Title: Neuroimaging in Epilepsy

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Neuroimaging in Epilepsy

Abstract

Purpose: Epilepsy neuroimaging is important for detecting the seizure onset zone, predicting and preventing deficits from surgery and illuminating mechanisms of epileptogenesis. An aspiration is to integrate imaging and genetic biomarkers to enable personalised epilepsy treatments.

Recent Findings: The ability to detect lesions, ion particularly focal cortical dysplasia and hippocampal sclerosis is increased using ultra high-field imaging and post-processing techniques such as automated volumetry, T2 relaxometry, voxel based morphometry and surface based techniques. Statistical analysis of PET and SPECT (STATISCOM) are superior to qualitative analysis alone in identifying focal abnormalities in MRI negative patients. These methods have also been used to study mechanisms of epileptogenesis and pharmacoresistance.

Recent language fMRI studies aim to localise as well as lateralise language functions. Memory fMRI has been recommended to lateralise mnemonic function and predict outcome after surgery in temporal lobe epilepsy.

Summary: Combinations of structural, functional and post-processing methods have been used in multi-modal and machine learning models to improve the identification of the seizure onset zone and increase understanding of mechanisms underlying structural and functional aberrations in epilepsy.

Key words: Epilepsy, functional magnetic resonance imaging, 7-Tesla MRI, PET, SPECT

Introduction

Epilepsy is a condition affecting up to 1% of the population world-wide (1). Approximately a third of people with epilepsy are pharmacoresistant and over two thirds of these have focal epilepsy some of whom may be amenable to curative epilepsy surgery. Significant advances in imaging, post-processing and computational techniques have increased the detection of seizure-onset zones, which increases the odds for seizure freedom after surgery.

This review focuses on recent innovative and translational applications of neuroimaging in epilepsy; older publications are included where relevant.

Structural imaging

In pursuit of personalised approach to optimise epilepsy treatment, imaging and genomics have been assessed in combination in an attempt to define bio-markers. The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA)-epilepsy, described widespread and distinct cortical thickness and subcortical volume changes between epileptic syndromes suggesting targets for genetics and pathological studies(2**)

The 'standard protocol' for epilepsy-specific structural imaging was based on a balance between diagnostic accuracy and clinical feasibility (3). This includes 3-Dimensional $1mm^3$ isotropic voxel, volumetric T1 weighted imaging (malformations of cortical development), axial and coronal T2 weighted (hippocampal architecture) and FLAIR sequences (hippocampal sclerosis (HS), focal cortical dysplasia (FCD), scarring) and axial T2* gradient echo (GRE) or susceptibility weighted sequences (vascular and calcified lesions).

Hippocampal Sclerosis

Features most commonly associated with HS on qualitative structural imaging include atrophy (on 3D T1 volumetric scans), architecture disruption assessed on T2 weighted images and hypointensity onT1 weighted MR-imaging (4**). Quantification of hippocampal volumes by manual and more recently, automated segmentation (5,6) have increased diagnostic sensitivity. T2-relaxometry (7*) and FLAIR identify pathology such as astrogliosis (8) but requires time-

consuming post-processing including region of interest segmentations. Recently, an automated technique was described and made freely available online. Automated values were more reproducible on test-retest than conventional manual techniques (7).

In TLE, morphometry has frequently identified neocortical abnormalities in addition to mesial pathology. These are thought to be multifactorial, related to biological factors such as seizure frequency and propagation. A surface based approach in characterising T2-FLAIR neocortical signal changes in TLE has been described. (9). The cause of these neocortical changes is not yet clear. People with TLE have bilateral limbic and paralimbic cortical abnormalities not associated with variables such as age at onset or epilepsy duration. The extent of signal change did not correlate with post-surgical seizure outcome (9). Whilst it represents a technical advancement in describing grey matter abnormalities, its translational use is still uncertain.

Longitudinal relaxation time (qT1) is sensitive to intracortical myelin and useful for detecting micro-architectural changes. This provides an alternative to morphometry to describe geometrical changes. In TLE ipsilateral qT1 changes were seen within medial temporal and orbital frontal cortices with altered connectivity particularly to the prefrontal cortex. These were associated with age of epilepsy onset and possibly reflect atypical neurodevelopment (10).

Focal Cortical Dysplasia

Focal cortical dysplasia is a common finding in MR-negative pharmacoresistant epilepsy (11). MR changes associated with FCDs include subtle change in gyral size and shape, decreased cortical T1 intensity, increased T2 signal, and poor gray and white matter differentiation Imaging using a higher field (3 and 7T vs 1.5T) and MRI techniques such as double inversion recovery (12**) in which CSF and white matter signals are supressed (Figure 1) and arterial spin labelling (13) can increase the yield of FCD detection.

Implementing cortical and surface based post-processing techniques have improved lesion detection. Voxel-based morphometric analysis programme (MAP) is a voxel-by-voxel quantitative comparison of gray-matter probability maps of individuals with a mean gray-matter image from a normative database. This is an automated technique

derived from T1-maps and identifies abnormal extension of gray matter into white matter (MAP-E) and blurring of the gray-white matter junction (MAP-J). It has an increased sensitivity for FCD detection when compared to visual analysis of qualitative MRI and concordance with SISCOM, FDG-PET and scalp EEG (Figure 2) (14*). The specificity of MAP-E and MAP-J were 94 and 96% respectively. Individually, each had false positive clusters, but when used together, MAP-E and MAP-J significantly improved detection, improving post-surgical outcomes. Importantly, in a group of MR-negative individuals in whom seizure freedom was not achieved by surgery, retrospective MAP led to a second resection with seizure remission (15).

Whilst voxel-based analysis of MRI data may identify occult abnormalities, an important caveat is the occurrence of false-positives so interpretation in a clinical context must be cautious (16).

Ultra-high-field imaging

There has been a surge in research using 7T-imaging in epilepsy. The 7T increased spatial resolution allows for greater signal-to-noise ratio and more accurate subfield analysis of mesial temporal structures. Subfields have been identified by manual segmentation but these are not sensitive to cyto-architectonic features and variable hippocampal folding. A computational method for unfolding the hippocampus and improving this variability has been described (16). It provides a coordinate system that improves the detection of inter-individual morphological differences.

Qualitative 7T MRI can be reliably used to detect HS but not more subtle pathology such as gliosis within the temporal lobe (18). Subfield analysis between controls, HS and non-HS individuals showed selective subfield atrophy in non-HS individuals which did not correlate with post-surgical seizure outcome (19). In a separate study, individuals with MR-Negative TLE underwent hippocampal subfield analysis and 7T MR Spectroscopy (MRS). Subfield analysis showed atrophy in two-thirds and differences in MRS between cases and controls. Neither of these findings lateralised the epileptogenic hippocampus but were associated with impaired verbal memory (20*).

In non-lesional epilepsy at 1.5 and 3T, GRE and FLAIR sequences at 7T identified focal lesions in a third of cases. Histopathology confirmed FCD in those who were operated. In those who remained MR- Negative at 7T, gliosis was shown histo-pathologically (21*).

Specific sequences on 7T imaging hold promise in improved detection of FCD and HS but its use in pathologies beyond these remains to be explored. Hippocampal subfield analysis may be useful in evaluating mnemonic processes and its use in predicting memory outcome after surgery may be of particular interest.

Machine Learning applied to Epilepsy Imaging

In focal epilepsies, structural and functional changes are more widespread than the seizure onset zone. Advanced machine learning techniques such as multivariate pattern analysis (MVPA), using a support vector machine (SVM) devised for pattern recognition have been used on a single subject level to increase the accuracy of diagnosis (22–24) and predict post-surgical outcome (25,26).

Recently, four cortical parameters (thickness, surface area, gray matter volume and curvature) extracted from T1 scans were explored for discriminative analysis using a SVM (24*). Regions were weighted according to their discriminative abilities. When all parameters were taken together it accurately identified a quarter of individuals with TLE who were MRI negative by conventional methods. Using a single parameter for classification, accuracies were 86-92% but with all four parameters, accuracies increased up to 96%.

Using surface morphometry within the mesial temporal lobe structures alone, machine learning predicted the outcome of surgery with 92% accuracy (26). Using a multimodal approach, incorporating quantitative MRI measures, intracranial EEG data, and clinical demographics, a machine learning model predicted post-surgical seizure outcome in 95% of TLE cases (25).

Functional Imaging in Epilepsy

The role of functional imaging is two-fold: to identify epileptogenic zones in MR-negative epilepsy or multiple pathologies, and to map eloquent cortex. PET and SPECT are most commonly used to

investigate the epileptogenic focus. Language, memory, motor and sensory fMRI can be used to investigate eloquent functions. In the pre-surgical setting, multimodal imaging, normalised to individual T1 imaging, is used is to investigate the spatial extent of relevant modalities to the proximity of the lesion/epileptogenic zone. This has revolutionised epilepsy surgery with improvements in outcomes (4).

Additionally, integration of 3D multimodal imaging in computer-assisted planning of intracranial EEG has been shown to increase the accuracy, safety and speed of this procedure (27**).

Seizure localisation

PET scanning

^{18}F-fluoro-deoxyglucose (FDG)-PET has long been used in presurgical assessment. It can be useful in MR-negative cases and guide intracranial implantation (28). In people with HS, FDG-PET showed widespread ipsilesional temporal and extra-temporal hypometabolism (29), suggesting its use to lateralise and broadly localize rather than precisely localise the epileptogenic zone. Those who continued to have seizures post-operatively showed ipsilesional insular hypometabolism, which may imply that these individuals had insular epilepsy. A post-surgical study of opercular-insular epilepsy, however, showed that insular hypometabolism on FDG-PET was not specific for the syndrome with many false positives, whilst ictal SPECT was concordant in about three-quarters of cases (30).

Localised anterior temporal hypometabolism on FDG-PET in HS has consistently been shown to be a predictor of good long-term seizure outcome (31,32). In a separate group with dominant TLE, greater hypometabolism within the medial temporal lobe, predicted not only favourable seizure outcome but also better post-operative naming and verbal memory performance (33*).

In those with MRI negative epilepsy who underwent intracranial EEG evaluation, congruent ipsilateral PET hypometabolism was associated with favourable seizure outcome in TLE cases but not in extra-temporal cases (34). The accuracy of PET scanning is enhanced using post processing techniques compared to visual analysis alone (32). In cases with probable FCD, quantitative analysis of FDG-PET-CT concurred with visual analysis in TLE but in FLE quantitative methods were superior and showed concordance in an additional 50% of cases (Figure 2) (12**). The software is available online and

conducts a voxel-by-voxel statistical comparison of individual PET scans with that of controls. The quantitative analysis delineates areas of significant hypometabolism (>2 SDs from the mean) and displays this as an image and in a table.

Co-registration of PET and SPECT with MRI averted the need for invasive monitoring in paediatric cases (35). The accuracy of quantitative PET was further improved when combined with surface based quantitative MRI analysis in histopathologically proven FCD, accurately classifying 93% compared to 65% with multimodal visual analysis alone (36**).

SPECT

Ictal SPECT is mostly used in extra-temporal MRI negative cases or in individuals with discordant findings. Like PET, it can guide implantation for intracranial studies(37). Regional cerebral blood flow measured by SPECT is seen as a surrogate marker for neuronal activity. The most sensitive and specific application is by subtracting the interictal from the ictal SPECT with MRI co-registration (SISCOM), using either ^{99m}Tc-hexamethyl-propylene-amine-oxime (HMPAO) or ^{99m}Tc-ethylene-cysteine-diethylester (ECD) with concurrent EEG-monitoring.

The accuracy of SPECT in defining seizure onset is further enhanced by the application of statistics using statistical parametric mapping, (STATISCOM) or a commercially available statistical programme (MIMneuro, MIM Software Inc., Cleveland, OH, USA). A recent comparison of these three methods in temporal and extra-temporal MRI negative cases showed that STATISCOM and MIMNeuro were superior to SISCOM, with STATISCOM being the best performer (38).

A review article described the innovative use of specific MRI contrasts, translocator protein 18kDA (TSPO)- PET, SPECT and proton MRS in the assessment of preclinical and clinical biomarkers of epileptogenesis. Findings included imaging signatures of the onset of the epileptogenic cascade with blood brain barrier dysfunction, glial activation and neuroinflammation. Although novel, these techniques hold promise for future translational clinical use (39**).

Assessment of Eloquent Functions

An eloquent review of the translational use of f-MRI and tractography in the presurgical setting was recently published (4). In the last two years, there has been an increasing network and connectivity approach in the assessment of eloquent functions and multivariate analyses using machine learning.

Language fMRI

Language fMRI has replaced WADA-testing to lateralise language functions in most centres. There is often a difference between temporal and frontal lateralisation of activations that can be difficult to interpret, leading to a move towards tasks for localising language functions. To improve the clinical utility of presurgical language assessment, The American Academy of Functional Neuroradiology have recommended performing Sentence Completion, Silent Word Generation, Rhyming, Object Naming, and/or Passive Story Listening (40). A cohort of people with FLE underwent language fMRI using expressive language tasks and electrocortical stimulation (ES) for language localisation. Those in whom the resected area overlapped with language fMRI maxima, despite negative ES, showed significant post-operative naming decline, supporting a role for fMRI in presurgical evaluation (41).

In a multimodal TLE study, lateralisation indices were calculated from language fMRI, DTI and volumetric data. Language reorganisation to the right hemisphere was associated with greater right sided fractional anisotropy of the arcuate fasciculus on DTI and greater cortical thickness in the right temporo-occipital region. These were associated with better language function (42*). A useful extension to this study would be to see if this multimodal method accurately predicts post-surgical language function.

In a separate study, a multimodal approach with machine learning was used to predict post-surgical language outcome. People had language assessment using four modalities; fMRI, magnetocephalography (MEG), transcranial magnetic stimulation, and electrocorticography to predict decline. As a trade-off between model complexity and prediction accuracy, fMRI and MEG in combination were superior to individual modality prediction (43**)

Memory fMRI

In TLE, re-organisation of memory encoding networks been shown to

involve extra-temporal regions (44) with implications for post-operative memory outcome (45). In the months after temporal lobe resection, there are changes in memory function over time with corresponding dynamic functional memory plasticity demonstrable with fMRI (46).

Fronto-temporal verbal memory lateralisation provided an objective parameter to predict verbal memory outcome in individual subjects, and was the best outcome predictor when compared to clinical parameters (45). A recent study showed that visual lateralisation of memory MRI activations using a picture recognition paradigm was predictive of verbal and visual memory decline in two-thirds of those with TLE (47). The lateralisation of memory fMRI has implications on post-surgical memory outcome and is superior to WADA. In a practise guideline summary of the pre-surgical use of fMRI, the American Association of Neurology recommended the use of memory fMRI to lateralise and predict verbal and non-verbal memory outcome after TLE surgery (48**).

Reduced inter-hemispheric functional connectivity of resting state networks in anterior and posterior hippocampal networks has been associated with reduced verbal and visual memory in people with TLE (49,50). The use of this method for hemispheric seizure lateralisation and cognitive outcome prediction remains to be explored.

Future directions

There has been accruing evidence that epilepsy is a network disease and focal epilepsy is a consequence of localised network dysfunction rather than localised pathology (51). Graph theory is a mathematical tool that allows for the analysis and quantification of networks and has been recently used in DTI studies (52), resting state fMRI for risk stratification of SUDEP (53*) cortical thickness in FCD (54) and describing patterns of hypoperfusion in generalised epilepsy using arterial spin labelling (55).

Topological brain disorganisation has been seen in MRI-negative focal epilepsy and may represent a network that is involved in seizure generation or propagation. This method holds promise in a multi-modal approach and with ultra-high field imaging to identify seizure onset zones in focal epilepsies and to provide a bio-marker for response to anti-epileptic drug treatments.

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Figure Legends

Figure 1. Left frontal angiocentric glioma. This patient was included because focal cortical dysplasia was one of the differential diagnoses. A,B Double inversion recovery and T1 axial MRI show the lesion in the left superior frontal gyrus. This is better characterised on curvilinear reconstrution C, D. E shows left frontal hypometabolism on axial visual-positron emission tomography (PET). F, quantitative PET confirms left frontal lobe hypometabolism with -3.4 SD (12).

Figure 2: Structural T1-weighted MRI (A), with left frontal cortical dysplasia. (B) MAP+ extension image. (C) MAP+ Junction image. (D) Sagittal post-resection T1 structural image (14). MAP (Morphometric analysis programme). Reproduced with permission rom Elsevier