with frontotemporal forms of dementia regarding the duration of disease, severity and diagnostic subgroup. It is therefore surprising that the intra-group analysis of exclusively patients identified correlations based on differences in relaxation times in a deep gray matter structure: the pallidum of the MAH. Despite this and further initial promising correlations between clinical parameters and relaxation times, such as T1 relaxation times in the amygdala and hippocampus, the small diagnostic subgroups were not uniform and hence results must be interpreted with utmost caution. They need confirmation by a larger, preferably multi-centric and diagnostically more homogeneous sample to study the capacity of MRF-based relaxometry to monitor disease progression and differentiate frontotemporal dementia subgroups. Another important target will then be the differentiability of frontotemporal from Alzheimer type dementia by MRF-based relaxometry.

Frontotemporal dementias are comparatively rare and affect the most sensitive organ to express consent and opinion: speech. This study was therefore limited to the eight current patients of our memory clinic outpatient department, who in presence of their closest caregivers either still verbally or by their action indisputably expressed their will to participate as part of a clinically indicated MRI scan.

Due to the large size of MRF raw data to be reconstructed, only partial brain coverage was included in this study and 5 mm slices were used. This represents a bias regarding the analysis of GM and WM, since coverage can vary due to brain size, and CSF contamination may be stronger in more atrophic patients compared to controls in more superficial structures in particular. However, the covered FOV is identical for both patients and controls including an identical angulation.

In conclusion, this pilot study MRF-based T1 and T2 relaxometry have the potential to become diagnostic imaging and monitoring tools for patients with frontotemporal spectrum dementias. The MRF sequence is a minor extension to a standard MR protocol and to the patients' great comfort could even shorten a lengthy protocol due its capacity to synthetically generate T1- and T2-weighted brain images. MRF should therefore be explored in larger, preferably multicentric, studies.
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