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The role of high-frequency oscillations in epilepsy surgery planning

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Abstract

Background—Epilepsy is a serious brain disorder characterized by recurrent unprovoked seizures. Approximately two-thirds of seizures can be controlled with antiepileptic medications (Kwan 2000). For some of the others, surgery can completely eliminate or significantly reduce the occurrence of disabling seizures. Localization of epileptogenic areas for resective surgery is far from perfect, and new tools are being investigated to more accurately localize the epileptogenic zone (the zone of the brain where the seizures begin) and improve the likelihood of freedom from postsurgical seizures. Recordings of pathological high-frequency oscillations (HFOs) may be one such tool.

Objectives—To assess the ability of HFOs to improve the outcomes of epilepsy surgery by helping to identify more accurately the epileptogenic areas of the brain.

Search methods—We searched the Cochrane Epilepsy Group Specialized Register (15 April 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (*2013*, Issue 3), MEDLINE (Ovid) (1946 to 15 April 2013), CINAHL (EBSCOhost) (15 April 2013), Web of Knowledge (Thomson Reuters) (15 April 2013), www.clinicaltrials.gov (15 April 2013), and the World Health Organization International Clinical Trials Registry Platform (15 April 2013).

Selection criteria—We included studies that provided information on the outcomes of epilepsy surgery at at least six months and which used high-frequency oscillations in making decisions about epilepsy surgery.

Data collection and analysis—The primary outcome of the review was the Engel Class Outcome System. Secondary outcomes were responder rate, International League Against Epilepsy (ILAE) epilepsy surgery outcome, frequency of adverse events from any source and

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CONTRIBUTIONS OF AUTHORS

David Gloss wrote the draft and made additions to it.
Rick Staba reviewed and added to the draft.
Sarah Nolan modified the draft and wrote part of the statistical sections of the review.

quality of life outcomes. We intended to analyse outcomes via an aggregated data fixed-effect model meta-analysis.

Main results—Two studies met the inclusion criteria. Both studies were small non-randomised trials, with no control group and no blinding. The quality of evidence for all outcomes was very low. The combination of these two studies resulted in 11 participants who prospectively used ictal HFOs for epilepsy surgery decision making. Results of the postsurgical seizure freedom Engel class I to IV outcome were determined over a period of 12 to 38 months (average 23.4 months) and indicated that six participants had an Engel class I outcome (seizure freedom), two had class II (rare disabling seizures), three had class III (worthwhile improvement). No adverse effects were reported. Neither study compared surgical results guided by HFOs versus surgical results guided without HFOs.

Authors' conclusions—No reliable conclusions can be drawn regarding the efficacy of using HFOs in epilepsy surgery decision making at present.

Medical Subject Headings (MeSH)

*Decision Making; Electroencephalography [*methods]; Epilepsy [*surgery]; Seizures [surgery]; Treatment Outcome

MeSH check words

Humans

PLAIN LANGUAGE SUMMARY

The role of high-frequency oscillations in epilepsy surgery planning

Seizures are typically short events with changes in awareness, changes in feelings or sensations, and strange body movements. Epilepsy is characterized by recurrent seizures. More than half of the people with epilepsy have seizures which can be controlled with medication. For those with epileptic seizures that do not respond to medication, surgery can treat the seizures in many, but not all, individuals. New tools are being investigated to more accurately find the area in the brain which produces the seizures, to help remove the area of the brain causing the seizures. Recordings of high-frequency oscillations (HFOs) (these are signals in the brain that oscillate faster than the typical signals that are recorded) may be one such tool. Our literature searches, carried out on 15 April 2013, found that so far 11 participants have been enrolled in two small prospective studies that used recordings of abnormal HFOs to help delineate the epileptogenic zone and guide resective surgery. No reliable conclusions can be drawn from the limited evidence that exists at present.

BACKGROUND

Description of the condition

Epilepsy is a common disorder of the human brain, accounting for approximately 1% of the global burden of disease (Murray 1994). It has an incidence of 33 to 57 per 100,000 person-years (Annegers 1999; Hirtz 2007; MacDonald 2000; Olafsson 2005) and a lifetime risk

(risk of a person developing epilepsy in their lifetime) of 1300 to 4000 per 100,000 (Hauser 1993; Juul-Jenson 1983). One study estimates that the lifetime prevalence of epilepsy is almost 70 million people world-wide (Ngugi 2010).

"Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED [antiepilepsy drug] schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan 2010). More than one-third of individuals with epilepsy will be drug-resistant (Kwan 2000; Mohanraj 2006). In individuals with drug-resistant epilepsy, the probability of further drug trials using other proven medications to stop all seizures is extremely low (Kwan 2000; Mohanraj 2006); in these cases, epilepsy surgery is often considered (Engel 2003). Unfortunately referral of individuals who are candidates for epilepsy surgery can take many years. One study had a range of referral for surgery that was from zero to 46 years (Berg 2003). This large range was in part owing to the fact that some individuals who have been seizure free for some time for unknown reasons develop seizures while stable on antiepileptic drug medication. The range of referral for surgery is one of the many factors that determines the likelihood of postsurgical seizure freedom in individuals with drug-resistant seizures (Berg 2003; Berg 2006).

Another important factor contributing to postsurgical seizure freedom is determination of the epileptogenic zone, which is the area necessary and sufficient for the generation of spontaneous seizures. Identification of the epileptogenic zone can be difficult because it cannot be measured directly and has to be derived from the following diagnostic tests:

1. clinical history including seizure semiology (the attempt to localize the epileptogenic zone from the behavioural manifestation of the seizure);
2. electroencephalogram (EEG) recordings of both ictal (during a seizure) and interictal (baseline state, when the individual is not having a seizure) activity;
3. magnetic resonance imaging (MRI).

Other modalities are also used that depend on the individual; the specialists who are available; local, regional, and national practice; and sometimes cost and availability, which can vary across centres. These include:

1. neuropsychological testing;
2. magnetoencephalography (mapping brain activity using the tiny magnetic fields induced from the electrical activity of the brain);
3. invasive EEG recordings (in which an EEG recording is done either on the surface of the brain or where wires are inserted into the brain to perform the recording, which require surgery to be done to accomplish the recordings);
4. intracarotid amobarbital testing (this is a test of language and memory, where half of the brain is put in a sleep state for a couple of minutes to see if the other side can maintain language and memory);
5. other imaging modalities using a specialized computed tomography (CT) scanner such as positron emission tomography (PET), single photon emission computed

tomography (SPECT) (this test shows blood flow in the brain during or immediately after a seizure), or special MRI studies like the use of a surface coil or looking at fibre tracts.

Concordance of the localization of the seizure focus from multiple tests is thought to significantly improve the prognosis of postsurgical seizure freedom because the epileptogenic zone is more clearly ascertained, and thus can be more clearly removed in surgery. When there is discordance, and it is less clear how to measure the epileptogenic zone, it makes the surgical decision more prone to error. There is some controversy about the reasons for failures of epilepsy surgery but the most common reason is that there is incomplete resection of the epileptogenic zone (Bautista 1999; Hennessy 2001; Jehi 2009; Mathern 2007).

EEG recordings to identify sites of ictal onset are most commonly used to localize the epileptogenic zone, although such recordings may not be accurate. Intracranial depth evaluation can better distinguish between neocortical and subcortical ictal onsets. Recordings of interictal EEG spikes are often used to help determine the epileptogenic zone. There is evidence that some interictal EEG spikes correspond to the epileptogenic zone, while others do not (Engel 2009). High sampling (a minimum of 800 Hz) of scalp and depth electrodes can show interictal local field potentials called high-frequency oscillations (HFOs). In the normal mammalian brain, HFOs occur spontaneously during slow wave sleep and can be evoked during sensory information processing. In the epileptic brain, interictal pathological HFOs are associated with brain areas capable of generating spontaneous seizures and can occur either independently or coincident with some EEG spikes. Based on these latter findings, some have proposed that pathological HFOs may identify interictal EEG spikes that reliably reflect the epileptogenic zone (Engel 2009). Furthermore, pathological HFOs can occur before or during the onset of some epileptic seizures. Capturing pathological HFOs, therefore, could provide important information to identify the epileptogenic zone and help plan surgical resection that may ultimately improve the prognosis of seizure freedom.

Description of the intervention

The intervention we proposed studying was the use of interictal (activity between seizures) or ictal (immediately before or during seizures) HFOs recorded from the scalp, intracranial recordings, or intraoperative electrocorticography (when brain signals recorded from the surface of the brain during surgery are used to help determine the limits of resection) in individuals with drug-resistant epilepsy who undergo epilepsy surgery.

How the intervention might work

Interictal pathological HFOs are believed to reflect the spiking activity of small groups or clusters of neurons that are responsible for epileptogenicity (Bragin 2010; Engel 2009; Ogren 2009). There is evidence that HFOs occur immediately before or during the onset of some seizures, which suggests that HFOs could be involved in the generation of seizures (Jirsch 2006; Khosravani 2009; Worrell 2004) even though the mechanisms for their potential role in ictogenesis are not known. Nevertheless, pathological HFOs could be an

electrophysiologic biomarker of brain areas that are capable of generating spontaneous seizures (Staba 2011).

Why it is important to do this review

Current methods used to map and measure the epileptogenic area of the brain are not always accurate or reliable. There is a clear need for new diagnostic tools and techniques in order to improve surgical outcomes (Wiebe 2001). An example of a new tool that is not in common use is interictal pathological HFOs, which may be an independent predictor of the epileptogenic zone (Bragin 2000; Jacobs 2008; Staba 2004; Worrell 2008; Wu 2010). Most importantly, there is a retrospective (meaning this study was conducted after surgery was already complete) study that examined HFOs in 20 participants who underwent epilepsy surgery (Jacobs 2010). The study found that a good epilepsy surgery outcome was significantly correlated with resection of the majority of areas generating high rates of HFOs. The small number of participants and the retrospective nature of this evidence makes it at high risk of bias, therefore a larger-scale review of all available evidence should provide more reliable results.

OBJECTIVES

To assess the ability of HFOs to improve the outcomes of epilepsy surgery by helping to identify more accurately the epileptogenic areas of the brain.

METHODS

Criteria for considering studies for this review

Types of studies—This review included both randomised trials and non-randomised trials that included information about both HFOs and the outcomes of epilepsy surgery. All participants in these studies had to have surgery. The treatment groups we considered were those that either used HFOs to make surgical decisions or used HFOs as part of electrocorticography and used that information in making surgical decisions. The control groups did not use HFOs in the decision making.

Of the non-randomised studies, we included prospective cohort studies. We excluded case-control studies and retrospective cohort studies since they do not prove causation; and retrospective studies where participants were ascertained after surgery (for example, case reports and case series). We considered other trial designs on a case-by-case basis.

Types of participants—The participants could include males and females, adults, children of all ages with any diagnosis of epilepsy, as long as they were drug-resistant. We did not exclude participants with a comorbidity.

Types of interventions—The participants needed to have had epilepsy surgery and electrophysiologic recordings containing evidence for HFOs that were reviewed before or during surgery and used as part of surgical decision making.

Types of outcome measures

Primary outcomes: The primary outcome was the Engel Class Outcome System (Engel 1993), which is defined as follows:

- class I is free of disabling seizures;
- class II is rare disabling seizures;
- class III is worthwhile improvement;
- class IV is no worthwhile improvement.

We measured the classes as an ordinal outcome (meaning that the different classes follow an order). An intention-to-treat (ITT) approach was taken with this outcome.

We accepted all data provided on the outcomes of epilepsy surgery. We converted outcomes, whenever possible, to the Engel Class Outcome System (Engel 1993) in order to compare results across studies from different epilepsy centres. The data for individual papers were presented in the rawest possible form where they used other forms of grading of outcome.

Secondary outcomes

- Responder rate (the proportion of participants who experience a 50% or greater reduction in seizure frequency from baseline to maintenance period). We included any maintenance period of at least six months.
- We included any dichotomous (data that can be divided into two categories) measure in cases where we were unable to analyse the data as ordinal data: 'good' Engel Class Outcome (classes I and II) versus 'bad' Engel Class Outcome (classes III and IV).
- International League Against Epilepsy (ILAE) epilepsy surgery outcome (Wiser 2001).
- Proportion of patients that experienced at least one adverse event from any source.
- Proportion of patients that experienced each separate adverse event from any source.
- Quality of life outcomes measured with objective data.

An ITT approach was taken with all outcomes.

Search methods for identification of studies

Electronic searches—We searched the following databases with no language restrictions.

1. The Cochrane Epilepsy Group Specialized Register (15 April 2013), using the search terms 'high frequency oscillations', 'ripples' or 'fast ripples', and 'epilepsy surgery'.

2. The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2013, Issue 3) using the search strategy outlined in Appendix 1.
3. MEDLINE (Ovid) (1946 to 15 April 2013) using the search strategy outlined in Appendix 2.
4. CINAHL (EBSCOhost) (searched on 15 April 2013) using the search strategy outlined in Appendix 3.
5. Web of Knowledge (Thomson Reuters) (15 April 2013) using the search strategy outlined in Appendix 4.
6. ClinicalTrials.gov (15 April 2013) using the search terms 'frequency oscillation'.
7. World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/Default.aspx) (searched on 15 April 2013) using the search terms outlined in Appendix 5.

For any articles identified for full review, we used the 'related search' function (where available) and also reviewed the first 25 related abstracts for possible inclusion. While it was likely that this search strategy would lead to redundant information, it was possible that it would yield additional articles to consider for inclusion.

An initial search was planned. An updated search was also performed, so that the information would be recent enough for publication.

Searching other resources—We contacted experts in the field for information about any unpublished or ongoing studies.

We reviewed the reference lists of retrieved studies to search for additional reports of relevant studies.

Data collection and analysis

When authors disagreed, they used the consensus-oriented decision making model to create consensus. They used a decision rule of unanimous agreement.

Selection of studies—Once the list of non-redundant abstracts had been compiled, two authors (DG and RS) independently searched for trials and assessed them for inclusion. Any disagreements were resolved by mutual agreement.

Data extraction and management—Two review authors (DG and RS) extracted data onto a data extraction form; any disagreements were resolved by mutual agreement.

The data form included:

- study design, including information about randomisation and clusters, blinding, allocation concealment, sequence generation, a priori protocol, a priori analysis plan, type of study;
- study size, including number participants, type of epilepsy, information about participants;

- type of intervention with HFOs;
- outcomes, including number of dropouts and time points collected, follow-up, adverse effects, addressing incomplete outcome data, selective reporting;
- identification of and method used to control for confounders;
- ORBIT classification of the primary outcome (Kirkham 2010).

We recorded the raw form of the data, when possible.

Assessment of risk of bias in included studies—For randomised trials, we assessed the risk of bias in the included studies using the Cochrane Collaboration's tool for assessing risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and contained in RevMan 5.2 (RevMan 2011) (see Appendix 6).

For non-randomised trials, we assessed the risk of bias using the tools developed by B Reeves and G Wells, which address confounding, study design features, and a specific non-randomised risk of bias table. Their non-randomised risk of bias tool was further edited by Jen Pulman (see Appendix 7).

It is important to understand that both randomised and non-randomised trials were assessed using the same criteria, although the tables may look somewhat different. Both were subjected to the GRADE profiler for applicability, and both were subjected to an assessment of confounding (see Appendix 8).

We assessed the impact of outcome reporting bias via the ORBIT tool (Kirkham 2010).

Measures of treatment effect—We measured the primary outcome as an ordinal outcome; frequency and percentage of individuals classified as classes I to IV of the Engel Class Outcome System (Engel 1993).

We measured the secondary outcomes as follows:

- responder rate measured as the frequency and the proportion of patients who experienced a 50% or greater reduction in seizure frequency from baseline to maintenance period;
- 'good' Engel Class Outcome (classes 1 and 2) versus 'bad' Engel Class Outcome (classes 3 and 4) was measured as a dichotomous outcome and expressed as risk ratio (RR) with 95% confidence interval (CI);
- adverse events were measured as the frequency and proportion of patients who experienced each single adverse event;
- quality of life outcomes measured with objective data, depending on how such outcomes were reported in the individual trials.

We used an ITT approach for all outcomes.

For individual listed adverse effects, 99%CIs were quoted to make allowances for multiple testing.

Unit of analysis issues—We did not expect any unit of analysis issues, except possibly for repeated measures (data measured at different time points). We considered measurements at three months, six months, one year, and two years, and we analysed the outcomes at each of these time points separately. If studies were found that used other times for measuring outcomes, they were considered on a case-by-case basis.

Dealing with missing data—We collected data missing from published studies, abstracts, and posters by accessing data from unpublished sources, which we attempted to obtain from the authors. We undertook further sensitivity analysis to determine the effect of the addition of these data on the final results.

We investigated, where data were missing, why they are missing and whether the data were missing at random.

We did not attempt to complete missing individual patient data.

Assessment of heterogeneity—We planned to assess clinical heterogeneity by comparing the distribution of patient demographic factors (age, seizure type, number of antiepileptic drugs (AEDs) taken at randomisation) included in the trials. Statistical heterogeneity was planned to be assessed by visually inspecting forest plots and using a Chi^2 test for heterogeneity (with a P value of 0.10 for significance) and the I^2 statistic as a measure of inconsistency across studies (Higgins 2011).

The interpretation of I^2 values was the following:

- 0% to 40%, may not be important;
- 30% to 60%, may represent moderate heterogeneity;
- 50% to 90%, may represent substantial heterogeneity;
- 75% to 100%, represents considerable heterogeneity.

If significant statistical heterogeneity was found to be present, or considerable heterogeneity according to the I^2 statistic, we planned to perform meta-analysis with the random-effects model rather than a fixed-effect model, and sensitivity analyses investigating differences in study design and characteristics or patient demographic factors.

Assessment of reporting biases—We used the ORBIT study classification scheme to classify trials and assign a risk of bias for the primary outcome (Kirkham 2010). Funnel plot asymmetry was planned to be assessed if more than 10 studies were found. The Cochrane Collaboration recommends a minimum of 10 studies to be combined when examining funnel plots (Higgins 2011). Reasons for asymmetry include publication bias, outcome reporting bias, language bias, citation bias, poor methodological design, and heterogeneity. These can be assessed for each trial.

Data synthesis—We would have liked to have been able to perform an individual participant data analysis since we expected that different trials would report different time endpoints. An individual participant data analysis could standardize the different outcomes

to a single outcome (Engel Class Outcome System) for meta-analysis (Engel 1993). If we were able to obtain individual patient data, we could have combined the data in a stratified fixed-effect model analysis. As we were not able to obtain individual patient data for all the trials, we did not try to perform a combined individual patient data and aggregate analysis. Instead we planned to carry out a conventional aggregate data fixed-effect model meta-analysis.

If considerable statistical heterogeneity was found to be present (Chi^2 test for heterogeneity P value < 0.1 or I^2 greater than 75%, or both), we could have performed a random-effects model meta-analysis rather than a fixed-effect model meta-analysis and we would have investigated differences in study characteristics and patient demographics.

A Bayesian analysis for combining randomised and non-randomised evidence could have been performed if the data that we obtained allowed for it.

If any outcome was not reported sufficiently to perform a meta-analysis (for example adverse events or quality of life), we described such outcomes narratively.

Subgroup analysis and investigation of heterogeneity—If there were randomised trials and non-randomised trials, we would have examined the randomised trials alone to see if the combined estimate of effect was similar to the combination of randomised and non-randomised trials.

Sensitivity analysis—We would have performed a sensitivity analysis for any outcome involving a trial with substantial missing data (more than 10% of data missing).

For missing outcome data, we planned to use a best-case and worst-case scenario analysis where the best case assumed all patients with missing outcome data had a good outcome (Engel class I) and the worst case assumed all patients with missing outcome data had a bad outcome (Engel class IV).

Summary of Findings—We used the GRADE process to consider the measures of treatment effect of the included studies. A Summary of Findings table was created which summarized the GRADE process for these outcomes.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search—The search yielded 742 abstracts of which 26 were deemed likely to be relevant and 717 were excluded because they did not meet the inclusion criteria. Searching the 26 references led to one additional paper (Khosravani 2009). Of the 27 papers, two met the inclusion criteria. An updated search found 127 abstracts of which six were deemed likely to be relevant. There were an additional six papers that the authors were aware of, which had been published after the search was completed, and one additional

paper found by searching the references. None of these additional papers met the inclusion criteria.

Included studies—Two studies met the inclusion criteria and included Engel class outcome data. Neither were randomised studies and neither had a specific time point for analysis, but as both included patients whose outcome was measured at least at 12 months, both papers were included.

In Modur 2011, a prospective cohort study, there were six participants with medically refractory neocortical epilepsy undergoing intracranial EEG recording with subdural grids and depth electrodes. The six participants were three females and three males between the ages of 19 and 32 years with a duration of epilepsy ranging from 6 to 30 years. The delineation of the seizure onset zone for surgical resection was based on contiguous recording sites that contained sustained evolution of ictal HFOs (> 70 Hz), including areas of spread during the first 2 sec of ictus, plus 1 cm of cortex surrounding the seizure-onset zone. The surgical boundaries were modified to exclude eloquent areas identified with functional stimulation, as well as sites with or without ictal HFOs that were not contiguous with the area of the seizure onset zone. There was no control group in the study.

In RamachandranNair 2008, a prospective cohort study, there were five participants with medically refractory epileptic spasms undergoing intracranial EEG recording with subdural grids. The five participants were three females and two males between the ages of 4 and 14 years with a duration of epilepsy ranging from 0.4 to 8 years. A combination of neocortical ictal HFOs (80 to 250 Hz), magnetoencephalography (MEG) dipole spike source localization, lesions present on MRI, and eloquent cortex were used to determine the resective zone for epilepsy surgery. There was no control group in the study.

Excluded studies—Of the 38 studies that were excluded, 14 were retrospectives series that specifically looked at HFOs. Ten were retrospective series that looked in higher frequency bands that included HFOs but did not specifically look at HFOs. Ten provided HFO data but the data were not included in epilepsy surgery decision making. Four did not provide any outcome data at all, in any format.

Risk of bias in included studies

See: Characteristics of included studies.

Allocation—There was no randomisation in either trial. Therefore, there was no allocation concealment.

Blinding—Neither trial had blinding of either researchers or participants and, therefore, there was a high risk of performance bias in both studies.

Incomplete outcome data—There was no evidence of incomplete follow-up. Every participant reported in both of the papers had a follow-up long enough to be included in the epilepsy surgery outcome (Engel class outcome).

Selective reporting—We were unable to look for reporting bias in a funnel plot due to the small number of papers included. We do not know of any negative reports that were not published. The ORBIT classification was F (low risk of bias) for both papers.

Other potential sources of bias—Both trials involved extremely small numbers of patients, making it hard to draw any conclusions from the trials. Because of the small numbers of patients, there is a high risk for spectrum bias. Neither trial examined possible confounders.

Effects of interventions

See: Summary of findings for the main comparison High frequency oscillations for epilepsy surgery in medically refractory epilepsy

We are not able to extract sufficient data from the two studies to perform a meta-analysis as neither study included a comparator group and the two studies reported outcomes at different time points. Therefore, we could only combine the outcomes narratively for the 11 participants in the two groups.

In Modur 2011, the outcome of the six participants was determined over a follow-up period of 20 to 38 months (mean 26.5 months). The outcome was Engel class I in three participants (50%), II in three participants (33.3%), and III in one participant (16.7%). No adverse effects were reported. Quality of life data were not gathered. In RamachandranNair 2008, the outcome of the five participants was determined over a period of 12 to 29 months (mean 19.6 months). The outcome was reported to be seizure free in three participants (60%), 50% to 75% seizure reduction in one participant (20%), > 90% seizure reduction in one participant (20%). Converting to Engel class, three participants (60%) had Engel class I and two participants (40%) had Engel class III. There were no adverse effects reported. Quality of life data were not gathered.

Taken together, the two studies included 11 patients that prospectively used ictal HFOs for epilepsy surgery decision making. For the primary outcome of Engel class, determined over a period of 12 to 38 months (mean 23.4 months), six participants (54.5%) had Engel class outcome I, two participants (18.2%) had class II, and three participants (27.3%) had class III.

With respect to secondary outcomes, eight participants (72.7%) had a good (Engel class I or II) outcome and three participants (27.3%) had a poor (Engel class III) outcome. For one trial (Modur 2011), one participant was classified as Engel class III, which meant worthwhile improvement. It was unclear if this meant more or less than 50% improvement. Due to the small numbers of participants, and the fact that we would had to exclude one (9% of total 11 participants) due to lack of information, we did not think it was reliable to provide a responder rate. Quality of life data were not provided. No adverse effects were reported.

DISCUSSION

Summary of main results

No reliable conclusions can be drawn at present regarding the efficacy of HFO recordings in epilepsy surgery decision making. The use of ictal HFOs in epilepsy surgery decision making may be safe, although the number of patients treated is too small to be sure, and no adverse effects of the use of HFOs in surgery decision making were reported.

Overall completeness and applicability of evidence

The evidence from the two trials is far from complete. The two included studies are of very low quality for assessing the outcome of the use of HFOs in epilepsy surgery decision making. Neither were randomised. Neither had blinding of either researchers or patients. Neither had a comparator group. There is a high risk of bias in both trials with the treating provider determining a non-objective outcome. The total number of patients included in both trials is 11, which is too small a number to suggest recommending a new intervention.

Quality of the evidence

See: Summary of findings for the main comparison

Under contemporary standards, both of the small non-randomised trials provide evidence of very low quality. Neither study was blinded, had a comparator group, and both were at high risk of spectrum bias. Due to the low number of participants, we also considered there to be serious imprecision.

There were many retrospective studies excluded. When writing the protocol we decided to a priori exclude retrospective studies since they are less likely to show causality of the intervention and are at higher risk of bias than prospective studies.

Potential biases in the review process

No source of bias was identified.

Agreements and disagreements with other studies or reviews

There is no other comprehensive review of HFOs used in epilepsy surgery decision making of which we are aware, which was part of the reason for undertaking this review.

AUTHORS' CONCLUSIONS

Implications for practice

No reliable conclusions can be drawn at present regarding the efficacy of using ictal or interictal HFOs in epilepsy surgery decision making. The use of ictal HFOs in epilepsy surgery decision making may be safe although the number of patients treated is too small to be sure and no adverse effects following the use of HFOs in surgery decision making were recorded.

Implications for research

Due to the size of the current two trials, there is a need for additional trials to show the safety of using ictal or interictal HFOs in epilepsy surgery decision making. Preferably the trials should have a comparator group and measure the safety of using HFOs in surgery decision making. The safety question is particularly important for HFOs because in the epileptic mammalian brain there are both normal and pathologic HFOs, and we do not yet have a reliable way to distinguish between the two. We do not even know if we need to distinguish between the normal and pathologic HFOs when dealing with ictal HFOs. Once safety is assured, there is a need for properly designed, high quality, and adequately powered, randomised trials to determine if ictal or interictal HFOs are effective and should be recommended for use in epilepsy surgery decision making.

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DECLARATIONS OF INTEREST

David Gloss received a Research and Training Fellowship for Clinicians from the Epilepsy Foundation of America to perform research on HFOs. Dr Gloss is an evidence-based medicine methodologist for the American Academy of Neurology.

Rick Staba has participated in NIH/NINDS R01 NS071048, RO1 NS33310, P01 02808, and a joint grant from Citizen's United for Research in Epilepsy and Department of Defense, all of which relate to the study of HFOs.

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** Indicates the major publication for the study*

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APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Epilepsy] explode all trees
#2	epilepsy near/4 surg* (Word variations have been searched)
#3	MeSH descriptor: [Seizures] explode all trees
#4	seizure* (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	“high frequency oscillation” or “high frequency oscillations” (Word variations have been searched)
#7	ripple* (Word variations have been searched)
#8	#6 or #7
#9	#5 and #8

Appendix 2. MEDLINE search strategy

1. exp Epilepsy/
2. (epilepsy adj4 surg$).tw.
3. exp Seizures/
4. seizure$.tw.
5. or/1–4
6. high frequency oscillation$.tw.
7. ripple$.tw.
8. 6 or 7
9. 5 and 8

Appendix 3. CINAHL search strategy

S9 S5 and S8

S8 S6 or S7

S7 TX ripple*

S6 TX “high frequency oscillation” OR TX “high-frequency oscillation” OR TX “high frequency oscillations” OR TX “high-frequency oscillations”

S5 S1 or S2 or S3 or S4

S4 TX epilepsy N4 surg*

S3 TX seizure*

S2 (MH “Seizures+”)

S1 (MH “Epilepsy+”)

Appendix 4. Web of Knowledge search strategy

#3	#2 AND #1 *DocType=All document types; Language=All languages;*
#2	Topic=(epilep*) OR Title=(epilep*) OR Topic=(seizure*) OR Title=(seizure*) *DocType=All document types; Language=All languages;*
#1	Topic=(high frequency oscillation*) OR Title=(high frequency oscillation*) OR Topic=(ripple*) OR Title=(ripple*) *DocType=All document types; Language=All languages;*

Appendix 5. WHO International Clinical Trials Registry Platform search terms

With the 'Standard search' option, we used the following search terms:

epilep* AND high-frequency

epilep* AND high frequency

epilep* AND HFO

seizure* AND high-frequency

seizure* AND high frequency

seizure* AND HFO

Appendix 6. Risk of bias (randomised trials)

Risk of bias assessment (completed for all articles meeting eligibility)

Item		Judgement[a]	Description (quote from paper, or describe key information)
1. Sequence generation			
2. Allocation concealment			
3a. Blinding?	Outcome 1		
3b. Blinding?	Outcome 2		
4a. Incompl. outcome data addressed?	Outcome 1		
4b. Incompl. outcome data addressed?	Outcome 2		
5a. Free of selective reporting?	Outcome 1		
5b. Free of selective reporting?	Outcome 2		
7. Free of other bias?			

Judgment High/Low/Unclear

See *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 8 for assessing risk of bias for RCT evidence (Higgins 2011).

Appendix 7. Risk of bias (non-randomised studies)

Risk of bias table (non-randomised studies)

Item		Judgment[a]	Description (quote from paper, or describe key information)
1. Sequence generation			
2. Allocation concealment			
3a. Confounding[b]	Outcome 1		
3b. Confounding[b]	Outcome 2		
4a. Blinding?	Outcome 1		
4b. Blinding?	Outcome 2		
5a. Incompl. outcome data addressed?	Outcome 1		
5b. Incompl. outcome data addressed?	Outcome 2		
6a. Free of selective reporting?	Outcome 1		
6b. Free of selective reporting?	Outcome 2		
7. Free of other bias?			
8. A priori protocol?[c]			
9. A priori analysis plan?[d]			

[a] Some items on low/high risk/unclear scale (items 1–2), some on 5-point scale/unclear (items 3–7), some on yes/no/unclear scale (items 8–9). For all items, record 'unclear' if inadequate reporting prevents a judgment being made.

[b] Based on list of confounders considered important at the outset and defined in the protocol for the review (*and assessment against worksheet*)

[c] Did the researchers write a protocol defining the study population, intervention and comparator, primary and other outcomes, data collection methods, etc. in advance of starting the study? N.B. May be outcome specific.

[d] Did the researchers have an analysis plan defining the primary and other outcomes, statistical methods, subgroup analyses, etc. in advance of starting the study?

Risk of bias (RoB) tool for non-randomised studies (NRS)

Studies for which RoB tool is intended

Only suitable for 'cohort-like' studies, individually or cluster-allocated. This can include secondary analyses of clinical databases providing the analysis is clearly structured as a comparison of control and intervention participants. Refer to Ch. 13, tables 13.2.a and b:

Table 13.2.a: individually allocated study designs

- RCT - randomised controlled trial
- Q-RCT - quasi-randomised controlled trial
- NRCT - non-randomised controlled trial
- CBA - controlled before and after study (not common use of this label, see CChBA below)
- PCS - prospective cohort study
- RCS - retrospective cohort study

Table 13.2.b: cluster allocated study designs

- ClRCT - cluster randomised controlled trial
- ClQ-RCT - cluster quasi-randomised controlled trial
- ClNRCT - cluster non-randomised controlled trial
- CITS - controlled interrupted time series
- CChBA - controlled cohort before and after study (Shadish 2002)

Assessment of risk of bias

Issues when using modified RoB tool to assess cohort-like non-randomized studies:

- Follow principle for existing Cochrane RoB tool: score judgment and provide information (preferably direct quote) to support judgment;
- Modified RoB tool include an additional item on confounding;
- 5-point scale for some items (distinguish 'unclear' from intermediate risk of bias);
- Keep in mind the general philosophy - assessment is not about whether researchers could have done better but about risk of bias; the assessment tool must be used in a standard way whatever the difficulty/circumstances of investigating the research question of interest and whatever study design features were used;
- Use of a 5-point scale is uncharted territory; very interested to know whether this makes things easier or more difficult for reviewers;
- Anchors for 5-point scale: '1/No/low risk' of bias should correspond to a high quality RCT. '5/high risk' of bias should correspond to a risk of bias that means the findings should not be considered (too risky, too much bias, more likely to mislead than inform).

1. Sequence generation
    - Low/high/unclear RoB item
    - Always high RoB (not random) for a non-randomised study
    - Might argue that this item redundant for NRS since always high RoB - but important to include in RoB table ('level playing field' argument)
2. Allocation concealment
    - Low/high/unclear RoB item
    - Potentially low RoB for a non-randomised study, e.g. quasi-randomised (so high RoB to sequence generation) but concealed (reviewer judges that the people making decisions about including participants didn't know how allocation was being done, e.g. odd/even date of birth/hospital number)
3. RoB from confounding (additional item for NRS; assess for each outcome)
    - Assumes a pre-specified list of potential confounders defined in the protocol for the systematic review

- Low (1)/2/3/4/high (5)/unclear RoB item
- Judgment needs to factor in (see 'worksheet'):
    - proportion of confounders (from pre-specified list) that were considered
    - whether most important confounders (from pre-specified list) were considered
    - resolution/precision with which confounders were measured
    - extent of imbalance between groups at baseline
    - care with which adjustment was done (typically a judgment about the statistical modeling carried out by authors)
- Low RoB requires that all important confounders are balanced at baseline, i.e.
    - not primarily/not only a statistical judgment, OR
    - measured 'well' and 'carefully' controlled for in the analysis.

  We have provided an optional 'worksheet' to help reviewers to focus on the task (rows=confounders and columns=factors to consider). Reviewers should make a RoB judgment about each factor first and then combine these (by eyeballing rather than quantitatively) to make the judgment in the main RoB table.

4. RoB from lack of blinding (assess for each outcome, as per existing RoB tool)
    - Low (1)/2/3/4/high (5)/unclear RoB item
    - Judgment needs to factor in:
        - nature of outcome (subjective / objective; source of information)
        - who was/was not blinded and the risk that those who were not blinded could introduce performance or detection bias
        - see Ch. 8
5. RoB from incomplete outcome data (assess for each outcome, as per existing RoB tool)
    - Low (1)/2/3/4/high (5)/unclear RoB item
    - Judgment needs to factor in:
        - reasons for missing data

- whether amount of missing data balanced across groups, with similar reasons
- whether group comparison appropriate (e.g. 'analysed in allocated group' issue)
- see Ch. 8

6. RoB from selective reporting (assess for each outcome, N.B. more wide ranging than existing Ch. 8 recommendation). Key issue is whether outcomes were clearly defined, and methods of analysis, were pre-specified and adhered to.

- Low (1)/2/3/4/high (5)/unclear RoB item
- Judgment needs to factor in:
  - existing RoB guidance on selective outcome reporting, see Ch. 8
  - also, extent to which analyses (and potentially other choices) could have been manipulated to bias the findings reported, e.g. choice of method of model fitting, potential confounders considered/included
  - look for evidence that there was a protocol in advance of doing any analysis/obtaining the data (difficult unless explicitly reported); NRS very different from RCTs. RCTs must have a protocol in advance of starting to recruit (for REC/IRB/other regulatory approval); NRS need not (especially older studies)
  - Hence, separate yes/no items asking reviewers whether they think the researchers had a pre-specified protocol and analysis plan?

Appendix 8. Assessment of confounding

Assessment of how researchers dealt with confounding	
Method for *identifying* relevant confounders described by researchers:	Yes/No
If yes, describe the method used:	
Relevant confounders described:	Yes/No
List confounders described below:	
Method used for controlling for confounding:	
At design stage: matching by characteristics of subjects (see below for matching by propensity score)	
Variables on which subjects matched:	……
	……
	……
	……

Assessment of how researchers dealt with confounding	
At analysis stage:	stratification
	multivariable regression
	propensity scores (matching)
	propensity scores (multivariable regression)
Describe confounders controlled for below	

Confounders described by researchers

Enter / preprint prespecified list of confounders (rank order in importance? Important in bold?)

Tick (yes/no judgment) if confounder considered by the researchers [Cons'd?]

Score (1 to 5) precision with which confounder measured

Score (1 to 5) imbalance between groups

Score (1 to 5) care with which adjustment for confounder was carried out.

Confounder	Considered	Precision	Imbalance	Adjustment
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o
	o	o	o	o

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

High frequency oscillations for epilepsy surgery in medically refractory epilepsy						
Patient or population: patients undergoing epilepsy surgery with medically refractory epilepsy **Settings:** hospital setting **Intervention:** high frequency oscillations						
Outcomes[1]	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**High frequency oscillations**				
Epilepsy Surgery Outcome Engel Class Outcome Follow-up: mean 23.4 months	See comments and footnote [2]	See comments and footnote [2]	Not estimable	11 (2 studies)	⊕◯◯◯ **very low**[3,4]	In the 11 enrolled participants in the two trials, six had Engel Class I, two had II, three had III, and none had IV.
Adverse Events Follow-up: mean 23.4 months	See comments and footnote [2]	See comments and footnote [2]	Not estimable	11 (2 studies)	⊕◯◯◯ **very low**[3,4]	No adverse effects were reported in any of the participants in either trial
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.						

[1] We did not include a quality of life outcome, because there was no data about quality of life provided in either of the included studies.

[2] We could not calculate assumed or corresponding risk as neither study included in the review had a control group. Therefore we also could not calculate relative effect. Outcome data is described narratively in 'Comments.'

[3] Both studies were non-randomised studies, without blinding of either the participants or the practitioners. There is a risk of bias in Engel class II versus III outcome due to the fact that the treating provider determined outcome, and, in one case, we determined outcome post-hoc from the data provided in the study. One study did not pre-specify Engel Class Outcome as an outcome. Both studies were at high risk of spectrum bias, due to the small number of enrolled patients.

[4] The number of included participants in the studies are 5 and 6. Due to the very wide confidence intervals that this would include, it makes any data that these papers would generate imprecise.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Modur 2011

Methods	In participants with medically intractable neocortical epilepsy, participants were prospectively followed but retrospectively identified. Particpants were recorded at 1000 Hz. Seizures were recorded with conventional video-EEG methods, using subdural grids, or a combination of grids and depth electrodes. Spontaneous HFOs (>70 Hz) at the seizure onset were detected manually in the bandpass filtered (53–300 Hz, with 60 Hz notch filter) intracranial recordings that were displayed using an expanded time base of 2 sec per window. Recording sites were then divided into two groups. 'HFO+ channels' were defined as those with HFOs that showed subsequent evolution at less than 70 Hz, and had to have either HFOs or slower frequencies present at the time of first behavioural change. 'HFO− channels' were those that did not meet all the criteria for HFO+ channels The seizure onset zone was determined to be the union of all HFO+ channels for all seizures, 1 cm of cortex surrounding it, and the channels involved in the first 2 sec of spread. The boundaries of the seizure onset zone were modified to avoid eloquent cortex, and HFO+ channels non-contiguous with the primary seizure onset zone were not resected. If no HFOs were found, it was preplanned to use conventional frequency activity to construct the seizure onset zone Inclusion criteria were well defined seizure onset, seizure onset defined by discrete HFOs (≥ 70 Hz activity, ≥ 400 ms duration). Exclusion criteria were 1. multi-focal, or bilateral seizure onset, 2. recordings at <1000 Hz, 3. non-resective surgery The outcome of Engel class was not pre-specified in the methods
Participants	Fourteen consecutive participants were enrolled. Six met inclusion criteria while the remaining eight participants either did not meet inclusion criteria or met specific exclusion criteria. The six participants included three males and three females. Participants were between 19 and 32 years old and had a duration of epilepsy from 6 to 30 years. Four were MRI normal
Interventions	The six patients who met inclusion criteria underwent epilepsy surgery using the pre-specified method of determining the seizure onset zone for the limits of the resection
Outcomes	Outcome was determined over a follow-up period of 20–38 months (mean 26.5 months). Outcome was Engel class I in three, II in two, III in one
Notes	The study also retrospectively had a spectral analysis of the HFOs, but this information is not included here as it was not part of the surgical decision making On surgical pathology, four of six participants had heterotopic neurons, one had focal dysgenesis, one had both

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	There was no randomisation
Allocation concealment (selection bias)	High risk	There was no randomisation, and therefore no allocation concealment
Confounding	High risk	There is no consideration of the confounders in the study. There was only one group that was treated the same way, but the group was very small, so the potential for a confounder to alter results may be high. Risk of bias tool for non-randomised studies level of risk: 4
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not performed
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome was not blinded. While Engel class I versus others is an objective outcome, distinguishing between II versus III is not, and at risk of detection bias. Risk of bias tool for non-randomised studies level of risk: 3
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study. Risk of bias tool for non-randomised studies level of risk: 1

Selective reporting (reporting bias)	Low risk	The Engel class outcome was not pre-specified in their methods, giving a possible risk of selective reporting. 2 on the risk of bias for non-randomised studies tool ORBIT classification F (outcome measured, but not analysed). For ORBIT, low risk of bias, 1 on the risk of bias for non-randomised studies
Other bias	High risk	Patients were consecutively enrolled, and each patient excluded was accounted for in their pre-specified exclusion criteria Due to the small numbers of patients, there is a high risk of spectrum bias. 4 on the risk of bias for non-randomised studies tool The authors' only disclosure was a National Institutes of Health grant. 1 on the risk of bias for non-randomised studies tool
A priori protocol	Low risk	The protocol was determined a priori. Yes on the risk of bias for non-randomised studies tool
A priori analysis plan	Low risk	No statistical analysis was planned for the Engel class outcome, and none was performed. No on the risk of bias for non-randomised studies tool

RamachandranNair 2008

Methods	All participants with medically intractable epileptic spasms, older than 2 years of age, who underwent intracranial monitoring from July 2004–December 2005 were considered for inclusion. Participants underwent MRI, MEG with MEG spike dipole source localization (MEGSS) for each spike. Subdural grids were planned to include all of the MEGSSs, recorded at 1kHz. Ictal HFOs were determined by analysing 5–10 seconds of ictal intracranial EEG, including 1–2 seconds before the clinical epileptic spasm, using software to perform a multiple band pass frequency analysis between 5 and 300 Hz, with a 2 Hz resolution and a 20 millisecond time window The resection area was determined based on both HFOs and non-HFO information. The HFO information used was ictal onset zone (defined by the authors as the area having ictal HFOs) and the area of ictal HFOs (presumably this means that the authors used both an aggregate area but looked at the individual electrodes that had HFOs on them, although this is not entirely clear in their paper). The non-HFO data used was the eloquent cortex, the MRI lesions, and MEGSSs
Participants	In the time period studied, five participants met inclusion criteria, three females and two males. They were aged 4.5 – 14 years and had epilepsy from 0.4–8 years. Three had asymmetric spasms. One had focal scalp EEG onset, three had a lead-in from either a lobe or a hemisphere, and one had generalized spasm onset
Interventions	Each participant underwent resective surgery using the above protocol for determination of the area to resect
Outcomes	Outcome was determined over a period of 12–29 months (mean 19.6). The outcome was reported as seizure free in three, 50–75% seizure reduction in one, >90% seizure reduction in one. (Converting to Engel class, three had Engel class I, two had Engel class III)
Notes	On surgical pathology, three had gliosis, one had microdysgenesis, one had polymicrogyria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	There was no randomisation
Allocation concealment (selection bias)	High risk	There was no randomisation, so therefore there was no allocation concealment
Confounding	High risk	There is no consideration of the confounders in the study. There was only one group that was treated the same way, but the group was very small, so the potential for a confounder to alter results may be high. Risk of bias tool for non-randomised studies level of risk: 4
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessment was not blinded. Engel class I is an objective assessment. Engel class III is liable for bias, especially as we are determining this post hoc. Risk of bias tool for non-randomised studies level of risk: 3

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study who they reported. Risk of bias tool for non-randomised studies level of risk: 2
Selective reporting (reporting bias)	Low risk	ORBIT classification F (outcome measured, but not analysed). For ORBIT, low risk of bias, 1 on the risk of bias for non-randomised studies
Other bias	High risk	We have no information about patients who were considered for the study but not included. Risk of bias tool for non-randomised studies level of risk: 3 Due to the small numbers of patients, there is a high risk of spectrum bias. 4 on the risk of bias for non-randomised studies tool There were no disclosures mentioned in the article. Risk of bias tool for non-randomised studies level of risk: 1
A priori protocol	Low risk	The protocol was determined a priori. Yes on the risk of bias for non-randomised studies tool
A priori analysis plan	Low risk	No statistical analysis was planned for the Engel class outcome, and none was performed. No on the risk of bias for non-randomised studies tool

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akiyama 2009	This abstract of a retrospective cohort examined 21 pediatric participants with intractable neocortical epilepsy who had undergone intracranial video EEG, and had 20 minutes of interictal during non-REM sleep. Although statistical results are not indicated in this abstract, they report that interictal neocortical fast ripples (> 250 Hz) which were resected were a better indicator of outcome than interictal neocortical ripples (> 80 Hz)
Akiyama 2011	This study retrospectively reviewed paediatric epilepsy participants with intractable epilepsy, undergoing extraoperative intracranial video EEG, who did not have known bilateral seizure foci or status epilepticus, and who had postsurgical outcome data at two years. They detected interictal HFOs (80–300 Hz) from subdural grid and depth electrode recordings using automated detection software, examining 10 2-minute non-rapid eye movement sleep epochs, at least one hour away from seizures. This information was not part of the surgical decision making. 14 participants were excluded, 28 were included. Areas of high HFO rates were determined, with the rate of high HFOs determined individually using a statistical threshold on the distribution of HFO rates. No primary outcome was pre-specified. They found that complete resection of regions with a high rate of fast ripples (200–300 Hz) was associated with better outcome than resection of regions with high rates of ripples (80–200 Hz). No mention of correction for multiple outcomes was mentioned in the methods section. If a Bonferonni correction for multiple outcomes was performed, this significance would not be sustained
Aubert 2009	This study examined 36 participants with focal pharmacoresistant epilepsy who either had neuroradiological findings consistent with focal cortical dysplasia (FCD) or neroectodermal tumour, or had non-lesional imaging with FCD found on postsurgical pathology. All participants had stereoelectroencephalography with depth electrode implantation. They calculated the epileptigenicity index (EI), which is an energetic measure of how soon an area becomes involved after seizure onset. While the beta (12–24 Hz), gamma (24–90 Hz) subbands were included in the calculation, there was no specific information about peri-ictal HFOs. Complete resection of the lesion was significantly associated with Engel Class I Outcome (P=0.0004). For an EI of at least 0.4, the number of epileptogenic sites was 1–8. They observed a trend in better outcome associated with a focal (single) lesion by EI
Bartolomei 2008	This study examined 17 participants with drug resistant temporal lobe epilepsy who had stereoencephalography with depth implantation. They calculated an epileptogenicity index (EI), which is an energetic measure of how soon an area becomes involved after seizure onset. While the gamma sub-band was included in the calculation, with a definition of gamma being frequencies between 24 and 97, there was no specific information about HFOs. For an EEI of at least 0.3, the number of epileptogenic sites was 1–6. They observed a trend for better outcome with fewer epileptogenic sites. They did not discuss a correlation between outcome and removal of these sites
Cho 2012	This study prospectively enrolled seven medically refractory epilepsy participants who had undergone subdural grid electrode implantation. The epileptogenic zone was determined by conventional presurgical evaluation, so HFOs were not used in epilepsy surgery decision making. The spatial distribution of interictal neocortical ripples (80–200 Hz) and fast ripples (200–500 Hz) were detected using a semi-automated algorithm, which was compared to the epileptogenic zone in each participant. Post hoc analysis found higher rates of neocortical ripples and fast ripples in the seizure onset compared to rates in the irritative zone and the sites outside the seizure onset zone. When most of the regions corresponding to ripple and fast ripple generating tissue were resected, patients had good postsurgical outcome (i.e. 6 of 7 participants had Engel class I outcome), although no statistics were performed
Fujiwara 2012	This study retrospectively examined 44 participants for ictal neocortical HFOs, and compared postsurgical seizure-free outcome in participants who had complete removal of ictal HFO sites versus participants who did not. Ictal HFOs were detected by the presence of spectral power within frequency bands of 80–150, 150–300, 300–500 Hz from two or more 5 minute seizure epoch recorded from intracranial grid electrodes. Ictal HFO recordings were not used in resective surgery decisions. Postsurgical seizure freedom was determined at most recent clinic visit (duration of follow up between 12 and 26 months, mean 14 months) 22 patients had complete cortical resection of ictal HFO sites and 18 were seizure-free (82%). By contrast, of the 19 participants who did not have complete removal of ictal HFO sites, only 4 were seizure free (21%), which was significantly fewer compared to the group with complete resection of ictal HFOs (P<0.0001). This appears to be a pre-specified primary outcome of the study
Guggisberg 2008	Twenty-seven patients with medically refractory mesial temporal lobe or neocortical epilepsy were examined in this retrospective cohort study. This study sought to compare the accuracy of conventional MEG using equivalent current dipole methods (ECD) versus new adaptive spatial filtering methods to localize EEG spike-locked beta and gamma power (12 to 55 Hz) in relation to the putative epileptogenic zone. Analysis found that in patients with more than 50 EEG spikes, the new method had greater accuracy compared to conventional ECD methods (100% versus 88%). However, in patients with less than 50 EEG spikes, the accuracy of the adaptive spatial filtering methods declined to levels that were lower than those produced by ECD method. In patients with good surgical outcome (Engel class I and II) after a mean follow-up of 16 months, the new method had an accuracy of 85% versus 69% for the conventional MEG
Haegelen 2013	This retrospective cohort study extends the results from the prior publication from Jacobs and colleagues (Jacobs 2010). Thirty patients with drug-resistant temporal (n=21) or extra-temporal lobe (n=9) epilepsy were retrospectively examined. Depth and grid electrode-recorded interictal EEG (2 kHz sampling, 500 Hz low pass filter) during 5–10 minute epochs of slow wave sleep was manually inspected to detect spontaneous ripples (80–250 Hz) and fast ripples (250–500 Hz). Among temporal lobe patients, they found that both ripple and fast ripple rates were significantly higher inside the seizure onset zone than outside (95% confidence intervals given). Among extratemporal lobe patients, there was no difference in HFO rates in relation to the seizure onset zone. There was no difference in ripple or fast ripples rates in temporal or extra-temporal lobe groups between recording contacts inside the area of resection and those outside the area of resection. With respect to postsurgical seizure-free outcome, in the entire cohort, the ratio of ripple, but not

Study	Reason for exclusion
	fast ripple, rates on contacts removed compared to rates on contacts not removed was significantly higher in good outcome (ILAE class 1–3) versus bad outcome (ILAE class 4–6) (no 95% confidence interval given). In the temporal, but not extra-temporal, lobe epilepsy group, the ratio of ripple and fast ripple rates on contacts removed to rates on contacts not removed was significantly higher in good versus poor outcome
Jacobs 2010	This is a retrospective review of 20 participants who underwent surgical resection for medically intractable epilepsy. HFOs were recorded, but not presented as part of surgical decision making. 5–10 minutes of slow-wave sleep were reviewed for HFOs. Areas of high frequency of HFOs were compared with areas resected in surgery. There was borderline significance for the ratio between number of removed versus non-removed contacts for areas of high rates of HFOs and good (Engel class 1,2) versus poor (Engel class 3,4) outcome
Kanazawa 2012	In this abstract, 12 subjects with partial epilepsy were studied with subdural electrodes. Both Ictal DC shifts and HFOs (>100 Hz) occurred in 4 patients, Ictal DC shifts only in 4, and only HFO in 1. No information was given about resection or outcome. No reason was given why HFOs were not found at all in some patients
Kerber 2013	This is a retrospective cohort study of 22 participants with focal cortical dysplasia. In participants found to have pathologically confirmed focal cortical dysplasia Palomini type 2a or 2b, the rates of high frequency oscillations were significantly higher than those found to have focal cortical dysplasia type 1a or 1b
Khosravani 2009	7 participants with medically intractable epilepsy were prospectively recruited, who had macroelectrode depth implantation as part of their presurgical work-up. They found that one could use commercial macroelectrodes, and that focal increases in HFOs occurred in areas of seizure onset. They included seizure outcome data but there is no evidence in the paper that the HFO data were included in epilepsy surgery decision making
Kobayashi 2011	This study examined 200 scalp EEG records from 32 children with benign childhood epilepsy with centrotemporal spikes, and 13 with Panayiotopoulos syndrome. They looked for ripples in EEG records with enough spikes (22–30), using power spectral analysis. They found that 97 EEGs had HFOs associated with spikes. The peak power of the spike associated ripples appeared to be negatively associated with time from last seizure in years. They give an R^2 as 0.122 yielding a $P<0.001$, from 97 values, but this low R^2 suggests poor correlation. There was no data about surgical outcome, or with other outcomes in this review
Lemesiou 2012	A retrospective cohort of 15 subjects had MEG and intracranial EEG investigated in this abstract. 10 minutes of slow waves sleep was used for intracranial EEG analysis and compared with high frequency oscillatory activity on MEG. Both were found to co-localize to the left frontotemporal region, which they report was consistent with other localizing data. No outcome data were provided
Matsumoto 2013	Five subjects in a prospective cohort were investigated comparing HFOs that were found by either a visual or motor task and HFOs collected in the seizure onset zone during ictal onsets. They tested for differences in spectral amplitude, frequency, and duration in four patients, and created a classifier. In the final patient, they used the classifier to try to classify the HFO data. No outcome data were provided
Miocinovic 2012	A retrospective cohort of five subjects with ictal evolution were investigated in this abstract. The results talked about increases of HFO rates occurred more prominently preictally than ictally. HFO power increased preictally in seizure onset channels. The conclusions describe HFOs defining the epileptogenic network more than the seizure onset zone
Modur 2012	This is a retrospective review of 11 seizures, comparing HFOs with infraslow activity, and seizure outcome. This paper does not substantively add to the information about HFOs published in Modur 2011, but it does suggests infraslow activity, particularly, ictal baseline shifts, may be another possible marker of the seizure onset zone
Mohamed 2012	17 consecutive children with tuberous sclerosis complex and refractory epilepsy, with poor non-invasive seizure location or persistent seizures after a priori tuberectomy, underwent strip and grid electrode studies. Ten minutes of slow wave sleep was analysed, as was 10 second epochs before and after ictal onset. Interictal fast ripples were seen in contacts related to 49 of the 124 tubers. Ictal fast ripples were noted during 15/38 localized electroclinical distinct events. Of the 15, 11 were confined to tubers, and 4 involved the tuber and surrounding cortex. There was no evidence this information was considered in surgical decision making, so this paper was excluded
Nariai 2011	This is a retrospective review of 636 epileptic spasms examining HFOs. HFOs were not used in epilepsy surgery decision making. Spasm events were defined as a sustained, widespread burst of HFOs>30 Hz, lasting 0.5 second or longer. There were 11 children, and 18 spasm types. In 14 of the spasm types, there was an initial greatest amplitude augmentation in the ripple band (more than the other bands). In 3, the initial greatest augmentation was gamma-band, and in one it was fast ripple. There did not appear to be a pre-specified primary outcome. They state that there was a significant correlation between seizure outcome and complete resection of the seizure onset zone. With Bonferonni correction for multiple outcomes, this significance is not sustained
Nowacki 2012	Eighteen focal seizures from six consecutive patients were retrospectively collected in this abstract. Channels were divided up into seizure onset zone, secondary propagation, or uninvolved. Seizures were divided into preictal, ictal onset, and propagation time periods. They found that fast ripples significantly increased during the periods of seizure evolution with median counts of 19 during preictal, 55 during ictal onset, and 96.5 during propagation (presumably the counts were per minute). These were colocalized to be within the seizure onset zone in 5 of 6 patients
Ochi 2007	Nine children with intractable extrahippocampal location-related epilepsy had 79 seizures from subdural grids retrospectively reviewed. HFOs were not used in surgical decision making. In the seizure free group (Engel class I), 15 of 25 seizures, with HFOs present before onset, had HFOs present more often in the resection area than outside of it. Among the 35 seizures in the seizure free group with HFOs present after onset, 27 of them had electrode positions more often resected than not. In the residual group (all other outcomes), 14 of 35 seizures had HFOs present more often in the

Study	Reason for exclusion
	resection area than outside of it. Among the residual group's 43 seizures with HFOs after clinical onset, only 12 had more electrode contacts resected than not. The HFOs resected after ictal onset between the seizure free and residual groups were statistically significant, P<0.01. Other comparisons were not stated, so there is no clear way to perform a Bonferonni correction for multiple comparisons, without making assumptions
Park 2012	37 participants with medically intractable epilepsy underwent subdural or depth electrode implantation. 14 participants had mesial temporal lobe epilepsy (MTLE) or MTLE plus neocortical epilepsy, 23 participants had neocortical epilepsy. Video EEG ictal onset was investigated using wavelet analysis to examine ictal high gamma oscillations. They defined the highest cluster epileptogenicity index as the root mean square of a wave cluster divided by the time between ictal onset and the appearance of the cluster. This information was not used to make surgical decisions. Areas with high wave cluster indices being resected were correlated with better outcome. After Bonferonni correction for multiple outcomes, the significance was not sustained
Pearce 2013	5 subjects were retrospectively studied. They examined four different time epochs: interictal, preictal (30 minutes before a seizure), ictal, and postictal (30 minutes afterwards). They found that there were a unique pattern of changes in HFOs that occurred in the preictal and postictal time periods. They used the following six features to create a unique fingerprint of each participants data: fast ripple to ripple power ration, spectral centroid, spectral peak, line length after spectral equalizations, band passes line length, and zero-crossings per sample length
Ramp 2013	Four subjects with grid electrodes were retrospectively studied who underwent etomidate activation. HFO rates increased from 8–9/min to 24/min after etomidate administration. The additional HFOs were consistent with the seizure onset zone in the two patients who underwent resection
Ray 2008	6 subjects were recruited, but 3 were excluded. Auditory and tactile stimuli were presented, and high gamma (80–150 Hz) oscillations were recorded from subdural grids. They found a correlation of these activities with selective attention. There was no postsurgical data presented
Schindler 2010	This study included 3 participants examined retrospectively. They did not use HFOs for epilepsy surgery decision making. Large scale correlations were investigated. It was found that the total correlation strength increased significantly during ictus and again postictus. A second measure, which was not pre-specified, of the total correlation strength of j with the jth EEG channel left out, was significantly more negative in the epileptogenic channels. Outcomes were provided
Smart 2011	Six participants were retrospectively analysed. They compared a new method of detecting gamma oscillations (about 65–95 Hz) called grammatical evolution with three other methods. This new method appeared to be superior to two of the methods and similar in effectiveness with the third method. No data about surgical outcome were presented
Stamoulis 2012	Seven subjects with focal, medically refractory epilepsy who had at least two seizures recorded on scalp EEG were retrospectively analysed. There were 39 preictal intervals, 39 ictal EEGs, and 42 non ictal baseline segments analysed. They divided the EEG data into ≤100 Hz and >100 Hz. They found that there were significant differences in information theoretic measures (for example, mean relative entropy) during the preictal and ictal time periods compared to the interictal time periods, for the >100 Hz frequency band
Stamoulis 2013	Eight subjects with focal, medically refractory epilepsy who had at least one seizure recorded on scalp EEG were retrospectively analysed. Mutual information, conditional mutual information and their difference, and interaction information were measured to estimate the amount of network coordination. During some of the examined ictal periods, there was a concomitant increase of network coordination for frequencies >100 Hz, as well as a decrease in coordination at frequencies <100 Hz
Usui 2011	Nineteen participants with medically intractable epilepsy who had bilateral intracranial electrode implantation were examined for the presence of ictal HFOs. In 11, ictal HFOs were detected, each of these participants had hippocampal sclerosis on postsurgical pathology. Of the remaining 8 participants, only one had hippocampal sclerosis on pathology. The data was not clearly used in surgical decision making, with the article stating at one point that the seizure onset zone was identified with conventional EEG. Surgery outcome was provided. 8 of the 11 participants with ictal HFOs had Engel class I outcome. 3 of the 8 participants without ictal HFOs had Engel class I outcome
van Diessen 2013	A retrospective cohort of 12 subjects with bitemporal depth EEG recordings from both amygdala and hippocampus with conclusive intracranial EEG reports were investigated with a constructed network. Strength of connectivity and eigenvector contrality was investigated. They found that channels associated with the seizure onset zone showed significantly decreased strength of connectivity and eigenvector centrality in the theta band. It is not stated if there was a Bonferonni adjustment to their results, and if that is the case, their results do not appear to remain statistically significant
van't Klooster 2011	Thirteen participants underwent single pulse electrical stimulation (SPES). Conventional visually analysed SPES results were used in surgical decision making. The study cites another study when talking about the conventional SPES which did not look for HFOs. When examining epochs of significant changes in power spectra with a wavelet transformation, there was outcome data of at least one year for 9 participants. Two participants had 94–100% of the areas of fast ripples retrospectively removed. Both participants had Engel class I outcome. Of the remaining 7 participants, all had <50% of fast ripples removed, 2 had Engel class I outcome and 5 had Engel class II–IV (data not given for specific classes). The fast ripple data was retrospectively determined
Wang 2013	35 participants with medically intractable neocortical focal epilepsy underwent either stereotactic EEG or subdural grid with supplementary depth electrodes. The seizure onset zone was identified by the onset of repetitive spikes, background suppression, or paroxysmal fast activity. After seizures were collected, an additional 2–7 days of recording was collected, using a reduced number of electrodes with high frequency sampling. Fast ripples were only detected in

Study	Reason for exclusion
	the seizure onset zone of 4 participants. Ripples colocalized with spikes were found in the seizure onset zone of 14, but ripples not so colocalized were not associated with the seizure onset zone. Epilepsy surgery outcome was not given in a format that would allow correspondence between the HFOs and outcome
Wetjen 2009	Fifty one consecutive participants with normal MRI scans who underwent intracranial monitoring for extra-temporal epilepsy were retrospectively evaluated. HFOs were not used in epilepsy surgery decision making. 28 underwent resective surgery and had adequate follow-up information of at least one year. Focal high frequency seizure onset (20–100 Hz) occurred in 15. 12 participants were seizure free, and 3 were not
Wu 2012	This abstract described 15 subjects with medically refractory mesial temporal lobe epilepsy with depth intracranial monitoring. They tried to correlate HFOs with ictal DC shifts. They found that 96% of clinical seizures had ictal SDC shifts. They found 84% of clinical seizures had HFOs, which occurred after ictal onset. They state in all cases, the ictal DC shifts and HFOs occurred in the electrodes of ictal onset
Wu JY 2010	Fast ripples were retrospectively reviewed in 30 consecutive paediatric cases from electrocorticography during epilepsy surgery. The children had a variety of pathologies, most commonly dysplasia, which included such things as Ramusen encephalitis, tuber, and gliosis. HFOs were not used in epilepsy surgery decision making. 24 children has FR during the electrocorticography. 18 had FR containing cortex removed and all became seizure free. 1 had a second surgery and had all FR cortex removed and became seizure free. 5 had in complete resection of FR containing cortex, and none were seizure free after surgery
Wu M 2010	Seven participants with medically intractable epilepsy had extraoperative electrocortical stimulation to identify speech cortex. They examined both a low and a high-frequency band (HFB, the high-frequency band was 75–100 Hz). Using a combination or aural and visual stimuli, the HFB showed a significant change in power had a 100% sensitivity and 66% specificity for finding Wenicke's area, but only 50% sensitive and 57 specificity for Broca's area. The gold standard was electrocortical stimulation. There was no information provided for epilepsy surgery outcome or other outcomes considered in this review
Zijlmans 2012	Twelve participants with medically intractable mesial and/or anterior temporal lobe epilepsy underwent intraoperative electrocorticography during resection were analysed for the presence of HFOs, using propofol induction. The mean number of ripples and fast ripples were significantly increased when propofol induction wore off, but the number of spikes remained the same. Some participants had burst suppression on EEG, and these participants had significantly less ripples. After Bonferonni correction for multiple comparisons, none of the correlations remain significant. HFO data was not included in surgical decision making, although outcome information is provided