Changing concepts in presurgical assessment for epilepsy surgery

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Abstract | Candidates for epilepsy surgery must undergo presurgical evaluation to establish whether and how surgical treatment can stop seizures without causing neurological deficits. Various techniques, including MRI, PET, single-photon emission CT, video-EEG, magnetoencephalography and invasive EEG, aim to identify the diseased brain tissue and the involved network. Recent technical and methodological developments, encompassing both advances in existing techniques and new combinations of technologies, are enhancing the ability to define the optimal resection strategy. Multimodal interpretation and predictive computer models are expected to aid surgical planning and patient counselling, and multimodal intraoperative guidance is likely to increase surgical precision. In this Review, we discuss how the knowledge derived from these new approaches is challenging our way of thinking about surgery to stop focal seizures. In particular, we highlight the importance of looking beyond the EEG seizure onset zone and considering focal epilepsy as a brain network disease in which long-range connections need to be taken into account. We also explore how new diagnostic techniques are revealing essential information in the brain that was previously hidden from view.

The success of surgery for treating drug-resistant focal epilepsy largely depends on accurately predicting which resection or disconnection strategy will yield full seizure control. In 1966, Talairach and Bancaud defined the epileptogenic focus as the anatomical area where seizures originate[1]. Four decades later, on the basis of electrocorticography (ECoG), in which electrical activity is recorded from electrodes placed directly on the surface of the brain, Lüders et al. defined the epileptogenic zone as the cortical area that needs to be removed to obtain seizure freedom[2]. This definition implies the existence of one or more circumscribed cortical areas containing epileptogenic tissue, and has been challenged. Specifically, findings from stereo-EEG (SEEG), which simultaneously measures electrical activity from superficial and deeper structures of the brain, suggest the existence of epileptogenic brain networks involved in the initiation and propagation of epileptic activities, which might necessitate multitargeted treatments alongside focal resection[3–5].

Early surgical strategies to provide relief from seizures relied on semiology to determine the site of resection. This approach was later augmented by EEG, intraoperative ECoG and CT scans. Long-term invasive recordings with depth electrodes (SEEG), subdural strip and grid electrodes and, subsequently, MRI, PET and single-photon emission CT (SPECT) further improved presurgical decision-making[6]. Currently, people referred for epilepsy surgery undergo an extensive presurgical work-up, starting with MRI and EEG with synchronized video registration (video-EEG) and, if needed, PET or ictal SPECT[7]. This noninvasive phase is followed either by invasive diagnostics with long-term SEEG or ECoG to explore surgical possibilities, or directly by a resection, possibly guided by intraoperative ECoG. The various techniques visualize different aspects of the epileptogenic focus or network on the basis of structural, functional, electrographical and metabolic abnormalities. The planned resection requires delineation of the epileptogenic focus from functionally eloquent cortex, which can be partly achieved with noninvasive methods such as functional MRI (fMRI) and invasive methods such as electrocortical stimulation.

In this Review, we focus on the latest improvements in established diagnostics and the development of new methods to determine the most appropriate surgical strategy for patients with epilepsy. Our objective is to recognize shifts in thinking through the development of new techniques. We focus mainly on identification of the epileptogenic tissue and network — the localization of healthy brain function is beyond the scope of this article. We will evaluate how new diagnostics challenge our general concepts of focal epilepsy and how our changing view is directing developments to further enhance epilepsy surgery guidance.

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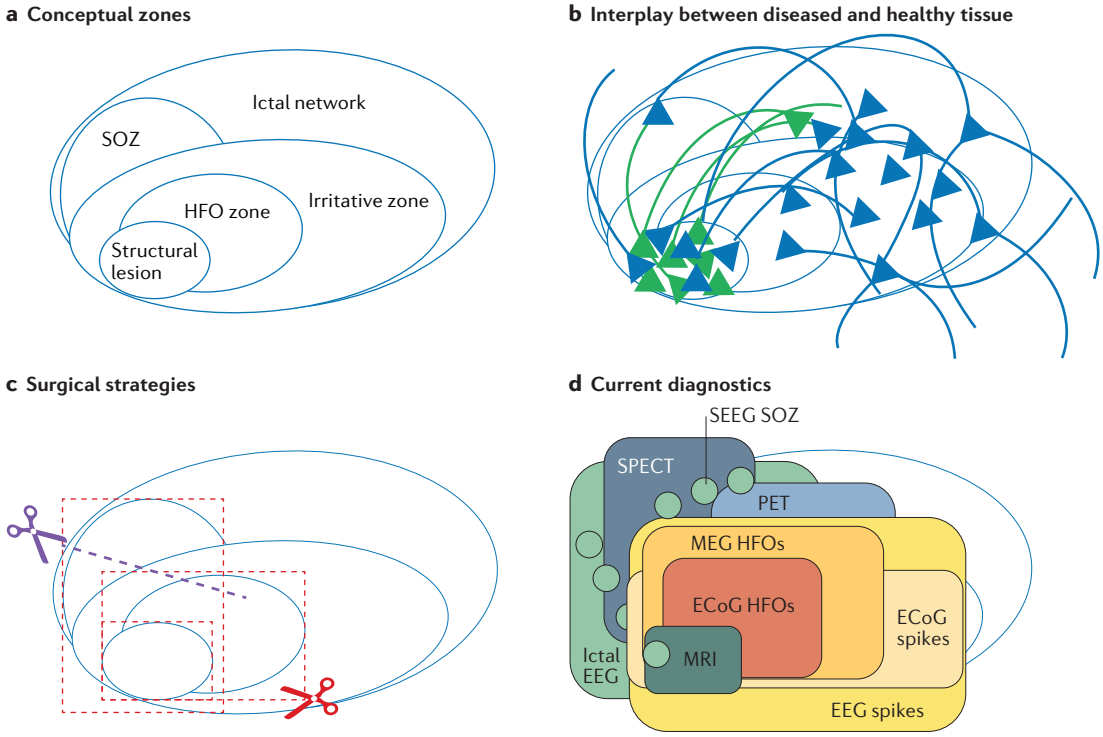

Fig. 1 | **Concepts of the epileptogenic brain. a** | Examples of conceptual zones from which the epileptogenic zone can be estimated. The high-frequency oscillation (HFO) zone generates HFOs, which can be detected by stereo-EEG (SEEG), electrocorticography (ECoG) or magnetoencephalography (MEG). The irritative zone generates interictal epileptiform discharges, which can be detected by ECoG, EEG, MEG or combined EEG and functional MRI. The seizure onset zone (SOZ) is the brain area from which seizures start, and can be recognized with SEEG, ECoG or ictal single-photon emission CT (SPECT). The ictal network consists of brain areas that are involved in seizures. The structural lesion is the area with visible abnormal brain tissue (for example, on MRI). **b** | Concepts of epileptogenic tissue and epileptogenic networks (green) that are fused with the healthy brain tissue and network (blue). **c** | Examples of surgical strategies, including resection (red rectangles) and disconnection (purple dotted line), that can lead to seizure freedom. **d** | Illustration of how different diagnostic techniques depict different areas that approximately correspond to the conceptual zones and might reveal different aspects of the epileptogenic tissue and network.

The epileptogenic brain

For presurgical planning, a key question is: what do the presurgical techniques need to disclose to optimize surgical decision-making? In addition to the structural lesion, which can be visualized by MRI, various zones have been conceptualized (FIG. 1a), such as the seizure onset zone as the brain area where seizures seem to arise, or the irritative zone, which includes all tissue that generates interictal epileptiform discharges. These zones do not yet answer the true clinical question at hand, namely, how these zones and networks need to be removed or interrupted to achieve permanent seizure freedom, stop other disruptive effects on brain function and optimally spare healthy brain functioning.

According to the definition of Lüders et al. of the epileptogenic zone, the best way to evaluate diagnostic techniques would be to determine how well removal of the depicted areas predicts postsurgical seizure freedom. However, this approach does not disclose the smallest part of the cortex that requires removal or disconnection and cannot provide confirmation that the chosen procedure was the best option. Ideally, the diagnostic techniques should enable us to understand the interplay between diseased tissue, the epileptogenic network and the healthy brain to devise the best possible surgical strategy (FIG. 1b,c). Current diagnostics depict one or more of the different conceptual zones, but none is 100% specific in differentiating diseased tissue or networks from healthy brain (FIG. 1d).

Current diagnostics

In FIG. 2, we distinguish 'established' diagnostics that are used by most centres and are supported by multiple clinical studies, 'upcoming' diagnostics that are used in some centres and have shown clinical validity in at least one study, and 'experimental' approaches that have potential clinical utility but have not yet entered clinical practice. In this section, we discuss the established methods, and the upcoming and experimental approaches are discussed below.

Semiology and deficits

Clinical symptoms resulting from changes in brain function — in particular, those symptoms that occur at seizure onset — provide clues about the focus or lateralization of epilepsy[8–10]. Not all brain regions produce recognizable symptoms, however, so the first symptoms might point towards an area of spread rather than the seizure onset. Neurological and cognitive deficits, identified by neuropsychological testing, provide information

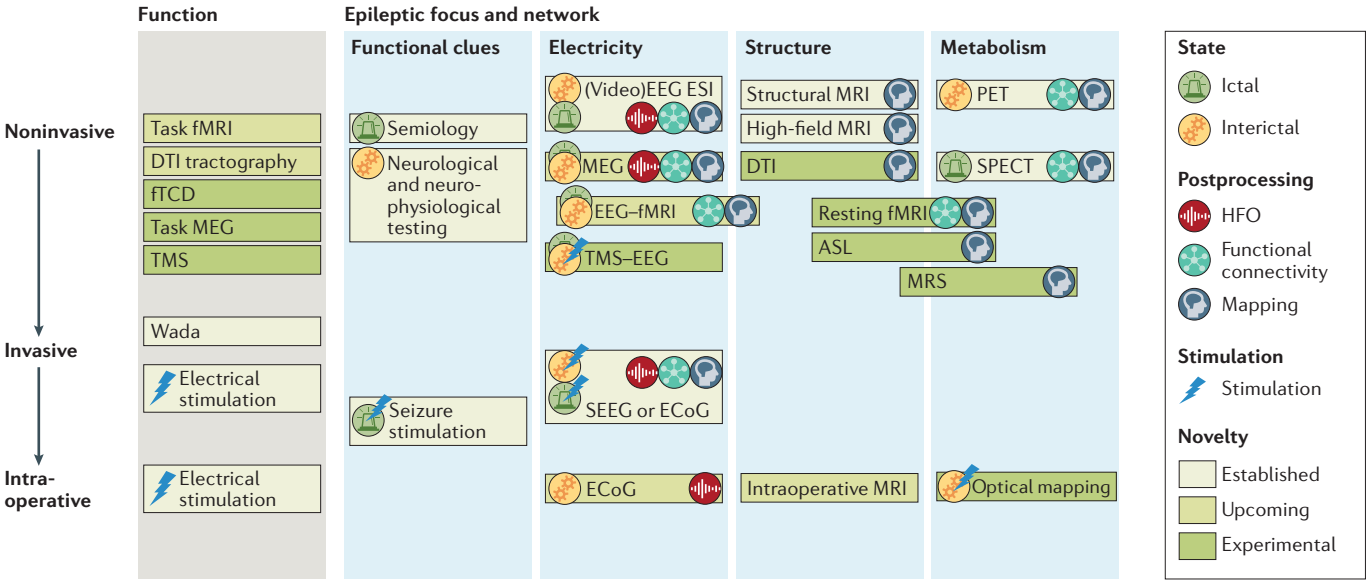

Fig. 2 | **Presurgical methods to locate the epileptogenic area.** The columns list methods for functional localization and delineation of the epileptogenic tissue and network. The latter category is subdivided into methods based on brain function, including deficits and seizure semiology; methods based on the (magneto)electrical signal, including EEG, magnetoencephalography (MEG) and invasive EEG (stereo-EEG (SEEG) and electrocorticography (ECoG)); methods based on changes in brain structure; and methods based on brain metabolism. Techniques are classified as being recorded in the interictal or the ictal state. Some methods can record both states, but sometimes with a preference for one state over another. Postprocessing signal analysis methods include high-frequency oscillations (HFOs), functional connectivity and mapping (for example, statistical parametric mapping, morphometric analysis, electrical source imaging (ESI) or magnetic source imaging). Established methods: used in many epilepsy surgery centres and shown to be clinically useful in several studies. Upcoming methods: used in some epilepsy surgery centres and validated at the patient level in at least one study. Experimental methods: mainly applied in research settings and might have clinical utility in the future. ASL, arterial spin labelling; DTI, diffusion tensor imaging; fMRI, functional MRI; fTCD, functional transcranial Doppler sonography; MRS, magnetic resonance spectroscopy; SPECT, single-photon emission CT; SPES, single-pulse electrical stimulation; TMS, transcranial magnetic stimulation.

on the lateralization or localization of the seizure origin, especially in temporal lobe epilepsy[11]. Secondary generalized seizures and mental retardation signify involvement of large brain areas and are associated with poor seizure outcomes after surgery[12–14].

EEG-based diagnostics

Interictal epileptiform discharges (IEDs) on the EEG indicate the irritative zone, which is most focal during rapid eye movement sleep[15,16]. Seizure activity on video-EEG can localize the seizure onset and initial spread, and helps to explain the observed semiology. Video-EEG is the only diagnostic tool to distinguish epileptic seizures from other paroxysmal clinical events with certainty. EEG mainly picks up activity from the convexity of the brain, even if this activity originates in deep structures. Placement of extra electrodes, such as invasive sphenoidal, foramen ovale or inferior temporal surface electrodes, facilitates detection of activity from mesiotemporal or basotemporal structures[17–19]. The growing diagnostic accuracy of MRI challenges the need to perform presurgical video-EEG in some cases; for example, in patients with mesiotemporal sclerosis, a surgical success rate of >80% was achieved without performing video-EEG[20].

Long-term invasive EEG with depth electrodes (SEEG) or subdural strip or grid electrodes (ECoG) records seizure onset and spread directly from the cortex. Seizure onset is characterized by several different discharge patterns, of which focal fast activity is the most specific marker in relation to postsurgical outcome[21]. SEEG can reach almost any part of the cortex and is more useful than ECoG when epileptic foci within deep brain structures (such as the insula) or distant from each other are hypothesized. In patients with temporal lobe epilepsy, bilateral depth electrodes provided better lateralization than bilateral subdural electrodes[22]. ECoG allows dense sampling of the cortical convexity and can be particularly helpful to delineate the extent of the irritative and seizure onset zones and their relationship with functionally eloquent cortex.

Intraoperative ECoG delineates the irritative zone during surgery and can directly guide the neurosurgeon with iterative recordings during the surgical procedure. Characteristic ictal or rhythmic spike patterns signify underlying dysplastic brain tissue[23,24]. The clinical value of sporadic IEDs in the tailoring of surgery has been debated because the irritative zone is often larger than the required resection area, and the resection and manipulation of cortical tissue can evoke novel spikes[25].

Structural imaging

The absence of structural abnormalities on MRI halves the odds of successful epilepsy surgery compared with lesional cases[26,27]. In turn, the persistence of any MRI lesion after surgery has been associated with a high

probability of seizure persistence after resection[28]. Therefore, optimal structural imaging is an essential component of the presurgical work-up. An MRI epilepsy scanning protocol should include whole-head high-resolution 3D T1-weighted and T2-weighted images, a fluid-attenuated inversion recovery (FLAIR) sequence, and sequences that are sensitive for haemosiderin and calcifications[29]. Coronal T2 and FLAIR sequences should be angulated perpendicular to the hippocampal axis for hippocampal volume estimation[30]. Phased array surface coils and high field strength improve the signal-to-noise ratio[31,32]. The MRI scan should be assessed by a neuroradiologist who specializes in epilepsy and reviewed by a second neuroradiologist[33].

Nuclear imaging

Various PET tracers are available to measure glucose, oxygen, neurotransmitters, blood flow and receptor binding. One commonly used tracer in epilepsy is ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Hypometabolism on ^{18}F-FDG–PET indicates dysfunctional cortex, which can be related to the epileptic focus. In one study, 33 of 498 ^{18}F-FDG–PET scans in children showed hypermetabolism, which often reflected focal cortical dysplasia[34]. Individuals with temporal lobe epilepsy who had no MRI lesions but showed lateralized hypometabolism on ^{18}F-FDG–PET had postsurgical outcomes similar to people with mesiotemporal sclerosis on MRI[35]. PET hypometabolism that extends beyond the diseased temporal lobe or is remote from the epileptic source predicts worse postsurgical outcome[36–38].

SPECT scanners produce 3D images of gamma rays from radioisotopes. The SPECT tracer that is most often used in patients with epilepsy is ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO). This tracer is injected both during an interictal phase and directly after seizure onset, and the ictal and interictal SPECT images are then compared. Computer-aided subtraction ictal SPECT coregistered to MRI (SISCOM) renders twice as many localized areas of hyperperfusion as does visual comparison[39]. SPECT is especially useful in nonlesional and extratemporal epilepsies[40,41]. Ictal SPECT hyperperfusion occurs in both the ictal onset zone and regions connected to this zone, meaning that SPECT findings need to be considered in the light of results from EEG, MRI and PET, rather than serving as a single measure for the epileptogenic area[42].

New developments

In this section, we discuss upcoming and experimental but promising diagnostic methods. Head-to-head comparison of the accuracy of new techniques is difficult, as many studies describe the advantages of single new techniques in a patient cohort who are otherwise undergoing standard work-up, and controlled prospective studies are currently lacking. Outcome measures include postsurgical outcome, in which the definition of 'good' ranges from seizure freedom to any improvement, and the ability to correctly define the area for resection, the seizure onset zone or another area of interest. In different studies, measures such as sensitivity and specificity have been calculated between patients (postsurgical outcome) or within patients (region of interest analysis) and, thus, are difficult to compare. Even similar calculations produce different results between studies because of differences in patient selection, diagnostic and surgical procedures, and the hardware and software used. Options for additional diagnostics that can be considered on the basis of MRI and video-EEG findings and the proximity of the lesion to eloquent cortex (TABLE 1) also differ between centres, depending on availability and experience. These factors, together with the generally low power of studies, make critical analysis of the literature challenging.

Locating the electrical source

Epilepsy involves aberrant electrical activity in the brain, ranging from clearly visible rhythmic EEG patterns during seizures to sporadic interictal epileptiform discharges between seizures and abnormal background rhythms. These proxies of the electrical source of epilepsy can be recognized with various EEG-based methods. Besides analysis of spontaneous EEG, epileptiform activity can be evoked. Below we will discuss potential advances within existing methods, and newly developed methods.

Stereo-EEG. Talairach and Bancaud introduced an SEEG technique in which a frame was used to coordinate electrode placement[1]. This approach has since been adapted for frameless navigated placement and, most recently, for robotic guidance. Robotic guidance seems to yield the best precision regarding entry and target points of the placed electrodes[43]. SEEG is gaining in popularity due to the lower complication risk and patient burden compared with grid electrode placement. Depth electrodes can also be used intraoperatively, either placed in combination with ECoG grids or, in patients with tuberous sclerosis, using several separate electrodes to reveal the epileptogenic tubers[44].

Electrical source estimation. Estimation of the source of interictal epileptiform EEG discharges is based on assumptions about the extent and shape of the source and conduction of surrounding tissue such as the skull, for which several models exist. Accurate segmentation of skull, scalp and brain tissue is important for clinically valid electrical source imaging (ESI)[45]. High-density EEG (>30 electrodes) leads to a higher precision of ESI (HD-ESI)[46]. Various ESI algorithms have been tested, both individually and in combination. A study that compared the performance of MRI, HD-ESI, SPECT and PET in 190 patients with epilepsy showed that the combination of HD-ESI and MRI had the highest predictive value for seizure freedom after surgery[47].

Magnetic source estimation. Magnetoencephalography (MEG) samples the magnetic correlate of electrical brain activity and, in contrast to EEG, is not attenuated by the conductance of the skull. MEG currently requires sensor cooling, which incurs high costs and limits the flexibility of the recordings. Optically pumped magnetometers might enable portable recordings in the future[48]. The high number of MEG sensors in the helmet (>250) renders visual analysis of the channels — as is done in EEG — impractical, but it provides opportunities for

Table 1 | **Additional presurgical diagnostics following EEG and standard MRI**

Electroclinical syndrome	MRI findings	Additional noninvasive diagnostics to consider	Noninvasive results	Invasive procedures to consider
Unifocal	Single lesion	–	–	• Resection • Laser ablation
Unifocal (typical mTLE)	Negative, bilateral abnormalities, or contralateral	• PET • Hippocampal volumetry • Neuropsychological testing	Unilateral	• Temporal lobe resection • Laser ablation
			Possible unilateral hypothesis	SEEG
Unifocal	Single lesion, incongruent to electroclinical syndrome	• 7 T MRI • MRI postprocessing • PET • SPECT[a] • ESI or MEG[b] • Multimodal imaging	Two hypotheses	• SEEG • long-term ECoG
Unifocal	Multiple lesions	• PET • SPECT[a] • ESI or MEG[b] • Multimodal imaging	One MRI lesion is the suspected lesion	• Resection (with intraoperative ECoG) • Laser ablation
			Unclear	SEEG
Unifocal	Lesion of unclear extent	• 7 T MRI • PET • ESI or MEG[b]	Extent uncertain	• SEEG • Long-term ECoG • Intraoperative ECoG
Unifocal	MRI negative	• 7 T MRI • MRI postprocessing • ESI or MEG[b] • PET • SPECT[a] • Multimodal imaging	Reasonable hypothesis	• SEEG • long-term ECoG
Bitemporal (typical mTLE)	Unilateral, bilateral or negative	• PET • Hippocampal volumetry • Neuropsychological testing	Possible unilateral hypothesis	SEEG
			Bitemporal epilepsy	No surgery
Multifocal	One congruent lesion	• MEG or ESI • EEG–fMRI[b] or SPECT	Congruent	Resection (with intraoperative ECoG)
			Incongruent	SEEG
Multifocal	One incongruent lesion or multifocal or negative	• 7 T MRI • MRI postprocessing • PET • SPECT[a] • ESI or MEG • EEG–fMRI[b] • Multimodal imaging	Reasonable hypothesis	SEEG
			No hypothesis	No surgery
Nonlocalizing	Unifocal lesion	• MEG or ESI • EEG–fMRI[b] • SPECT[a]	Congruent	• Resection (with intraoperative MRI) • Laser ablation
			Incongruent	• SEEG • long-term ECoG
Nonlocalizing	Multifocal	• MRI postprocessing • PET • SPECT[a] • ESI or MEG • EEG–fMRI[b] • Multimodal imaging	Reasonable hypothesis	SEEG
			No hypothesis	No surgery
Nonlocalizing	Negative	• 7 T MRI • MRI postprocessing • PET • SPECT[a] • ESI or MEG • EEG–fMRI[b]	Reasonable hypothesis	SEEG
			No hypothesis	No surgery

The table lists the potential choices of additional presurgical diagnostics, given the results from standard MRI and (video)-EEG in individual patients. This overview is based on knowledge from the literature and clinical practice in our own centre, which has access to EEG, magnetoencephalography (MEG), electrical source imaging (ESI), 3 T and 7 T MRI, functional MRI (fMRI), MRI postprocessing (MAP18), ^{18}F-fluorodeoxyglucose PET, single-photon emission CT (SPECT) with ictal–interictal SPECT analysis by statistical parametric mapping postprocessing, multimodal imaging, stereo-EEG (SEEG), long-term electrocorticography (ECoG), and intraoperative ECoG. A dash indicates that additional noninvasive diagnostics will usually not change the overall strategy, but may yield some additional information to guide the implantation or surgery. mTLE, mesiotemporal lobe epilepsy. [a]SPECT requires frequent seizures. [b]ESI, MEG and EEG–fMRI require frequent interictal (or ictal) discharges.

accurate source estimation. In a prospective comparison in 52 patients, source estimation of interictal MEG was better than video-EEG at identifying the epileptogenic tissue; resection of the source obtained by MEG and video-EEG yielded good postsurgical outcomes in 52% and 33% of patients, respectively[49]. MEG interictal spike cluster modelling might be useful to delineate a resection, and four cohort studies showed that removal of tissue with tight MEG spike clusters, especially if concordant with invasive EEG results, was associated with good postsurgical outcomes[50–53]. In a comparison of multiple MEG source localization algorithms, dipole modelling, current density reconstruction and beamforming demonstrated equal concordance with invasive EEG[54].

MEG and EEG yield complementary information as IEDs are sometimes seen with only one modality[55], and fusion of EEG and MEG data yields extra information compared with the separate methods[56]. Combining MEG, EEG and SEEG overcomes the inherently limited spatial sampling of SEEG[57]. Noninvasive interictal ESI might, however, recognize only part of the irritative zone compared with SEEG[58].

High-density ESI and MEG can also localize the ictal source in people with frequent seizures[59–61]. Comparison of ictal HD-ESI with SEEG showed that ictal spiking patterns and fast activity colocalized with SEEG seizure onset patterns, whereas scalp rhythmic discharges colocalized with seizure propagation[62].

Background EEG. Functional connectivity analysis based on interictal EEG has been used to identify brain networks and network abnormalities related to epilepsy. Studies investigating resting-state connectivity in epilepsy are partly incongruent. Some studies reported increased connectivity and others reported reduced connectivity in the suspected epileptogenic regions compared with other regions[63–69]. Seizure dynamics show that a part of the seizure onset zone is isolated from the network during the interictal phase but becomes more connected during seizure progression, suggesting that the brain's strategy to prevent spreading fails[70]. Adding functional connectivity to ESI doubled the accurately estimated areas that needed to be resected to achieve successful surgery[71]. Connectivity studies are as yet unable to provide advice at the individual patient level; however, in the future, dynamic computational models, informed by patient-specific functional EEG networks, might aid the formulation of alternative surgical strategies[72–74].

Besides analysis of spontaneous EEG, stimulation protocols can attempt to identify the epileptogenic tissue and network. Single-pulse electrical stimulation elicits early and delayed IED-like responses. Similar responses, known as corticocortical evoked potentials, are seen after 1-Hz stimulation. Fast activity overriding the corticocortical evoked potentials, repeated spiking and delayed single-pulse electrical stimulation responses, especially if they contain high-frequency activity, have been related to seizure onset areas and the prediction of surgical outcome[75–77]. Noninvasive transcranial magnetic stimulation (TMS) can provoke seizures, and single-pulse TMS can elicit epileptiform discharges that can be observed on the side of the seizure onset by simultaneously recorded EEG (TMS–EEG)[78,79]. Electrical impedance tomography is an alternative method that estimates aberrant tissue properties from changes in electrical conductance[80]. No proof exists of the clinical utility of stimulus-driven information for the individual patient.

Ictal patterns. Visual localization of the seizure onset zone in EEG is challenging owing to simultaneous involvement of distinct brain regions and rapid spread. Quantitative EEG analysis assesses three characteristic components of the ictal signal — timing, frequency and spread of activity — to objectify the ictal pattern. The epileptogenicity index quantifies the transition of background EEG activity to fast ictal activity for each EEG channel[81]. This index enables quantitative neuroimaging of the seizure onset[82] and discloses the extent of the epileptic network, which relates to surgical prognosis[83]. Several studies have determined the functional connectivity in ictal invasive EEG and have characterized strongly connected 'drivers' of epileptic activity that are important to include in the resection[63,64,84]. Machine learning algorithms can aid further specification of ictal activity through identification of the interictal-to-ictal transition[85].

As an alternative to the measurement of spontaneous seizure activity, direct electrocortical stimulation can provoke seizures and after-discharges. However, the area that is susceptible to stimulated seizures and after-discharges is larger than the seizure onset zone. The diagnostic value of stimulated seizures in comparison with spontaneous seizures is unclear and has only been studied retrospectively to date[86,87].

Combined EEG and functional MRI. Interictal EEG–fMRI analyses changes on fMRI at the time that IEDs occur on EEG. The spots of IED-related enhanced blood flow can direct planning of depth electrode placement, and removal of the spots with the strongest fMRI activation has been associated with good postsurgical outcome in several studies[88–94]. In one study, combining EEG–fMRI with ESI accurately predicted the surgical outcome in 9 of 9 patients with overlapping results, compared with 8 of 20 patients for EEG–fMRI alone and 13 of 16 patients for ESI alone[95]. Ictal EEG–fMRI images the dynamics of fMRI activity during seizures[96,97]. We do not yet know how ictal EEG–fMRI compares with IED-related fMRI activity in terms of predicting postsurgical outcome. Technical advances in EEG–fMRI over the past few years have focused on optimization of the MRI by motion correction, fast fMRI sequences and recording at high field strengths[98–100]. Invasive EEG combined with fMRI is also feasible[101]. Simultaneous EEG and near-infrared spectroscopy is a promising alternative measure of IED-related haemodynamic changes, without the difficulties of EEG recording in the MRI scanner[102,103].

High-frequency oscillations. High-frequency oscillations (HFOs) were originally discovered through the use of implanted microelectrodes, and were later recorded by depth electrodes, cortical electrodes, EEG and MEG, all of which are used in the clinic[104–107]. HFOs consist of transient oscillatory patterns with at least four cycles

and are divided into ripples (80–250 Hz), fast ripples (250–500 Hz) and very fast ripples (>500 Hz)[108,109]; the higher the frequency, the more localized and specific for the epileptogenic focus the HFO appears[108]. Several studies have shown that removal of areas that exhibit interictal HFOs on invasive recordings predicts good postsurgical outcomes, although other studies have contradicted these findings[110–119]. This discrepancy could be explained by differences in patient selection, recording and analysis.

Comparison of preresection and postresection ECoG recordings indicates that the area showing HFOs is generally larger than the actual lesion, and removal of the lesion leads to absence of HFOs after the resection[111,120]. These findings suggest that some of the brain tissue that shows HFOs on ECoG that covers the tissue is spreading rather than generating the HFOs. Persistent fast ripples on an intraoperative ECoG recording after a resection predicts a poor postsurgical outcome, and so the discovery of HFOs on these repeated measurements could indicate that more cortical tissue should have been removed[112].

Epileptic HFOs may be distinguished from physiological HFOs on the basis of their interaction with IEDs (epileptic HFOs often occur at the slope of epileptiform spikes), their morphology (physiological HFOs tend to be more smooth and flat and of longer duration, and often occur within a channel showing continuous high-frequency activity) and their spatial distribution (physiological HFOs occur mostly in functionally eloquent areas)[121,122].

Visual analysis of HFOs is time-consuming, and automatic detectors have been built[123]. However, we must be wary of relying on automatic detection alone, because high-pass filtering of sharp signal artefacts can generate activity that resembles HFOs[124]. Invasive and noninvasive high-density recordings facilitate HFO identification because the HFO area is often small[125]. Ictal HFOs, studied with MEG and invasive EEG, have been shown to be specific for the seizure onset and surgical resection areas, and removal of the tissue that produces these HFOs produces good postsurgical outcomes[87,126–128].

The structural lesion

More than 90% of individuals who undergo surgery for epilepsy show structural lesions on histopathological examination[129]. This observation, combined with the increased chance of postsurgery seizure freedom in patients with structural abnormalities on MRI, highlights the importance of trying to identify MRI lesions. The emergence of 7 T MRI and potentially even higher field strengths is increasing the signal-to-noise ratio for the detection of lesions[130,131]. Brain regions that are close to air-filled cavities (such as the nasopharyngeal sinuses) or to metal are susceptible to artefacts, and this susceptibility increases with the field strength. Susceptibility-weighted imaging takes advantage of this higher susceptibility, and susceptibility-weighted imaging abnormalities on 7 T MRI were found to be concordant with histopathological abnormalities, especially vascular malformations and calcified lesions[132,133].

MRI postprocessing using hippocampal volumetry helps to lateralize temporal epilepsy; temporal lobectomy produced good postsurgical outcomes in 34 of 35 people in whom hippocampal volumetry results were concordant with EEG lateralization[134]. MRI postprocessing can also reveal subtle changes within the cortical structures (for example, in cases where malformations of cortical development are suspected). Voxel-based postprocessing of T1-weighted MRI scans using a morphometric analysis program (MAP) compares individual patient data with a database of normal scans[135,136]. In 150 individuals with no apparent lesion on MRI, MAP revealed abnormalities in 65 cases[137]. The region identified by MAP was included in the resection in 45 of 50 patients with good postsurgical outcomes and five of 15 patients with poor postsurgical outcomes, suggesting that MAP can aid detection of epileptogenic lesions. SEEG electrodes implanted in regions of interest identified by MRI postprocessing yielded surgical targets in 10 of 14 people without clear MRI lesions[138]. The postprocessing results need to be critically reviewed, however, as false positives can occur.

Besides anatomical imaging, MRI techniques are advancing towards visualization of white matter tracts, oxygenation, perfusion and metabolites, all of which can contribute to noninvasive identification of diseased epileptic brain tissue and the epileptic network. Diffusion tensor imaging enables quantification of white matter tracts and was able to classify the side of the epileptic focus in patients with mesiotemporal epilepsy with 84% sensitivity and 89% specificity for surgical outcome[139]. Atypical white matter tracts outside the resected area were found to predict worse postsurgical outcomes[140]. Individualized patient brain network models based on tractography can be used to define the seizure propagation zone, the extent of which is inversely related to the success of resective surgery[141].

MRI can also be used to assess brain function. The resting-state activity of the brain can be visualized by fMRI, and independent component analysis of the fMRI signal can identify epilepsy-related activation[142]. Like the functional networks on EEG, fMRI networks can show increased regional connectivity within the resection site, which relates to good postsurgical outcome[143]. By contrast, high levels of connectivity in the contralateral thalamus have been related to poor postsurgical outcomes[144,145]. One study showed that connectivity, as measured by diffusion-weighted MRI and fMRI, predicted postsurgical outcomes with 100% accuracy in 22 individuals with temporal epilepsy[146]. Arterial spin labelling (ASL) reveals focal hypoperfusion after a seizure, and pulsed arterial spin labelling can identify pathological hippocampal tissue in temporal lobe epilepsy[147,148].

Various techniques can be used to visualize brain tissue during surgery. Intraoperative MRI can be used to modify the extent of resection during surgery[149,150], although it is unclear whether this approach leads to better outcomes[151]. Automated image registration based on segmentations of brain regions of interest can help to align preoperative and perioperative scans, with corrections for brain shifts due to the surgery[152].

In addition, intraoperative elastography provides an ultrasound-based method to recognize dysplastic brain tissue[153].

Cortical metabolism

Several PET ligands can be used to measure the function of neuronal receptors, transporters and other molecules. ^{11}C-flumazenil PET (^{11}C-FMZ–PET) targets the $GABA_A$–central benzodiazepine receptor complex and yields potential complementary information to ^{18}F-FDG–PET, especially in cryptogenic frontal lobe epilepsy[154]. Removal of the area of ^{11}C-FMZ–PET — but not ^{18}F-FDG–PET — hypometabolism is associated with good postsurgical outcomes in neocortical epilepsy[38]. The presence of periventricular increases in the ^{11}C-FMZ–PET signal in the white matter predicts worse outcome after resection of a hippocampus with sclerosis[155].

^{11}C-α-methyl-L-tryptophan PET (^{11}C-AMT–PET) studies label tryptophan, a precursor of serotonin. ^{11}C-AMT–PET can distinguish epileptogenic from nonepileptogenic tubers in patients with tuberous sclerosis, but the high costs of this technique limit its availability[156,157].

Advanced signal mapping facilitates the interpretation of PET and SPECT scans. 3D measures or reconstructions of PET and SPECT scans improve signal-to-noise ratios[158,159]. Application of MRI-based grey matter segmentation to the evaluation of PET scans doubles the sensitivity for detection of the seizure onset zone found with invasive EEG[160], and simultaneous PET and MRI increases the diagnostic yield for detecting potential epileptic lesions[161]. Statistical postprocessing of ictal–interictal SPECT and comparison to normal brain perfusion, using techniques such as SISCOM and ictal–interictal SPECT analysis by statistical parametric mapping (ISAS or STATISCOM), enhances localization of relative hyperperfusion in temporal lobe and extratemporal lobe epilepsy[162–164].

Magnetic resonance spectroscopy (MRS) can be used to acquire information on the relative concentrations and physical properties of several metabolites in localized brain regions. MRS shows reduced levels of lactate and increased levels of creatine plus phosphocreatine and choline in epileptic brain regions and decreased *N*-acetylaspartate to creatine and choline ratios in the epileptic temporal lobe[165,166]. This technique can independently identify the pathological hippocampus in people with normal anatomical MRI scans[148], and ^{1}H-MRS thermometry showed focal hyperthermia in the epileptogenic focus in children with continuous spiking[167].

Intraoperative dynamic optical signal imaging reveals interictal metabolism by visualizing changes in haemodynamic oscillations and might provide an intraoperative measure to distinguish epileptic from healthy brain tissue in the future[168].

Changing concepts

Advances in MRI have shifted the focus from studying the EEG characteristics and semiology of seizures to finding the underlying causative abnormality. Finding the cause of seizures is difficult with noninvasive neurophysiological recordings. Epilepsy is a bistable disease involving both nonseizing and seizing activity, and once the stability has crossed the tipping point to start a seizure the signal displays a large network, which can mask the initial precipitating event.

In the past, we have tended to emphasize the things that we can see, such as MRI lesions, apparent semiology and EEG signal changes during seizures. However, standard MRI sequences and EEG techniques do not recognize everything, as becomes apparent after increasing the resolution with high-field MRI, high-density and highly sampled EEG, MEG and ECoG, and improving signal-to-noise ratios with signal postprocessing. The increasing sensitivity of imaging is decreasing the number of truly nonlesional epilepsy cases, leading us to wonder whether we should expect all patients with focal epilepsy to display a structural abnormality at the microscopic level.

In parallel with the exhaustive search for structural abnormalities, the detailed analysis of EEG activity has intensified. Spikes are pathognomonic for epilepsy, but HFOs, especially fast ripples and very-high-frequency oscillations, can be specific for the epileptogenic area. An apparent lack of HFOs might be attributable to spatial or temporal under-sampling. Analogous to the situation with microscopic structural abnormalities, it might be essential to include tissue that generates these pathological high frequencies in the resection. Moreover, an aberrant high-frequency background signal that occurs between epileptiform spikes and HFOs might reflect the underlying abnormal micronetwork. Machine learning could improve the recognition of diseased cortex by MRI and EEG by recognizing small and complex signal pattern changes that are not easily recognized visually.

Focal epilepsy involves changes within the brain network, even if removal of a confined focus yields seizure freedom. The biggest clinical problems during seizures, such as loss of consciousness, result from the spread of seizure activity rather than from the focal neuronal disturbance. In addition, studies of lesions and networks beyond the presumed epileptogenic zone have shown that abnormalities and increased connectivity outside the resection area are predictors of poor outcome. Epileptic networks evolve over time owing to secondary epileptogenesis in epilepsy-prone anatomical structures, rapid involvement of physiological circuits or network activation of several diseased areas, such as in tuberous sclerosis[81,169,170]. A clinically useful network measure should be able to predict, at the individual patient level and before surgery, who will not profit from focal resection only, and how the network needs to be disrupted to achieve seizure freedom. Both removal of epileptogenic tissue and network disruption are restricted by the expected effects on eloquent brain function, and the surgical plan should be weighed against local and global interference of function. In individual cases, computer models based on neuronal networks might aid prediction of which surgical approach will be successful in terms of effective seizure control with maximal sparing or even improvement of brain functioning.

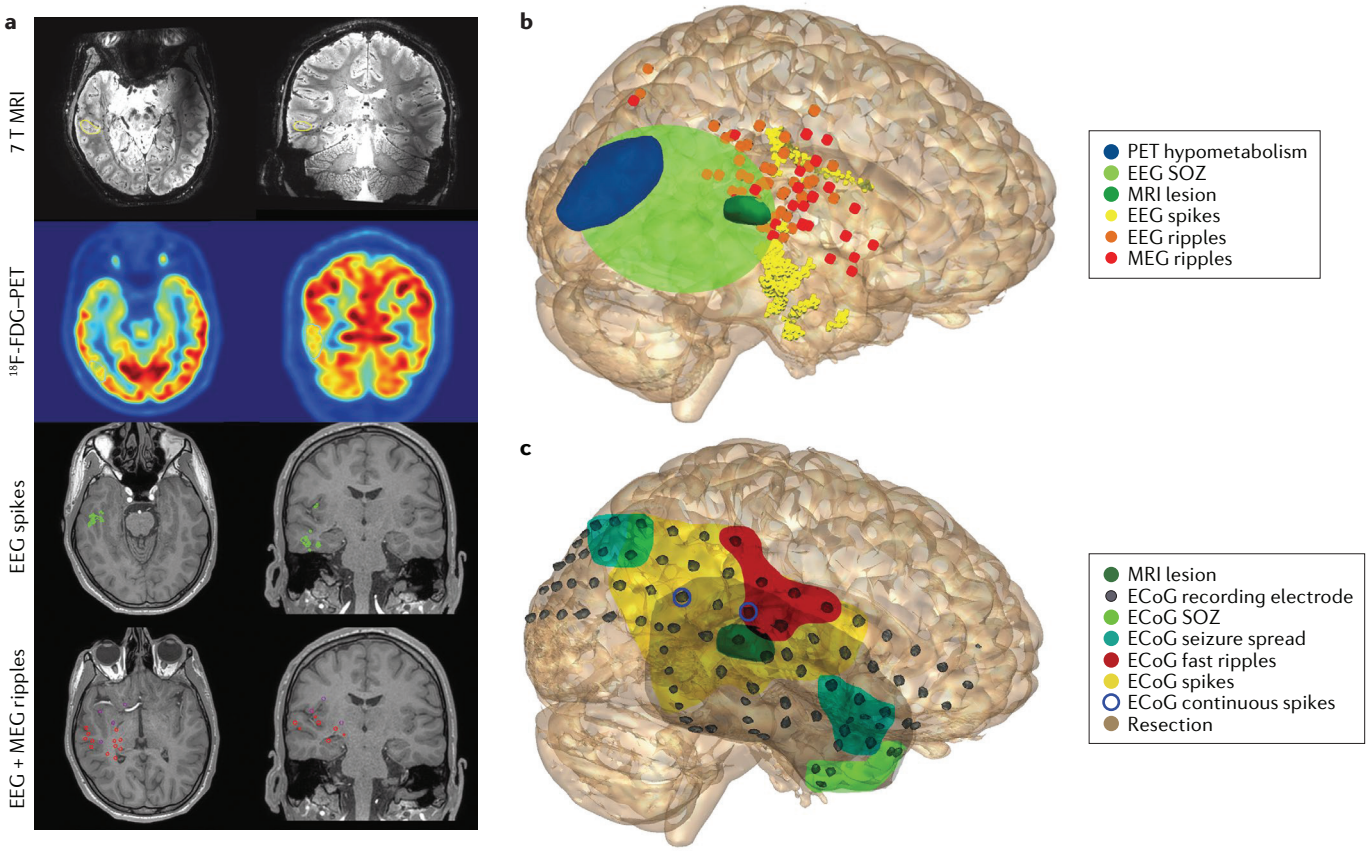

Fig. 3 | **Multimodal imaging.** The figure shows data from a patient with focal epilepsy who experienced bilateral tonic–clonic seizures preceded by dizziness as the presenting semiology. **a** | Transverse and coronal image slices from 7 T MRI and ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG–PET), along with projected EEG localized spikes and magnetoencephalography (MEG) + EEG ripples. **b** | Data from noninvasive techniques projected onto a 'glass brain'. The image depicts PET (dark blue), ictal EEG (light green), MRI (dark green), interictal EEG (yellow) and interictal ripples (orange for EEG and red for MEG). **c** | Invasive and intraoperative findings projected onto a 'glass brain'. The image shows the resected area (grey), the MRI lesion (dark green), the electrocorticography (ECoG) seizure onset zone (SOZ; light green) and seizure spread (turquoise), fast ripples (red), interictal spikes (yellow) and sites of continuous spiking (encircled with dark blue). The MRI findings show a close relationship with the fast ripples, continuous spiking pattern and EEG and MEG ripples. The irritative zone, SOZ and PET hypometabolism extend beyond the resection margin. After resective surgery, the patient received antiepileptic drugs and was seizure-free after a follow-up period of 24 months.

Although we are accustomed to waiting for spontaneous seizures and interictal events, a reproducible and on-demand situation can be generated with electrical, magnetic or optical stimulation. In fact, one might argue that epileptiform activity can never be truly spontaneous and always requires some sort of internal or external generating trigger. The most interesting stage is the tipping point where rest turns into activity, whether this encompasses interictal epileptiform discharges, HFOs or seizures. Important questions include how to find the stimulus that best resembles the natural trigger, and how to find the right threshold to prevent abundant triggers in healthy tissue. However, constant fluctuations in the state of the brain could make it impossible to delineate seizure triggers in a single consistent manner.

Owing to the multifactorial nature of the disease, localization of epilepsy requires the integration of multiple levels of information. Simultaneous visualization of different modalities, including PET, EEG, MRI and MEG, on cross-sections and 'glass brain' images (FIG. 3) is already improving the presurgical process and postsurgical outcomes[171], and software interfaces to facilitate this process are being developed[172]. The diagnostic procedure can be expedited by integrating several techniques into a single-session procedure[173]. Integration of multiple modalities requires technically and medically trained personnel transcending the specialized disciplines of neurophysiology, radiology and nuclear medicine. Correct interpretation of the integrated images, especially if based on metabolism, requires information on the state of the patient, such as the time lapse from the last seizure[174]. Information from one modality can also be used to direct the recording of another modality; for example, zoomed MRI can be steered by combined EEG and MEG[175]. In addition, multimodal imaging can be weighted for the predictive value of each modality, depending on patient factors, brain lobe and congruence with other modalities[176,177]. Prediction models based on multimodal imaging might predict the expected efficacy of surgery to aid surgical planning and patient counselling.

Identification of epileptogenic brain tissue during surgery has the advantage of giving the neurosurgeon direct feedback on the completeness of the resection. Direct surgical guidance could be enhanced by integrating presurgical information with intraoperative electrographical, structural and metabolic recordings. Recording of HFOs has revived interest in intraoperative ECoG. Advanced recording and analysis of high-frequency background EEG activity might enable direct recognition of underlying misconnected tissue. Several efforts involving signal analysis of interictal data have been undertaken to identify the electrodes that overlie the epileptogenic tissue. These studies have used various characteristics that are typical of HFOs; for example, linking high-frequency activity to the phases of the lower frequencies (susceptibility), finding sudden changes in the signal (suddenness) and looking for connectivity between channels (spread)[68,69,178]. Combining these different characteristics might further optimize signal analysis. The individual recording methods might also be improved by taking these characteristics into account. For example, electrical stimulation forces lower-frequency drivers of HFOs (susceptibility), low-noise recordings improve recognition of true sudden changes in the signal (suddenness) and recording at high density increases the connectivity information by multiplying the number of recording electrodes (spread)[179,180].

The increasing complexity of surgical cases calls for optimized diagnostics, as described above. Determination of the clinical value of the listed experimental techniques requires input from large numbers of well-defined clinical cases, but the group of people entering the diagnostic presurgical trajectory is relatively small and diverse. International collaboration is needed to build large datasets to enable data mining for prediction models. In the meantime, the surgical procedures themselves are changing, and thermoablation with stereo-EEG electrodes and laser surgery is gaining in interest.

Conclusions and future directions

The EEG seizure onset zone is the most intuitive target for surgery, but it is not the 'holy grail'. Integrating information from other resources that delineate aberrant brain tissue improves surgical outcome. On the basis of our own clinical experience, affirmed by the literature, we would suggest that centres should at least have access to a 3 T MRI scanner with a dedicated epilepsy protocol, as well as PET, video-EEG and invasive EEG. These resources should preferably be complemented by at least one electrical source localizing technique (ESI, MEG or EEG–fMRI), SPECT, and postprocessing of MRI, PET and SPECT scans.

Future technological developments can be expected in several directions. High-field MRI and high-density EEG recordings will allow all the available signal to be picked up, including microscopic signal abnormalities that can be contained within a macroscopically normal signal. In addition, focal epilepsy involves a large-scale network, and we need to understand how the epileptogenic tissue connects within the brain network in order to plan optimal surgical strategies. Electrical stimulation might help us to instantaneously identify the epileptogenic tissue and network and obviate the need to wait for spontaneous activity. Alternative resources such as metabolic and even molecular imaging may reveal epileptogenic tissue from a different perspective to structural MRI and EEG. Integration of patient-level information with prediction models based on large datasets will aid surgical planning and patient counselling. Finally, direct intraoperative guidance with on-site measurement and integration of multimodal information could increase surgical precision.

To incorporate the developments described above into our daily procedures, we will need to invest in equipment, upgrade analytical methods and hire medically trained technologists and/or train existing personnel to acquire the necessary technical skills. These investments should ultimately save money by speeding up the presurgical trajectory, reducing human energy and time spent on interpreting signals, shortening multidisciplinary meetings and increasing the surgical success rate. International and multidisciplinary collaboration is needed to combine viewpoints, penetrate to the essence of this multifactorial disorder and reach a full understanding of the epileptogenic tissue and epileptogenic network to enable optimization of surgical strategies.

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