EPILEPSY CURRENTS

Current Literature

In Clinical Science

Quantitative Measurement of Longitudinal Relaxation Time (qT1) Mapping in TLE: A Marker for Intracortical Microstructure?

Preferential Susceptibility of Limbic Cortices to Microstructural Damage in Temporal Lobe Epilepsy: A Quantitative T1 Mapping Study.

Bernhardt BC, Fadaie F, Vos de Wael R, Hong SJ, Liu M, Guiot MC, Rudko DA, Bernasconi A, Bernasconi N. Neuroimage 2017. In press.

The majority of MRI studies in temporal lobe epilepsy (TLE) have utilized morphometry to map widespread cortical alterations. Morphological markers, such as cortical thickness or grey matter density, reflect combinations of biological events largely driven by overall cortical geometry rather than intracortical tissue properties. Because of its sensitivity to intracortical myelin, quantitative measurement of longitudinal relaxation time (qT1) provides an in vivo proxy for cortical microstructure. Here, we mapped the regional distribution of qT1 in a consecutive cohort of 24 TLE patients and 20 healthy controls. Compared to controls, patients presented with a strictly ipsilateral distribution of qT1 increases in temporopolar, parahippocampal and orbitofrontal cortices. Supervised statistical learning applied to qT1 maps could lateralize the seizure focus in 92% of patients. Intracortical profiling of qT1 along streamlines perpendicular to the cortical mantle revealed marked effects in upper levels that tapered off at the white matter interface. Findings remained robust after correction for cortical thickness and interface blurring, suggesting independence from previously reported morphological anomalies in this disorder. Mapping of qT1 along hippocampal subfield surfaces revealed marked increases in anterior portions of the ipsilateral CA1-3 and DG that were also robust against correction for atrophy. Notably, in operated patients, qualitative histopathological analysis of myelin stains in resected hippocampal specimens confirmed disrupted internal architecture and fiber organization. Both hippocampal and neocortical qT1 anomalies were more severe in patients with early disease onset. Finally, analysis of resting state connectivity from regions of qT1 increases revealed altered intrinsic functional network embedding in patients, particularly to prefrontal networks. Analysis of qT1 suggests a preferential susceptibility of ipsilateral limbic cortices to microstructural damage, possibly related to disrupted myeloarchitecture. These alterations may reflect atypical neurodevelopment and affect the integrity of fronto-limbic functional networks.

Commentary

Structural MRI lesions play an important role in the clinical care of patients with epilepsy (1). However, finding clinically relevant MRI abnormalities depends heavily upon multiple parameters, including optimum image acquisition and adequate image interpretation. The sensitivity of focal lesion detection in subjects with chronic uncontrolled epilepsy improves with adequate image acquisition and expert interpretation (2). However, even after adequate image acquisition and visual interpretation, high-resolution MRI fails to demonstrate associated structural abnormalities in approximately 15 to 30 percent of subjects with refractory partial seizures (3). Such patients are often defined as "MRI-negative" (4). The ability to detect more subtle abnormalities using MRI is therefore clinically important and has led to development of new MRI acquisition sequences, image processing, analysis, and objective quantification methods.

In temporal lobe epilepsy (TLE), advances in structural image acquisition and postprocessing have permitted mapping of more specific structural MRI changes and regional distributions of network abnormalities. Using quantitative structural MRI techniques—such as volumetry, voxel-based morphometry, cortical thickness mapping, and structural covariance analysis—there is evidence of widespread, progressive loss of cortical and subcortical gray matter in TLE. Involved structures include deep gray matter structures such as the hippocampus, amygdala, and entorhinal cortex but also extend to extratemporal structures such as the thalamus and neocortical structures in the temporal, fronto-limbic and fronto-central lobes (5).

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Studies focusing on MRI-based surface morphology of the hippocampus have demonstrated accentuated regional volume loss over the CA1 hippocampal and subicular subregions in subjects with hippocampal volume loss and TLE due to mesial temporal sclerosis (MTS), showing good correlation between surface structural changes, and the known pathology of MTS, which preferentially involves Sommer sector (which includes CA1 and the subiculum; 6). However, evaluation of hippocampal surface structure in "MRI-negative" subjects shows a spectrum of hippocampal surface structural changes, with "MRI-negative" subjects showing subregional decreased volume over the subiculum but actual increased volume over the CA1 subregion (4). Using a machine-learning algorithm with data-driven criteria for pathogenic processes and prognosis in subjects undergoing surgery for TLE, Bernhardt et al, (7) showed four different patterns (TLE I-IV) of surface morphology of the hippocampus, entorhinal cortex, and amygdala. TLE-I showed marked bilateral atrophy; TLE-II showed ipsilateral atrophy; TLE-III showed mild bilateral atrophy; and TLE-IV showed hypertrophy. Patterns were predictive for outcomes after epilepsy surgery, with TLE I-IV groups showing Engel stage I outcome in 68%, 89%, 65%, and 44%, respectively. These studies demonstrate the spectrum of structural changes in the mesial temporal lobe in TLE, showing both decreases and increases in subregional hippocampal volumes in what are presumably different pathophysiological causes of TLE. Importantly, findings have implications for outcomes after epilepsy surgery.

There are also neocortical structural changes in TLE. Using diffusion MRI and cortical thinning with covariance analyses to map abnormal structural correlations between mesiotemporal, thalamic, and neocortical regions, investigators have documented changes in thalamic and neocortical regions and within cortico-cortical networks. In a cross-sectional and longitudinal analysis of subjects with TLE, there was significant neocortical thinning predominantly in frontocentral, temporal, and cingulate regions (5).

Most past MRI morphology studies, as the ones summarized above, assessed overall deep gray matter or cortical structure and geometry. However, the current paper by Bernhardt et al. examines a novel MRI technique for evaluating subjects with temporal lobe epilepsy (TLE) using qT1 mapping (or quantitative measurement of longitudinal relaxation time), which offers a more specific measurement of intracortical tissue properties. The precise mechanism of qT1 variations in cortical grey matter is uncertain. However, several studies have suggested high correlation of qT1 variations with myelin content, possibly related to myelin cholesterol contributing to longitudinal relaxation times. A key determinant of variable qT1 values and variation of myelin content across cortical areas is possibly the correlation of density of neurons and myelinated axons. Regions with highly myelinated axons are known to contain many neurons with relatively fewer dendrites, while lightly myelinated cortices show fewer neurons and more dendritic arborization. Therefore, qT1 may represent an in vivo surrogate measurement of cortical microstructure.

The study included 24 subjects with TLE, compared with 20 healthy controls, mapping regional distribution of qT1. Using an automated cortical surface extraction algorithm, the authors systematically placed surfaces using the inner gray matter-white matter and outer gray matter-CSF boundaries, then calculated surfaces at 25%, 50%, and 75% distances between the inner and outer cortical boundaries. These surfaces systematically sampled the axis perpendicular to the cortical ribbon for qT1 changes. Additionally, hippocampal subfields (i.e., CA1-3, CA4-DG) and the subiculum were automatically segmented, and analyzed in a similar manner to neocortical regions. Results showed increased cortical qT1 in the ipsilateral temporopolar, parahippocampal, fusiform, and lateral temporal regions, as well as medial orbitofrontal cortices. Further analysis of these regions showed a greater effect in the upper cortical levels as compared to those near the gray matter-white matter interface. Interestingly, the regions showing increased cortical qT1 differed from regions showing cortical thinning in this cohort, suggesting that these measurements represent different underlying pathophysiological mechanisms. Surface-based analysis of the hippocampus confirmed significant qT1 increases localized to ipsilateral CA1-3 and CA4-DG subfields, as well as the subiculum. Subjects with the most severe ipsilateral hippocampal qT1 increases also showed the greatest abnormalities in cortical qT1. A supervised statistical qT1 learning algorithm lateralized the seizure focus in 92% of patients.

Visual inspection of hippocampal histopathology showed alterations of cortical layering and organization. Opportunities for future studies will include objective correlation of qT1 findings with cortical disorders of myelination using cortical histopathology. Previous histopathological studies in TLE have reported anomalies in the myelination of cortical fibers with abnormalities in cortical layering, with presence of atypical horizontal fibers in upper cortical levels.

The pathophysiological etiology of qT1 changes remains uncertain. However, past histopathological reports have associated subtle abnormalities in temporal neocortical architecture with aberrant corticogenesis. In the current study, qT1 increases were most prominent in subjects with early-onset epilepsy, which is consistent with the idea that qT1 changes may represent subtle abnormalities in cortical development. Further studies evaluating clinical aspects of associated epileptic seizures, qT1 changes, and histopathology will be necessary to confirm whether qT1 is a marker of abnormal cortical development.

Advances in structural image acquisition and postprocessing have permitted mapping of more specific, global structural MRI changes. This study looks beyond geometric analysis of cortical structures by using qT1 MRI with postacquisition analysis to document specific changes in subjects with TLE. While further verification is needed, findings plausibly represent abnormalities of cortical myelination and may serve as a surrogate marker of cortical microstructure. Findings provide an interesting new avenue of investigation for patients with epilepsy, and hold promise for better understanding of patients with "MRI-negative" epilepsy.

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