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Untersuchung der Mikrostruktur bei Epilepsiepatienten ohne Läsionsnachweis mittels quantitativer MRT-Techniken

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Zusammenfassung in deutscher Sprache

Die vorliegende Studie widmete sich der Untersuchung von mikrostrukturellen Eigenschaften im Gehirn von Patienten mit Epilepsie, bei denen im herkömmlichen Magnetresonanztomografie (MRT) keine strukturellen Anomalien festgestellt wurden. Epilepsie ist eine komplexe neurologische Störung, die durch wiederkehrende epileptische Anfälle gekennzeichnet ist.[1] Bisher wurde die Beeinträchtigung der Hirnmikrostruktur in dieser Gruppe kaum erforscht, obwohl aufgrund pathologischer Umstrukturierungen zerebraler Netzwerke, neuronaler Hyperaktivität und Hypersynchronisation ähnliche Schäden wie bei Patienten mit sichtbaren Läsionen angenommen werden könnten.

Zur Untersuchung der zerebralen Mikrostruktur wurden in dieser Studie hochauflösende quantitative T1-, T2- und Protonendichte (PD)-Verfahren in Kombination mit einer Gewebesegmentierung auf Basis synthetischer Anatomien verwendet.

Es wurden insgesamt 27 Epilepsiepatienten rekrutiert, bei denen mittels herkömmlicher MRT keine strukturellen Läsionen im Gehirn festgestellt wurden. Die MRT-Daten wurden mit einem 3-Tesla-MAGNETOM-TRIO-MR-Scanner erfasst, der mit einer 8-Kanal-Kopfspule ausgestattet war. Die quantitative MRT-Technik ermöglichte die Messung von T1-, T2- und PD Werten, um die mikrostrukturellen Eigenschaften des kortikalen Gewebes zu analysieren. Die kortikale graue Substanz wurde analysiert, indem zur Vermeidung von Partialvolumeneffekten T1-, T2- und PD-Werte aus den zentralen 20% des Kortex ausgelesen und in Oberflächendatensätzen gespeichert wurden. Die Gruppenvergleiche wurden dann mittels statistischer Analysen (allgemeines lineares Modell) und Permutationssimulationen durchgeführt, um Cluster zu identifizieren, die auf mögliche Gruppenunterschiede hinweisen. Für die weiße und tiefe graue Substanz erfolgte eine „region of interest“-basierte Analyse und eine Voxel-weise Analyse.

Die beschriebenen Analysen der quantitativen MRT-Daten zeigten keine signifikanten Unterschiede der T1-, T2- oder PD-Werte zwischen den Gruppen. Weder in der grauen noch weißen Substanz ergaben sich demnach Hinweise auf mikrostrukturelle Veränderungen bei Patienten mit MRT-negativer Epilepsie.

Die Ergebnisse zeigen, dass zukünftige wissenschaftliche Untersuchungen erforderlich sein werden, um die maßgeblichen Faktoren und Mechanismen zu ermitteln, die zur mikrostrukturellen Schädigung von Gehirngewebe in unterschiedlichen Untergruppen von Epilepsiepatienten beitragen.

Zusammenfassung in englischer Sprache

The present study aimed to investigate microstructural cerebral properties in epilepsy patients without structural anomalies detected via conventional magnetic resonance imaging (MRI). Epilepsy is a complex neurological disorder characterized by recurrent epileptic seizures.[1] Network reorganization, neuronal hyperactivity and hypersynchronization might cause microstructural changes in these patients. Still, the impairment of the cerebral microstructure in this group has been scarcely explored.

27 epilepsy patients without structural lesions detected in conventional MRI and 27 age- und gender-matches healthy control subjects were recruited. MRI data were acquired using a 3-Tesla MAGNETOM TRIO MR scanner equipped with an 8-channel head coil. The quantitative MRI techniques allowed the measurement of T1, T2, and PD values to analyze the microstructural properties of the cerebral tissue. Cortical gray matter (GM) was analyzed by extracting T1, T2, and PD average values from the central 20% of the cortex to avoid partial volume effects and storing these values in surface datasets. Group comparisons were performed using General Linear Model (GLM) analyses and permutation simulations to identify clusters indicating potential group differences. Region-of-interest-based and voxel-wise analyses of the white and deep gray matter were performed.

The analyses of quantitative MRI data revealed no significant quantitative T1, T2, or PD differences between groups in white or gray matter.

The study did not indicate microstructural changes in patients with focal MRI negative epilepsy. Future studies will have to analyze the interaction of different factors that contribute to microstructural changes in different groups of epilepsy patients.

Abkürzungsverzeichnis

DTI	Diffusion Tensor Imaging (Diffusions-Tensor-Bildgebung)
EEG	Elektroenzephalogramm
FCD	Fokale kortikale Dysplasie
GE	Gradientenecho
GLM	General Linear Model (allgemeines lineares Modell)
GM	gray matter (graue Substanz)
ILAE	International League Against Epilepsy
MNI	Montreal Neurological Institute
MP-RAGE	magnetization-prepared rapid acquisition of gradient echos
MRT	Magnetresonanztomographie
Msec	Millisekunden
MTS	mesialer Temporalsklerose
qMRT	quantitative MRT
ROI	Region of interest
SE	Spin-Echo
T	Tesla
TE	Echo Time (Echozeit)
TFCE	threshold-free cluster enhancement (Schwellenwertfreie Cluster-Verstärkung/Erkennung)
TLE	Temporallappenepilepsie
VFA	variable Flipwinkel
WM	white matter (weiße Substanz)

Übergreifende Zusammenfassung

Einleitung

Die Epilepsie ist ein anhaltendes neurologisches Leiden, welches sich durch die Neigung des Gehirns auszeichnet, wiederkehrende epileptische Anfälle hervorzubringen. Dies geht einher mit vielfältigen neurobiologischen, kognitiven, psychologischen und sozialen Konsequenzen.[1] Epileptische Anfälle wiederum sind durch übermäßige, hochgradig synchronisierte Aktivitäten von Neuronen im Hirngewebe bedingt.[1]

Im Verlauf der Jahre haben sich die Klassifikation und Terminologie von epileptischen Anfällen und Syndromen durch wiederholte Überarbeitungen seitens der International League Against Epilepsy (ILAE) stetig weiterentwickelt. Das Ziel der medikamentösen und epilepsiechirurgischen Therapie besteht darin, einen Zustand ohne Anfälle anzustreben. Dieses kann bei manchen Patienten durch die Verabreichung eines einzigen Medikaments erreicht werden, während bei anderen die Kombination mehrerer Präparate notwendig ist. Hingegen zeigen 5% bis 25%[2] der Betroffenen eine Resistenz gegenüber medikamentöser Therapie. In solchen Fällen erfordert es einer sorgfältigen Prüfung der Indikation zu invasiven Maßnahmen wie epilepsiechirurgischen Eingriffen. Diese Herangehensweise ist allerdings im Regelfall lediglich für Epilepsieformen möglich, bei denen eine begrenzte kortikale Region eine epileptogene Veränderung aufweist. Beispiele hierfür umfassen Narben, tumoröse Veränderung und strukturelle Missbildungen wie die fokale kortikale Dysplasie (FCD).

In der klinischen Praxis bildet die Magnetresonanztomografie (MRT) die primäre Methode zur Detektion solcher Pathologien. Dennoch gelingt es den herkömmlichen MRT-Verfahren nicht in allen Fällen, vorhandene Läsionen zuverlässig zu erkennen. Darüber hinaus ist anzunehmen, dass diese Verfahren nicht immer das volle Ausmaß struktureller Veränderungen erfassen können. Beispielsweise zeigten neuere Untersuchungen mittels Diffusions-Tensor-Bildgebung (DTI) bilaterale Anomalien in der weißen Substanz bei Patienten mit Temporallappenepilepsie (TLE) und einseitiger mesialer Temporalsklerose (MTS), die über das mittels konventioneller MRT sichtbare Läsionsgebiet hinausreichten.[3] Im Gegensatz zu konventionellen MRT-Techniken, die

vorrangig in der klinischen Routine Verwendung finden, vermögen quantitative MRT-Methoden die physikalischen Eigenschaften des Gewebes abhängig von dessen Mikrostruktur zu quantifizieren.[4] Hieraus lassen sich Schlussfolgerungen über die mikrostrukturelle Zusammensetzung des untersuchten Gewebes und über pathologische Veränderungen ziehen.[5]

Beispielhaft konnten in der Studie von Ahmad et al. mittels T2-Relaxometrie bei FCD-Patienten erhöhte T2-Werte außerhalb der mittels konventioneller MRT-Techniken sichtbaren FCD-Regionen festgestellt werden.[6] Dieses Resultat legt nahe, dass die strukturelle Epilepsie bei diesen Patienten zu globalen kortikalen Veränderungen führt, die jedoch mit herkömmlichen MRT-Verfahren nicht aufzudecken sind. Hierbei stellt sich die Frage, ob die hohe Anfallshäufigkeit möglicherweise die Entstehung mikrostruktureller Veränderungen in dieser Gruppe begünstigt.

Die vorliegende Dissertation widmet sich der Untersuchung mikrostruktureller Veränderungen im Gehirn von Patienten mit fokaler Epilepsie, bei denen konventionelle MRT-Untersuchungen keine Anzeichen epileptogener Läsionen aufweisen. Das Ziel dieser Arbeit ist es, mittels quantitativer MRT-Methoden festzustellen, ob mikrostrukturelle Veränderungen im Gehirn nachweisbar sind und wie diese Erkenntnisse dazu beitragen können, das Verständnis der neuropathologischen Prozesse bei fokaler Epilepsie zu vertiefen.

Darstellung des Manuskripts

Teilnehmer

In der vorliegenden Studie wurden insgesamt 27 Epilepsiepatienten, bei denen mittels konventioneller MRT-Verfahren keine strukturellen Läsionen nachgewiesen wurden, und 27 hinsichtlich des Geschlechts und Alters passende („gematchte“) Kontrollprobanden untersucht. Die Studienpopulation setzte sich aus 12 Frauen und 15 Männern sowohl in der Patienten- als auch in der Kontrollgruppe zusammen. Das durchschnittliche Alter betrug 33,1 ± 14,2 Jahre (Mittelwert ± Standardabweichung) in der Patientengruppe und 33,0 ± 13,8 Jahre in der Kontrollgruppe. Das durchschnittliche Alter bei Erstdiagnose der Epilepsie in der Patientengruppe betrug 21,0 ± 16,9 Jahre. Bei Erstdiagnose waren 56% der Patienten noch im Kindes- und Jugendalter (4 bis 17 Jahre), während 44%

der Patienten bereits das 18. Lebensjahr erreicht hatten (18 bis 62 Jahre). Die durchschnittliche Dauer der Erkrankung zum Zeitpunkt der Messung betrug 12,3 ± 7,4 Jahre. Vor der Durchführung der Studie wurde ein Votum der Ethik-Kommission des Fachbereichs Medizin des Universitätsklinikums der Goethe-Universität eingeholt. Die Studie wurde gemäß den Grundsätzen der Deklaration von Helsinki durchgeführt. Nach der Rekrutierung der Probanden am Universitätsklinikum Frankfurt wurden sie ärztlich aufgeklärt und stimmten ihrer Teilnahme schriftlich zu.

Im Anschluss an die Aufklärung und Einwilligung wurde ein Termin vereinbart, an dem die Untersuchung mit einem 3-Tesla-MAGNETOM-TRIO-MR-Scanner unter Verwendung einer 8-Kanal-Kopfspule durchgeführt wurde. Zusätzlich wurden die Patienten bezüglich ihrer Krankheitsdauer, der aktuellen und früheren Medikation, der Häufigkeit von Anfällen in den letzten drei Monaten sowie dem Zeitpunkt des letzten Anfalls befragt. Auch mögliche epileptogene Risikofaktoren, Vorerkrankungen und andere relevante medizinische Faktoren wurden erhoben.

MRT-Datenerhebung und quantitative MRT-Kartierung

Im Rahmen der Studie kam ein 3-Tesla (T) MAGNETOM TRIO MR-Scanner von Siemens Healthineers (Erlangen, Deutschland) zur Anwendung. Der Scanner war mit einer Körperspule für die Hochfrequenzübertragung und einer 8-Kanal-Kopfspule für den Signalempfang ausgestattet. Die Akquisitionsparameter sind in der zugehörigen Publikation im Detail beschrieben. Für die B1-Kartierung wurden zusammengefasst zwei Gradienten-Echo (GE)-Datensätze aufgenommen (ein Referenzdatensatz und ein weiterer Datensatz nach entsprechender Vorbereitung/Magnetisierung). Die T2-Kartierung wurde mit Hilfe von vier Fast-Spin-Echo (SE)-Datensätzen mit unterschiedlichen Echozeiten (TE) durchgeführt. Die B0-Kartierung basierte auf zwei GE-Datensätzen mit unterschiedlichen Echozeiten. Für die T1- und PD- Kartierung wurden zwei GE-Datensätze mit unterschiedlichen Anregungswinkeln aufgenommen.[7]

Daten-Nachverarbeitung und Analyse

Die weitere Datenanalyse wurde unter Verwendung von selbst erstellten Perl- und Matlab-Skripten durchgeführt. Hierbei wurden Funktionen und Programme aus der FMRIB Software Library (FSL, Oxford)[8], von MatLab (MathWorks, Natick, MA) und von FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, Boston)[9] verwendet. Die B0-Kartierung erfolgte mit FSL PRELUDE und FUGUE durch Verarbeitung der GE-Datensätze mit unterschiedlicher TE. Die Quantifizierung von T1 wurde mittels der „variable flip angle“ (VFA)-Technik durchgeführt.[7] Es wurden vorläufige T1-Karten erstellt und anschließend hinsichtlich B1- und B0-Inhomogenitäten sowie der restlichen transversalen Magnetisierung bereinigt.[10] Die PD wurde wie in der Literatur beschrieben gemessen[11], wobei die PD-gewichteten Bilder hinsichtlich T2*-, T1- und B1-Effekten sowie des spezifischen Empfangsspulenprofils korrigiert wurden. Zusätzlich wurden synthetische T1-gewichtete magnetization-prepared rapid acquisition of gradient echos (MP-RAGE) Datensätze aus quantitativen T1-Daten generiert[12] und für die Segmentierung verwendet.

Für die Gewebesegmentierung wurde der "recon-all"-Befehl der FreeSurfer-Toolbox auf die synthetischen MP-RAGE-Datensätze angewandt, und die Co-Registrierung der T2-Datensätze zu den synthetischen MP-RAGE-Datensätzen erfolgte mittels BBRegister.[13]

Um im Rahmen der kortikalen Analyse Partialvolumeneffekte von weißer Substanz und Liquor zu minimieren, wurden die T1-, T2- und PD-Werte aus der Mitte des Kortex ausgelesen[14] und in Oberflächendatensätzen abgespeichert. Die mittleren kortikalen Parameterwerte wurden mittels eines ungepaarten t-Tests zwischen den Gruppen verglichen. Im Rahmen der oberflächenbasierten Analyse wurden die T1-, T2- und PD-Oberflächendatensätze normalisiert und geglättet. Die Gruppenvergleiche wurden mit einer allgemeinen linearen Modellanalyse (GLM) durchgeführt. Um Cluster zu identifizieren, die auf mögliche Unterschiede zwischen den Gruppen hinweisen, wurden Permutationssimulationen durchgeführt. Diese Methode ermöglichte auch die Kompensation von Mehrfachvergleichen.[14]

Für die „region-of-interest“-basierte Analyse der weißen und tiefen grauen Substanz wurden entsprechende Masken erstellt, durchschnittliche

Parameterwerte in den Regionen bei den einzelnen Probanden ausgelesen und mittels ungepaarter t-Tests zwischen den Gruppen verglichen.
Die Voxel-weise Analyse der weißen und tiefen grauen Substanz umfasste Schritte mit FLIRT und FNIRT zur Normalisierung in den 152-Raum des Montreal Neurological Institute (MNI). Hiernach wurden für jede qMRT-Parameterkarte (T1, T2, und PD) Voxel-weise statistische Vergleiche zwischen den Gruppen mit FSL"randomize" unter Verwendung von threshold-free cluster enhancement (TFCE) durchgeführt.

Ergebnisse:

Bei den meisten Patienten befand sich nach elektroenzephalographischen Kriterien die epileptogene Zone entweder im frontalen (n=9) oder im temporalen Lappen (n=11). Die Anzahl der antikonvulsiven Medikamente der Patienten betrug 2 (Median) mit einer Spannweite von 1–3. Darunter waren 8 der 27 (29,6%) Patienten in dieser Periode anfallsfrei. Die übrigen Epilepsiepatienten zeigten im Durchschnitt unter Medikation vier Anfälle (Median) in den letzten drei Monaten vor der Studie.
Die oberflächenbasierte kortikale GLM-Analyse mit nachfolgender Permutationssimulation zeigte keine Cluster, die auf Gruppenunterschiede hindeuteten. Weder die mittleren kortikalen T1 Werte (Patienten: 1556,79 ± 51,14 msec, Kontrollgruppe: 1543,58 ± 41,28 msec, p=0,30) noch die PD Werte (Patienten: 80,74 ± 2,00 pu, Kontrollgruppe: 80,74 ± 1,74 pu, p=0,99) oder die T2-Werte (Patienten: 80,97 ± 2,82 msec, Kontrollgruppe: 80,46 ± 2,21 msec, p=0,46) unterschieden sich zwischen den Gruppen.
Die mittleren Parameterwerte, die aus den „regions of interest“ ausgelesen und mittels ungepaarter t-Tests zwischen den Gruppen verglichen wurden, zeigten ebenfalls keine signifikanten Unterschiede zwischen den Gruppen, weder in der weißen noch in der tiefen grauen Substanz.
Die durchgeführte Analyse auf Voxel-Ebene im standardisierten MNI-Raum zeigte keine signifikanten Cluster, die auf bedeutsame Unterschiede der untersuchten qMRT-Parameter auf Gruppenebene hinwiesen.

Diskussion

In dieser Studie wurden multimodale quantitative MRT-Techniken in Kombination mit unter anderem oberflächenbasierten Analyseverfahren angewendet, um die normal erscheinende graue und weiße Substanz bei MRT-negativen Epilepsiepatienten zu untersuchen und mit einer Kontrollgruppe zu vergleichen. In Anbetracht der anzunehmenden zerebralen Netzwerkveränderungen sowie neuronalen Hyperaktivität und Hypersynchronisation sowie der stattgehabten Anfälle in der Patientengruppe hätte vermutet werden können, dass die Patienten trotz einer unauffälligen konventionellen MRT-Bildgebung möglicherweise Veränderungen der mikrostrukturellen Gewebeintegrität im Gehirn aufweisen könnten. Allerdings konnten wir in unserer Studie keine signifikanten globalen oder regionalen Beeinträchtigungen der mikrostrukturellen Integrität des Gehirns mittels oberflächen-, „regions of interest“-basierten und Voxel-weisen Analysen feststellen.

Die in dieser Studie erfassten qMRT-Parameter werden von einer Vielzahl von mikrostrukturellen Prozessen beeinflusst. Zum Beispiel spiegeln PD-Werte die Protonenmenge und somit den Wassergehalt des Gewebes wider. Erhöhte PD-Werte könnten auf eine Ausdehnung des interstitiellen Raums z.B. bei Atrophie hindeuten.[5] Ebenso können T1-Werte Aufschluss über den Wassergehalt, aber auch den Eisengehalt des Gewebes geben.[15] Zudem lassen T1-Werte Rückschlüsse auf den Myelingehalt zu.[16] Eine erhöhte Wassermenge führt zu verlängerten T1-Zeiten, während vermehrte Eisenablagerungen und ein erhöhter Myelingehalt diese Zeiten verkürzen.[5] Die T2-Werte korrelieren mit dem Wassergehalt des Gewebes [17,18] sowie mit dem Grad der Myelinisierung.[19]

Strukturelle Gewebeveränderungen könnten möglicherweise als Folge wiederholter epileptischer Anfälle auftreten. Allerdings konnten Studien, die den Zusammenhang zwischen Anfallsfrequenz und zerebraler Atrophie untersucht haben, aufgrund unterschiedlicher Ergebnisse diese Annahme nicht eindeutig bestätigen.[6,20,21] Des Weiteren wird in der Literatur ein möglicher Zusammenhang zwischen Hirnatrophie und der Exposition gegenüber verschiedenen antikonvulsiven Medikamenten diskutiert, wobei angenommen wird, dass neurotoxische Nebenwirkungen der antiepileptischen Medikation dafür

verantwortlich sein könnten.[20] Allerdings stützten weitere Studien diese Annahme nicht.[6,22]

Erhöhte kortikale T2-Werte können auch durch gliotische Veränderungen des Gewebes bedingt sein.[23] Bei FCD-Patienten ohne Anzeichen einer kortikalen Atrophie wurde eine Verlängerung der kortikalen T2-Relaxationszeit über die FCD-Region hinaus nachgewiesen.[6] FCD-Patienten weisen allerdings im Allgemeinen eine ausgeprägte iktale Aktivität auf, welche in Zusammenhang mit den in der FCD-Gruppe gefundenen Veränderungen stehen könnte, und welche möglicherweise die der hier untersuchten Gruppe übersteigt.

Beitrag der Ergebnisse für die Beantwortung der Fragestellung

Zusammenfassend konnte mittels quantitativer MRT-Methodik in dieser Studie kein Nachweis für mikrostrukturelle Gewebeprozesse bei Patienten mit fokaler Epilepsie und unauffälligem konventionellem MRT-Befund erbracht werden, die als potenzielle mikrostrukturelle Pathologien interpretiert werden könnten. Dennoch bedarf es weiterer Untersuchungen mit alternativen Methoden, um diese Möglichkeit sicher auszuschließen. Eine eingehendere Erforschung dieses Aspekts ist entscheidend, um das Verständnis der neuropathologischen Prozesse bei fokaler Epilepsie zu vertiefen. Zukünftige Studien sollten diese Fragestellung weiter erforschen und die Komplexität dieser neurologischen Erkrankung weiter entschlüsseln.

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Focal epilepsy without overt epileptogenic lesions: no evidence of microstructural brain tissue damage in multi-parametric quantitative MRI

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Background and purpose: In patients with epilepsies of structural origin, brain atrophy and pathological alterations of the tissue microstructure extending beyond the putative epileptogenic lesion have been reported. However, in patients without any evidence of epileptogenic lesions on diagnostic magnetic resonance imaging (MRI), impairment of the brain microstructure has been scarcely elucidated. Using multiparametric quantitative (q) magnetic resonance imaging MRI, we aimed to investigate diffuse impairment of the microstructural tissue integrity in MRI-negative focal epilepsy patients.

Methods: 27 MRI-negative patients with focal epilepsy (mean age 33.1 ± 14.2 years) and 27 matched healthy control subjects underwent multiparametric qMRI including T1, T2, and PD mapping at 3T. After tissue segmentation based on synthetic anatomies, mean qMRI parameter values were extracted from the cerebral cortex, the white matter (WM) and the deep gray matter (GM) and compared between patients and control subjects. Apart from calculating mean values for the qMRI parameters across the respective compartments, voxel-wise analyses were performed for each tissue class.

Results: There were no significant differences for mean values of quantitative T1, T2, and PD obtained from the cortex, the WM and the deep GM between the groups. Furthermore, the voxel-wise analyses did not reveal any clusters indicating significant differences between patients and control subjects for the qMRI parameters in the respective compartments.

Conclusions: Based on the employed methodology, no indication for an impairment of the cerebral microstructural tissue integrity in MRI-negative patients with focal epilepsy was found in this study. Further research will be necessary to identify relevant factors and mechanisms contributing to microstructural brain tissue damage in various subgroups of patients with epilepsy.

KEYWORDS

epilepsy, quantitative MRI, tissue microstructure, voxel-wise analyses, tissue segmentation, brain networks

1. Introduction

Epilepsy is defined as a chronic condition with a sustained predisposition to epileptic seizures and resulting neurobiological, cognitive, psychological and social consequence (1). Consistent with the concept of epilepsy as a condition potentially affecting the entire brain, pathological changes of the cerebral microstructural tissue integrity in brain areas which exceeded or were remote to the putative epileptogenic focus or the presumed seizure onset zone have been reported in studies employing structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) (2, 3). Those findings include atrophy of the cerebral gray matter (GM) and extensive microstructural damage to the cerebral white matter (WM) in patients with temporal lobe epilepsy (TLE), malformations of cortical development and primary generalized epilepsy (2–7).

Besides structural imaging and DTI, quantitative (q)MRI has been used to investigate potential microstructural alterations in epilepsy patients within brain tissue appearing normal on conventional MRI. In contrast to DTI, which allows for the assessment of microstructural tissue in terms of the integrity of microstructural boundaries via the measurement of water diffusion (2), qMRI provides aggregate parameters at the voxel level that reflect microscopic tissue properties in a more differentiated manner (8, 9). Therefore, qMRI techniques may provide more profound insights into various aspects of pathological tissue alterations by depicting several distinct microstructural processes. While the interpretation of conventional MRI is mainly based on image contrast, qMRI mapping is value-based. A previous study applying quantitative T2 mapping in patients with TLE found increased T2 values even in patients without evidence of tissue atrophy or overt conspicuities in image contrast on conventional MRI (10). Furthermore, in a more recent work on patients with focal cortical dysplasia (FCD), widespread increases of cortical T2 values, widely exceeding the brain region harboring the FCD, were observed (11). These findings indicated global microstructural alterations in the cortical gray matter (GM) (11), since T2 is known to be sensitive to abnormalities in the relative myelin content, tissue iron deposition, the extra- and intracellular water content and gliotic tissue conversion (8, 12–14). Findings of cerebral microstructural tissue abnormalities have been interpreted as mainly reflecting secondary brain tissue damage as the consequence of continuously repeated ictal activity and its detrimental effects on the microstructural tissue integrity via structural and functional brain networks and cortical interconnections (10).

In general, most of the studies which assessed pathological changes of the microstructural brain tissue integrity with quantitative or structural imaging techniques included patients with known epileptogenic lesions such as FCD (11), hippocampus sclerosis previously diagnosed by conventional MRI protocols (10) or mixed patient collectives with focal epilepsies due to epileptogenic structural abnormalities of various etiologies and genetic epilepsies (15, 16). In the respective patient cohorts, the probability of extended microstructural tissue damage might be relatively high due to the presence of an already present circumscribed and clearly localized epileptogenic pathology and seizure onset zone.

In this study, we sought to investigate whether epilepsy patients with inconspicuous structural MRI (MRI-negative) and without evidence suggesting a genetic or metabolic etiology, exhibit signs of a microstructural pathology as a correlate of altered functional brain networks in comparison to a cohort of age-matched healthy control subjects. For this purpose, multiparametric qMRI with T1, T2, and proton density (PD) mapping was used, together with tissue segmentation based on synthetic anatomies and comprehensive analyses of qMRI parameters, including both a region-of-interest (ROI)-based approach and voxel-wise analyses.

2. Materials and methods

2.1. Participants

A total of 27 epilepsy patients (mean age 33.1 ± 14.2 years) for whom neuroradiological assessment based on clinical 3 Tesla (T) MRI data including an epilepsy-specific protocol (17) did not unveil a structural lesion (MRI-negative) and 27 healthy control subjects (mean age 33.0 ± 13.8 years) were recruited. The sex distribution was equal in both groups (n = 12 (44.4%) females in the patient and in the control group, respectively). The study was approved by the local IRB (Ethik-Kommission des Fachbereichs Medizin der Goethe-Universität). The patients/participants provided written informed consent to participate in this study. The study was performed according to the principles formulated in the Declaration of Helsinki.

2.2. Acquisition of MRI data

A 3T MAGNETOM TRIO MR scanner (Siemens Healthineers, Erlangen, Germany) was used for MRI data acquisition. This scanner is equipped with a body coil required for radio frequency (RF) transmission and with a phased-array head coil with 8 channels for signal reception.

T2 mapping was based on four fast spin echo (SE) datasets acquired with different TE. The parameters of the acquisition were the same as described earlier (11): matrix size = 256 × 176, slice thickness = 2 mm (no inter-slice gap), spatial resolution = 1 × 1 × 2 mm^3, number of axial slices = 69, interleaved slice sampling, field of view (FOV) = 256 × 176 mm^2, TR = 10 s, TE = [13, 67, 93, 106] ms, turbo factor = 13, echo spacing = 13.3 ms, bandwidth = 176 Hz/pixel, parallel imaging (reduction factor of 2), partial Fourier factor 6/8, refocusing angle = 160°, acquisition time for each dataset 1:32 min. Because each of the datasets was acquired twice for averaging purposes, the total acquisition time was 12:16 min.

For B1 mapping, a reference gradient echo (GE) and a magnetization prepared GE dataset were acquired. An RF-pulse followed by a crusher gradient was utilized for magnetization preparation, rotating the longitudinal magnetization by an angle β (nominal value $\beta_0 = 45°$). The other acquisition parameters were: matrix size = 64 × 56, slice thickness = 4 mm (no gap), isotropic spatial resolution = 4 mm, number of sagittal slices = 40, FOV =

256 × 224 mm^2, TR = 11 ms, TE = 5 ms, α = 11°, centric phase encoding, bandwidth=260 Hz/pixel, duration = 0:53 min.

B0 mapping was based on two GE datasets with different TE: matrix size, slice thickness, FOV, isotropic resolution, number of sagittal slices as described above for B1 mapping, TR = 560 ms, TE [1,2] = [4.89, 7.35] ms, bandwidth = 200 Hz/pixel, α = 60°, duration = 1:03 min, export of magnitude and phase data.

For T1 and PD mapping two spoiled GE datasets at different excitation angles ($\alpha_{1,2}$) were recorded. This approach results in different signal intensities (I) in both images. The parameters were: same volume coverage as described for B0 and B1-mapping, matrix size = 256 × 224 × 160, FOV = 256 × 224 × 160 mm^3, isotropic spatial resolution = 1 mm, TR =16.4 ms, TE = 6.7 ms, $\alpha_{1,2}$ = [4, 24]°, bandwidth = 222 Hz/pixel, acquisition duration (for both datasets): 9:48 min.

Signal loss in the variable flip angle (VFA) data caused by T2* relaxation effects occurring during the finite TE of 6.7 ms were compensated. To this aim, two GE datasets with different TE were recorded. The acquisition parameters were: same volume coverage as for T1, B1, and B0 mapping, matrix-size = 128 × 112, FOV = 256 × 224 mm^2, isotropic spatial resolution = 2 mm, number of sagittal slices = 80, slice thickness = 2 mm (no gap), TR = 1,336 ms, TE [1,2] = [4.3, 11] ms, α = 50°, bandwidth = 292 Hz/pixel, acquisition duration for both datasets: 5 min.

2.3. Quantitative MRI (qMRI) mapping

The analyses were performed with custom-built Perl (version 5.30) and Matlab scripts. Functions and programs included in the FMRIB Software Library (FSL, Oxford, version 5.0.7) (18), in Matlab [MathWorks, Natick, MA, version R2012b (8.0.0.783)], and in FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, Boston, version 6.0.1) (19) were used.

The single fast SE datasets for T2 mapping were co-registered to a common reference to account for motion artifacts. Subsequently, the datasets with identical TE were averaged for SNR improvement. T2 was estimated by exponentially fitting the dependence between the signal intensities in the averaged T2-weighted datasets and TE. Correction for the influence of stimulated echoes was performed as reported in the literature (20).

The applied B1 mapping algorithm was previously described in the literature (21). In summary, the magnetization prepared dataset was divided by the reference dataset (without magnetization preparation) to determine the cosine of the local preparation angle β B1 then followed from the quotient of β and the nominal value β_0. For B0 mapping, the phase differences between the two GE datasets acquired with different TE were analyzed with FSL PRELUDE and FUGUE.

The measurement of T1 was based on the VFA method (22). To account for motion artifacts, the two datasets acquired at different excitation angles were co-registered. Subsequently, the excitation angles $\alpha_{1,2}$ = [4, 24]° and the resulting signal intensities $I_{1,2}$ were utilized to plot $I_i/\sin(\alpha_i)$ vs. $I_i/\tan(\alpha_i)$, yielding a straight line with the slope exp(-TR/T1) from which preliminary T1 maps were derived and subsequently corrected for B1 and B0 inhomogeneities and for insufficient spoiling of the transverse magnetization (23).

Measurement of PD was performed as reported in the literature (24). In summary, the co-registered VFA dataset acquired with the lower excitation angle (which is PD weighted) was further processed to compensate for T2*, T1, and B1 effects and for the specific profile of the receive-coil.

For segmentation purposes, synthetic T1-weighted magnetization-prepared rapid acquisition of gradient echoes (MP-RAGE) datasets were calculated from quantitative T1 maps as described previously (25, 26). The following virtual acquisition parameters were utilized: matrix size = 256 × 224 × 160, field of view = 256 × 224 × 160 mm^3, isotropic resolution = 1 mm, TR = 1,900 ms, TI = 900 ms, α = 9°, echo spacing = 8.1 ms.

2.4. Data post-processing and analysis

The tissue segmentation was performed via the "recon-all" command implemented in Freesurfer utilizing the synthetic MP-RAGE datasets. PD and T1 maps, which had the same orientation as the synthetic anatomies, were transferred to the Freesurfer space and the tool BBRegister (27) was used for the boandary-based coregistration of the T2 maps to the synthetic MP-RAGE anatomies.

2.4.1. Cortical analysis

For analysis of the cortical GM, the T1, T2, and PD values were read in the middle 20% of the cortical layer (28) and stored in surface datasets. This approach was followed to reduce partial volume effects (PVE) with WM and cerebrospinal fluid (CSF). For the analysis of global qMRI parameter values across the entire cortex as an initial evaluation for group comparisons, average cortical T1, T2, and PD values were calculated for each subject, including all non-zero vertices into this calculation. Values were compared between both groups via two-sided unpaired *t*-tests. For surface-based cortical group analysis, the T1, T2, and PD surface datasets were normalized to the average subject ("fsaverage") and smoothed (Gaussian kernel, full width at half maximum = 10 mm). Cortical T1, T2, and PD values after normalization and smoothing are shown for a representative epilepsy patient in Figure 1. Employing the script mri_glmfit, general linear model (GLM) analyses were calculated for surface-based comparisons between groups. Permutation simulations (vertex-wise threshold = 0.001, cluster-wise threshold = 0.05) were performed to identify clusters indicating significant differences between groups and to compensate for multiple comparisons.

2.4.2. Region-of-interest-based WM and deep GM analysis

WM masks excluding WM lesions and combined bilateral deep GM masks (including the caudate nucleus, putamen, thalamus and pallidum) were derived from the Freesurfer segmentation results. Partial volume effects from cerebrospinal fluid (CSF) were reduced by eliminating pixels with T1 values > 2,000 ms from the masks (29). The masks were co-registered to the T2 maps, while the T1 and PD maps had the same orientation as the MP-RAGE datasets and the resulting tissue masks. Similar

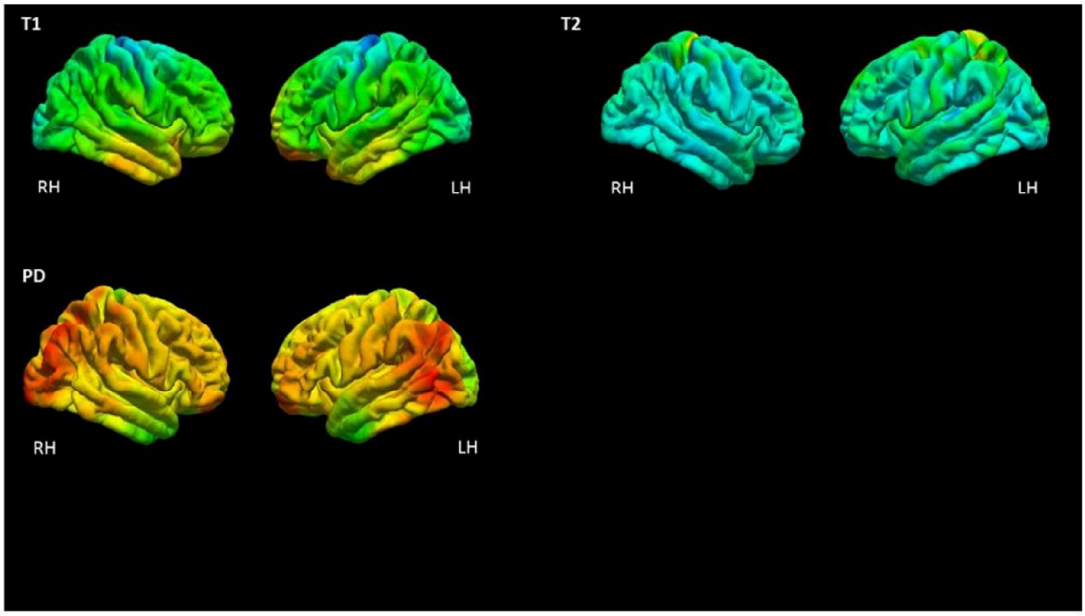

FIGURE 1
Illustration of qMRI values of a representative epilepsy patient after sampling from the middle 20% of the cortical ribbon and mapping to the surface (corresponding to a projection fraction 0.4–0.6 of the entire cortical layer). Values are shown on the pial surface of the average subject ("fsaverage") created by the Freesurfer software after smoothing with a Gaussian kernel (full width at half maximum = 10 mm) as used for the GLM analysis. RH, right hemisphere; LH, left hemisphere; ms, milliseconds; p.u., percent units.

to the analyses performed in cortical GM, mean parameter values were extracted from the WM and deep GM ROIs as a first evaluation and compared between groups using two-sided unpaired *t*-tests.

2.4.3. Voxel-wise WM and deep GM analysis

First, the quantitative T2 datasets were linearly co-registered to the synthetic anatomies using FSL FLIRT. For the PD and T1 maps, this step was not required since these parameter maps had already the same orientation as the anatomies. The WM masks excluding WM lesions and the deep GM masks obtained from the Freesurfer segmentation were applied to the quantitative maps to isolate voxels in these regions in order to generate T1, T2 and PD maps of the WM and the deep GM. Spatial normalization of the MP-RAGE anatomies into Montreal Neurological Institute (MNI) 152 space was performed by non-linear registration (FSL FNIRT) after linear initialization with FLIRT (Figure 2). Afterwards, the co-registration matrices (from the T2 map to the MP-RAGE anatomies for the T2 values and from the MP-RAGE datasets to MNI space) for all parameters were applied to the WM and deep GM T1, T2 and PD maps for normalization (Figure 2). Voxel-wise statistical group comparisons were calculated with RANDOMIZE as included in the FSL toolbox, using threshold-free cluster enhancement (TFCE) to compensate for multiple comparisons. The cluster-wise significance level was set to $p < 0.05$.

2.5. Statistical analysis

Two-sided unpaired *t*-tests were used to perform group comparisons of the qMRI mean parameter values in cortical GM, deep GM, and cerebral WM. *P*-values below 0.05 were considered significant for all statistical tests. Due to the exploratory character of the study and the small number of tests with three parameters investigated, no correction for multiple comparisons was performed for the group comparisons of mean parameter values in the cortical and deep GM as well as in the cerebral WM.

3. Results

3.1. Clinical baseline characteristics of epilepsy patients

In the majority of patients, the epileptogenic zone was located either in the frontal ($n = 9$) or in the temporal lobe ($n = 11$), according to recurrent localization-typical or stereotyped seizures and focal interictal or ictal epileptiform discharges on electroencephalography (EEG). The median number of antiseizure medication (ASM) was $n = 2$ in the patient group [interquartile range (IQR) 1–3]. The median number of seizures in the last 3 months before inclusion in the study was 4 (IQR 0–12). $N = 8$ patients (29.6%) had been completely seizure-free in the last 3 months before enrolment. Demographic and clinical

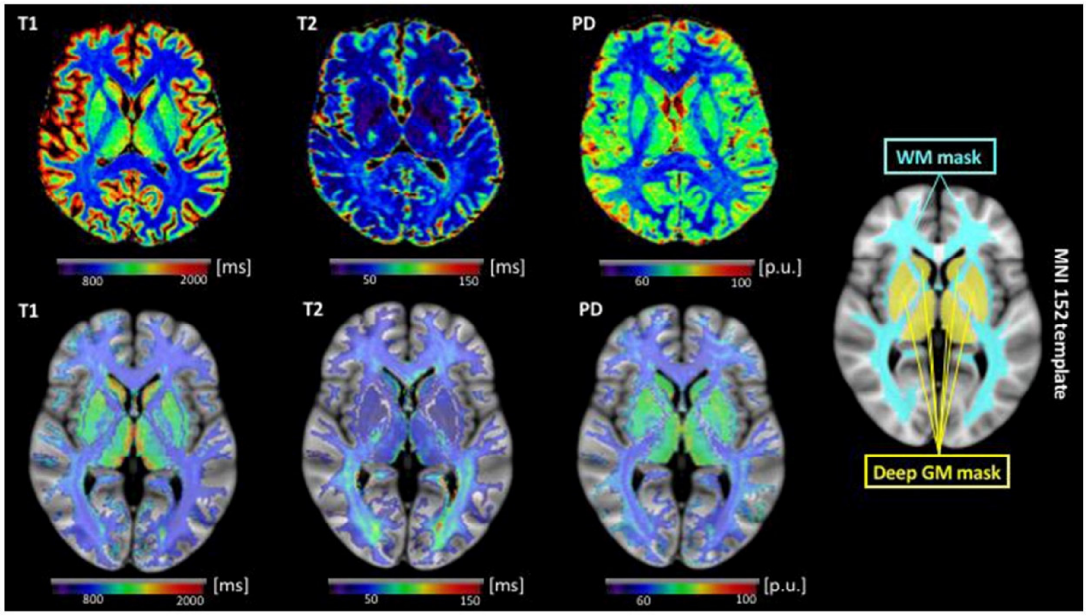

FIGURE 2
Illustration of qMRI parametric maps after co-registration to the respective synthetic anatomy **(top row)** and data preparation for the voxel-wise analysis of the cerebral WM and deep GM in MNI standard space **(bottom row)** for a representative epilepsy patient (same as in Figure 1). In the **bottom** row, below each parametric map, the corresponding WM and deep GM extracted from the parametric map by the means of the individual tissue segmentation is shown after non-linear co-registration to MNI standard space. Here, a transparency of 50% on the background was applied to the parametric maps to allow for visualization of the alignment of the segmented maps with the underlying anatomy. For the voxel-wise analysis between patients and control subjects with FSL randomize, the calculations were restricted to the binary WM and deep GM masks shown on the right, for minimization of partial volume effects. ms, milliseconds; p.u., percent units; WM, white matter; GM, gray matter; MNI, Montreal Neurological Institute.

baseline characteristics for patients and healthy control subjects are summarized in Table 1.

3.2. Analysis of qMRI parameters

3.2.1. Cortical qMRI parameters

After averaging of the cortical qMRI parameter values across the surface, there were no significant differences for mean cortical T1 (patients vs. controls: 1,556.79 ± 51.14 vs. 1,543.58 ± 41.28 ms), T2 (patients vs. controls: 80.97 ± 2.82 vs. 80.46 ± 2.21 ms), and PD values (patients vs. controls: 80.74 ± 2.00 vs. 80.74 ± 1.74 p.u.) between patients and control subjects (Figure 3). Furthermore, the surface-based cortical GLM-analysis did not reveal any cluster indicating group differences after compensation for multiple comparisons, neither for T1, T2 nor for PD.

3.2.2. QMRI parameters in the cerebral WM and deep GM

The ROI-based analyses of qMRI parameters for cerebral WM and deep GM did not reveal any significant differences for mean T1, T2, and PD values between the groups. Mean values and SD for T1, T2, and PD in cerebral WM and deep GM are summarized in Table 2. Furthermore, the voxel-wise analysis performed in MNI standard space did not show any significant cluster indicating significant differences for the investigated qMRI parameters on a group level.

4. Discussion

In this study, multiparametric qMRI was used to investigate possible pathological alterations of the brain tissue microstructure in patients with focal epilepsies and inconspicuous structural MR imaging at a group level. To this end, mean qMRI parameter values across the entire cortical GM, the deep GM, and the cerebral WM were analyzed along with voxel-wise group comparisons of qMRI parameter values for these tissue compartments in standard space. Voxel-based quantification (VBQ) (30) is an alternative approach of performing tissue-specific analyses of qMRI parameter maps, which in principle is similar to the approach employed in this study and has been well-described in the literature. We found no significant differences between the patient and the control group for global qMRI parameter values across the different tissue classes. Furthermore, no significant clusters for group differences in qMRI parameters could be identified in voxel-based analysis.

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TABLE 1 Demographic and clinical baseline characteristics for patients and control subjects.

	Patients ($n = 27$)	Control subjects ($n = 27$)
Age [years] (Mean ± SD)	33.1 ± 14.2	33.0 ± 13.8
Female sex [n (%)]	12 (44.4%)	12 (44.4%)
Disease duration [years] (Mean ± SD)	12.2 ± 7.72	
Seizures in the last 3 months [n] [Median (IQR)]	4 (0–12)	
Present ASM [n] [Median (IQR)]	2 (1–3)	
Overall ASM in medical history [n] [Median (IQR)]	3 (2–6)	
Epileptogenic zone [n (%)]		
A frontal/frontocentral	9 (33.3%)	
B temporal	11 (37.1%)	
C occipital/temporooccipital	4 (14.8%)	
D other/unknown[a]	4 (14.8%)	

SD, standard deviation; IQR, interquartile range; ASM, antiseizure medication. [a]localization of epileptogenic zone not exactly known (suspected left-hemispheric: $n = 2$, suspected right-hemispheric: $n = 1$, completely unknown: $n = 1$).

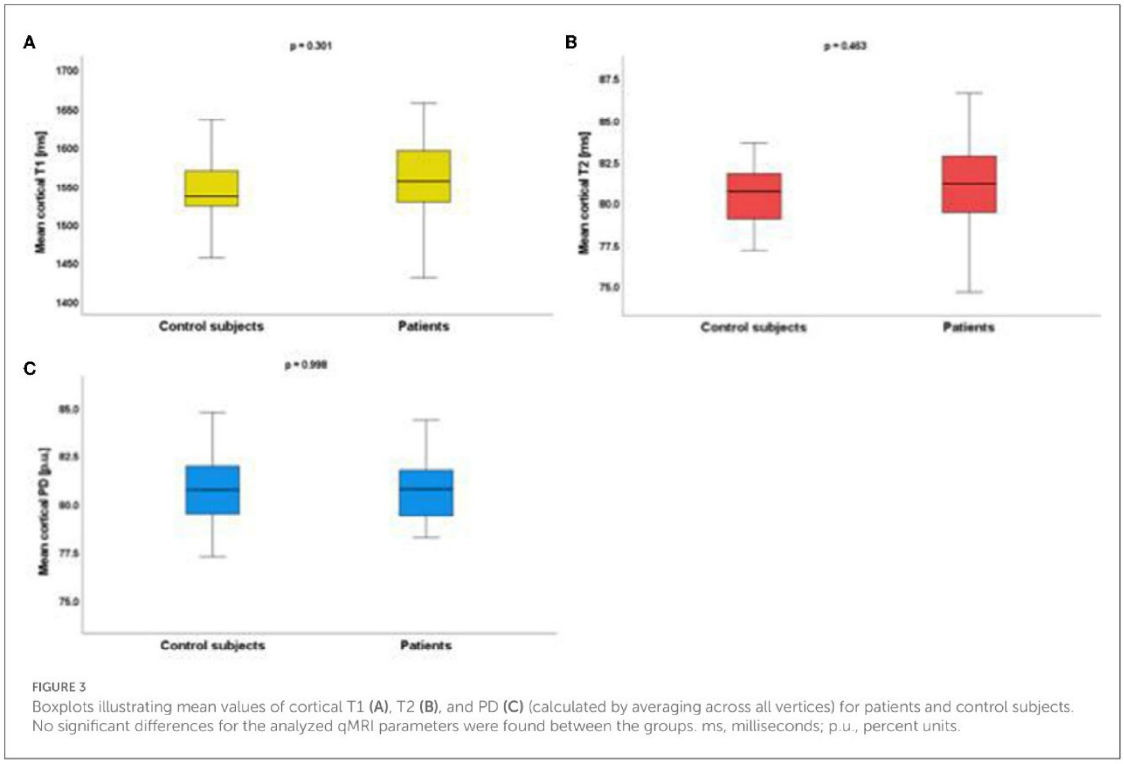

FIGURE 3
Boxplots illustrating mean values of cortical T1 **(A)**, T2 **(B)**, and PD **(C)** (calculated by averaging across all vertices) for patients and control subjects. No significant differences for the analyzed qMRI parameters were found between the groups. ms, milliseconds; p.u., percent units.

Since increased network connectivity with hyperexcitability and neuronal hypersynchronization must be hypothesized in epilepsy patients with a sustained predisposition to epileptic seizures, it is generally plausible to assume that patients with focal epilepsy may exhibit pathological alterations of the cerebral tissue microstructure despite unremarkable conventional MRI without evidence of epileptogenic lesions. However, given the lack of significant differences in qMRI parameters between patients and healthy control subjects, our results do not point toward a relevant impairment of the cerebral microstructural tissue integrity in epilepsy patients without overt epileptogenic lesions in structural imaging. The qMRI parameters acquired in this study cover

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TABLE 2 Mean qMRI parameter values obtained from the cerebral white matter and deep gray matter in patients and control subjects.

	Patients ($n = 27$)	Control subjects ($n = 27$)	p-value
WM			
T1 [ms] (Mean ± SD)	894.07 ± 57.08	886.48 ± 57.1	0.298
T2 [ms] (Mean ± SD)	62.15 ± 12.99	62.66 ± 12.59	0.431
PD [p.u.] (Mean ± SD)	66.24 ± 3.41	66.46 ± 3.47	0.789
Deep GM			
T1 [ms] (Mean ± SD)	1,249.95 ± 158.94	1,242.18 ± 157.37	0.287
T2 [ms] (Mean ± SD)	58.6 ± 12.47	60.33 ± 13.21	0.762
PD [p.u.] (Mean ± SD)	75.79 ± 5.93	76.24 ± 5.56	0.993

WM, white matter; GM, gray matter; ms, milliseconds; SD, standard deviation; p.u., percent units.

a broad range of microstructural processes potentially involved in pathological tissue remodeling. PD is a surrogate marker of microstructural tissue atrophy, since increased PD values indicate an enlargement of the interstitial space and thus a (relative) reduction of the local tissue volume fraction (31, 32). Quantitative T1 mapping is sensitive to changes of the tissue water and myelin content as well as tissue iron deposition (33, 34), while T2 mapping especially detects demyelination, microstructural axonal injury and gliotic tissue conversion (13, 14). Furthermore, quantitative T2 is particularly sensitive to tissue net water uptake, including both an enlargement of the extracellular space due to interstitial edema (e.g., due to increased permeability of the blood-brain-barrier) and cellular swelling due to intracellular edema, e.g. caused by excitotoxicity (35–37).

Based on structural imaging with volumetric assessment of the cerebral GM, pathological changes of the cerebral microstructure reflected by tissue atrophy and progressive cortical thinning have been described in a variety of epilepsy syndromes (15, 16, 38). Several of these studies included mixed patient collectives, which were not explicitely stratified according to the presence of a putative epileptogenic lesion (15, 16, 38). Patients with TLE represented the majority of patients, respectively an important subgroup in those studies (15, 16, 38). Since seizure activity is potentially based on or even contributes to altered structural networks, an association between seizure frequency and atrophic tissue alterations seems generally plausible. However, studies investigating the correlation between seizure frequency and cerebral atrophy yielded inconsistent results and the association could not be shown in a reproducible manner (16, 39–41). For instance, a comprehensive longitudinal study by Liu et al. found no association between structural parameters and seizure recurrence (16). Rather, an association between atrophy and exposure to multiple anticonvulsive drugs, driven by neurotoxic side effects of the antiepileptic medication, was suggested (16). Galovic et al. did not find any association between accelerated cortical thinning and seizure frequency or the antiepileptic drug load (38).

The microstructural processes underlying or potentially preceding cerebral atrophy in epilepsy patients are largely unknown. A recent study on epilepsy patients with FCD but no evidence of cortical atrophy reported widespread prolongation of cortical T2 relaxation times, with increases of cortical T2-values extending far beyond the area harboring the FCD, both in the ipsilateral and the contralateral hemisphere (11). The mechanisms underlying the observed cortical T2 changes are not entirely clear. Since a previous study described that hippocampal T2 increases correlate with gliosis in patients with TLE (42), it is conceivable that gliotic tissue changes either cause a prolongation of the tissue parameter T2 or influence the T2 measurement (11). Cortical regions harboring the FCDs were mainly located in the frontal and temporal lobe as well as in the cingulum, where also the most pronounced cortical T2 increases were detected on a group level after correction for multiple comparisons (11). FCDs were shown to alter the cerebral functional and structural connectivity (43, 44), a finding suggesting that FCDs might be the underlying cause of a network disease affecting the whole-brain network. Therefore, it might be possible that pathological microstructural tissue remodeling in patients with focal epileptogenic brain lesions is related to a pathological network reorganization with a sustainably altered neuronal activity, irrespective of the actual seizure frequency or the antiepileptic medication. Alterations of the large-scale brain network structure involving network hyperactivity and increased connectivity have been linked to network hyperexcitability, neuronal hypersynchronization and seizure predisposition (45–47), which are associated with (reactive) astrogliosis (48, 49). Furthermore, altered neuronal activity may yield an impact on the permeability of the blood-brain-barrier (50, 51) as another microstructural process affecting cortical T2.

Epilepsies result from a pathological alteration of a functional network instead of a specific region. Such alterations can be assumed to affect also MRI-negative epilepsy patients (52) but it can be speculated that they might be less pronounced with smaller and rather short-term effects on the functional connectivity and neuronal activity than for patients with abnormalities on structural imaging, thus potentially causing less widespread alterations of the tissue microstructure with a smaller magnitude. Therefore, in contrast to previous findings in patients with epileptogenic lesions, multiparamteric qMRI might not be sensitive enough to detect alterations of the cerebral microstructure in focal epilepsy patients with inconspicuous conventional MRI.

4.1. Limitations

Despite several strengths, which include especially the comprehensive qMRI protocol and the detailed analyses of various tissue classes, this study is not without limitations. First, the

sample size in this study is relatively small, which might have limited the detectability of smaller changes in qMRI parameters in patients compared to controls. Furthermore, the epilepsy patients included in this study were heterogeneous in terms of the type of epilepsy, respectively the (presumed) seizure onset zone, disease duration, seizure frequency and antiepileptic medication (Table 1). We cannot exclude an impact of the heterogeneity concerning the clinical characteristics within the patient collective on our results. Since this is not a longitudinal study, we are not able to comment on potential changes of qMRI parameters in epilepsy patients across time and their relation to seizure frequency and ASM. Finally, although the applied qMRI techniques cover a variety of distinct microstructural processes in terms of their sensitivity to pathological tissue alterations, we cannot exclude that cerebral microstructural changes in epilepsy patients might not be detected with the methodology employed in this study. In order to investigate the nature of potential microstructural tissue alterations in patients with focal epilepsy, histological examinations along with a validation of qMRI parameters, e.g., in patients undergoing epilepsy surgery, would be of major interest.

5. Conclusions

This multiparametric qMRI study did not reveal any evidence of a relevant global or regional impairment of the brain microstructural integrity in focal epilepsy patients with inconspicuous structural imaging in terms of a potentially epileptogenic structural pathology, suggesting no permanent microstructural tissue damage related to seizure activity in these patients. A future study on a more homogeneous patient collective, which takes global and regional network structures and connectivity into account and allows for mapping of connectivity changes and network hyperexcitability, would be of interest to further evaluate the utility and sensitivity of multiparametric qMRI for detecting alterations of the cerebral microstructure in MRI-negative patients with focal epilepsy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission des Fachbereichs Medizin, Goethe-Universität Frankfurt. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CH: conceptualization of the study, literature research, collection of clinical data, data analysis and interpretation, and writing. MM: conceptualization of the study, literature research, collection of clinical and imaging data, data interpretation, and writing. MW and SK: conceptualization of the study, literature research, collection of clinical and imaging data, data interpretation, and critical review of the manuscript. UN and RD: development of the quantitative MR imaging technique, data analysis, and critical review of the manuscript. R-MG: conceptualization of the study, literature research, MR image analysis, and statistical. AS: conceptualization of the study, literature research, MR image analysis, statistical analysis, and writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Darstellung des eigenen Anteils an der Publikation

C. Hamid trug zur Organisation der Studie bei und erhob selbstständig MRT-Daten. Sie führte die Auswertung unterstützt durch den Betreuer durch. Das Manuskript wurde durch sie selbstständig unter Supervision durch Prof. Dr. med. Gracien und unterstützt durch die Co-Autoren verfasst, eingereicht und überarbeitet.

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Lebenslauf

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Forschungsarbeiten

Laufende publikationsbasierte Promotion	„Epilepsy without overt epileptogenic lesions: no evidence of microstructural brain tissue damage in multiparametric quantitative MRI"
Erfolgreiche Publikation als Co-Autorin	„Multiparametric quantitative MRI reveals progressive cortical damage over time in clinically stable relapsing-remitting MS"; veröffentlicht am 11.05.2023 in Journal of Neurology, Neurosurgery, and Psychiatry

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Besondere Kenntnisse

Softwarekenntnisse	ORBIS
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Sprachkenntnisse	Deutsch: Muttersprache Dari Muttersprache Englisch Gute Kenntnisse Urdu Mittlere Kenntnisse Französisch Einsteiger Latein 6-jährige Schulausbildung

Mönchsdeggingen, den 27.09.2023

Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang-Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Untersuchung der Mikrostruktur bei Epilepsiepatienten ohne Läsionsnachweis mittels quantitativer MRT-Techniken

am Zentrum der Neurologie und Neurochirurgie, in der Klinik für Neurologie unter Betreuung und Anleitung von Prof. Dr. René-Maxime Gracien mit Unterstützung durch Dr. Alexander Seiler ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden in folgendem Publikationsorgan veröffentlicht:

Hamid C, Maiworm M, Wagner M, Knake S, Nöth U, Deichmann R, Gracien RM, Seiler A. Focal epilepsy without overt epileptogenic lesions: no evidence of microstructural brain tissue damage in multi-parametric quantitative MRI. Front Neurol. 2023 Jul 17;14:1175971. doi: 10.3389/fneur.2023.1175971.

Mönchsdeggingen, _____ _____

(Ort, Datum) (Unterschrift)