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Pre-surgical mapping of eloquent cortex for paediatric epilepsy surgery candidates: Evidence from a review of advanced functional neuroimaging

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Highlights

- A systematic review has not been published before.
- 34 papers met inclusion criteria with 353 paediatric participants identified.
- PPV 74% (95 % CI 61-87) and NPV 65% (95% CI 52-78) for fMRI language were obtained.
- It remains unclear which language paradigms produce optimal activation.
- Paradigms and analyses concordant with independent measures are needed.

Abstract

Purpose: A review of all published evidence for mapping eloquent (motor, language and memory) cortex using advanced functional neuroimaging (functional magnetic resonance imaging [fMRI] and magnetoencephalography [MEG]) for paediatric epilepsy surgery candidates has not been conducted previously. Research in this area has predominantly been in adult populations and applicability of these techniques to paediatric populations is less established.

Methods: A review was performed using an advanced systematic search and retrieval of all published papers examining the use of functional neuroimaging for paediatric epilepsy surgery candidates.

Results: Of the 2,724 papers retrieved, 34 met the inclusion criteria. Total paediatric participants identified were 353 with an age range of 5 months-19 years. Sample sizes and comparisons with alternative investigations to validate techniques are small and variable paradigms are used. Sensitivity 0.72 (95% CI 0.52-0.86) and specificity 0.60 (95% CI 0.35-0.92) values with a Positive Predictive Value of 74% (95 % CI 61-87) and a Negative Predictive Value of 65% (95% CI 52-78) for fMRI language lateralisation with validation, were obtained. Retrieved studies indicate evidence that both fMRI and MEG are able to provide information lateralising and localising motor and language functions.

Conclusions: A striking finding of the review is the paucity of studies (n=34) focusing on the paediatric epilepsy surgery population. For children, it remains unclear which language and memory paradigms produce optimal activation and how these should be quantified in a statistically robust manner. Consensus needs to be achieved for statistical analyses and the uniformity and yield of language, motor and memory paradigms. Larger scale studies are required to produce patient series data which clinicians may refer to interpret results objectively. If functional imaging techniques are to be the viable alternative for pre-surgical mapping of eloquent cortex for children, paradigms and analyses demonstrating concordance with independent measures must be developed.

299 words

Key words: paediatric; epilepsy surgery; fMRI; MEG; memory; language; motor

Introduction

Paediatric epilepsies are the most common serious neurological disorders of childhood, affecting between 0.5-1% of children and young people under the age of 16 years[1]. Childhood epilepsies are associated with the greatest amount of psychological and psychiatric morbidity with psychopathology three-to-six times greater than in the general childhood population[2]. Epilepsies are known to impair behaviour, affect, cognition and learning significantly [2-5]. Not all epilepsies respond to anti-epileptic drugs and other treatments such as the ketogenic diet, vagal nerve stimulators and resective and functional surgery have become available [6-8].

Epidemiological studies indicate that 27 in every million children might benefit from resective surgery for an epilepsy. While this equates to approximately 405 children per year in the UK; only about 25% of such procedures actually take place [9]. An epilepsy in adulthood may lead to detriment to already acquired functions. However, for a child, language, memory and motor functioning are acquired progressively and seizures interfere with what is to be developed, as well as what has been acquired [10]. The International League Against Epilepsy (ILAE) recommends resective surgery is considered for medically refractory epilepsies where a patient has not responded to two or three anti-epileptic drugs or where seizure activity is disabling [9]. The primary aim of resective surgery is seizure freedom although this is not always achieved. The likelihood of seizure freedom is related to the aetiology of the epilepsy and extent of the procedure undertaken [9]. For instance, surgery in the event of developmental malformations such as hemimegalencephaly has been associated with reduced likelihood of complete seizure freedom in comparison to other malformations [11]. Secondary to seizure control are outcomes for cognition and behaviour [12] with seizure freedom or reduction being associated with measured reductions in psychopathology and aggressive behaviours [13].

Surgical candidacy has traditionally been established via semiology, structural neuroimaging, vEEG and neuropsychological evaluation [9, 14]. These remain essential investigations. The purpose of epilepsy surgery is to abolish or significantly reduce epileptic seizures that are refractory to medication. However, the extent of resection is limited by the potential for cognitive, perceptual and motor deficits [15]. The mapping of eloquent areas for language, memory and motor function is critical for refractory epilepsies. Despite its reported limitations, the intracarotid amobarbital test or Wada continues to be used to estimate potential post-operative impairment to language and memory [15, 16]. As a demanding and invasive test, Wada has risks and it serves to lateralise and not localise function. Significant developments have led to the alternative use of advanced non-invasive techniques to map function, namely motor, language and memory with fMRI and MEG [17, 18]. fMRI is used to identify variations in magnetic resonance signalling associated with altered blood oxygenation level-dependency (BOLD) as the brain engages in an activity i.e. response to a cognitive task, creating the basis for mapping brain function [17]. A development associated with this is resting state fMRI (rs-fRMI) which is concerned with spontaneous BOLD variations in the absence of an explicit task with rs-fMRI being advocated as a reliable method for assessing large-scale brain networks in children[19]. MEG is also used to identify functional regions based on the examination of extra-cranial magnetic fields produced by neuronal activity. MEG is also able to produce localising information related to ictal onset zones [20, 21]; however, a review of this use is not an aim of this paper.

A review of all published evidence for advanced functional neuroimaging for paediatric epilepsy surgery candidates has not been conducted previously. Where reviews have been conducted for this population, none have used advanced search techniques and are fMRI [17], MEG [20, 22] or function [23] specific. In addition, the majority of studies examining the use and utility of fMRI and MEG for pre-surgical mapping of eloquent cortex in epilepsy surgery candidates have focused predominantly on adult populations [10]. This paper identifies and reviews all published papers using fMRI and MEG to map motor, language and memory function in children who are epilepsy surgery candidates. In addition, the paper specifies and reviews the relevant clinical, methodological and statistical aspects. The current status of these techniques is described and recommendations are made to improve the uniformity and yield of these techniques.

Methods

Search

A systematic search and retrieval of all literature was conducted and papers were identified. Devised search terms used were: (Infant/ OR Adolescent/ OR Minors/ OR Child/ OR Schools/ OR Schools, Nursery/ OR Infant, Newborn/ OR Puberty/ OR exp Pediatrics/ OR Infan* OR Newborn* OR New-born* OR Neonat* OR Neo-nat* OR Baby* OR Babies OR Postnat* OR Post-nat* OR Child* OR School* OR Kid OR Kids OR adoles* OR Teen* OR Girl* OR Boy* OR Minor* OR Underag* OR Under-ag* OR Puber* OR Prepubescent* OR Pre-pubescen* OR Youth* OR Kindergar* Or Kinder-gar* OR Prepuberty Or Pre-puberty OR P?ediatric*) AND (exp Epilepsy/ OR Seizure/ OR Cognit* OR Neuropsych* OR Neuro-psych* OR Epilep* OR Seizure*) AND (General Surgery/ OR Surg* OR Operat*) AND (Magnetoencephalography/ OR MEG OR Magnetoencephalograh*) OR (Magnetic Resonance Imaging/ OR MRI or fMRI OR Magnet* Resonance Imag*) OR (Language/ OR Communication/ OR Speech/ OR Languag* OR Speech* OR Communi*) OR (Movement/ OR Motor Activity/ OR Motor Skills/ OR movement* OR dexter* OR co-ordin* OR coordin*) OR (exp Memory/ OR Memor* OR Recall* OR Remember* OR Recogni* OR Forget*).

The databases searched were: AMED OVID SP, BIOSIS Previews OVID SP, CAB Abstracts OVID SP, EMBASE + EMBASE Classic OVID SP, Medline OVID SP, PsycINFO OVID SP, CINAHL EBSCO, Global Health OVID SP. A secondary search was conducted within the following databases: Cochrane Library including Cochrane Reviews, Database of Abstracts of Review of Effects and Clinical Trials. The period of search was unrestricted and auto alerts were set. The protocol for this systematic review was registered on PROSPERO (PROSPERO 2016:CRD42016042849) and is available in full on the PROSPERO International prospective register of systematic reviews (http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016042849).

Figure 1 illustrates this process which was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [24]. Subsequent outcomes/review criteria were developed and study quality was assessed.

INSERT Figure 1: PRISMA Diagram

Table 1 presents the studies identified for review following extraction and de-duplication.

INSERT Table 1: All Identified Studies

Data Extraction and Quality Appraisal

In order to identify relevant papers, the initial filters applied removed: duplicates; non-English language papers (the study was unfunded and did not have resources for translation); papers pertaining to adults; papers referring to non-epileptic conditions and papers that focused on paediatric epilepsies but were not relevant i.e. they did not meet the stated inclusion criteria. Identified papers were read independently by members of the review team. Inclusion was dependent on four criteria being met:

1. Papers related to the use of fMRI or MEG for the pre-surgical mapping of language, memory or motor functions in paediatric epilepsy surgery candidates.
2. A demonstrated rationale as to why mapping techniques had been implemented.
3. A coherent description of the paradigm used to assess language, memory or motor function with reference to the stimuli used and the manner of the response elicited.

4. An assessment as to whether mapping had made a significant contribution to treatment decisions.

Those papers whose inclusion criteria were unclear were reviewed by separate members of the team who were blind to the opinion of the original reviewer. Papers describing both adult and paediatric patients were included, if the reported paediatric case/s could be extracted and analysed independently of the adult data. The Oxford Centre for Evidence Based Medicine[25] levels of evidence was utilised to appraise the quality of included studies with the QUADAS-2 used to assess the quality of diagnostic accuracy [26].

Statistical Methods

An analysis was conducted on the fMRI studies reporting outcome data for language (n=68). These papers were chosen specifically as there was a higher frequency of this type of study in the literature. Further, the patient data reported within them were more robust. Results were dichotomised into typical (left) and atypical (right or bilateral) language lateralisation. The proportion of cases correctly identified as typical (PPV) and the proportion of cases correctly identified as atypical (NPV) by fMRI, along with their 95% confidence intervals, were calculated using Wada as validation. Bivariate meta-analysis was used to provide a meta-analytic summary of the available data with a continuity correction used for cases with a value of zero. Given heterogeneity of data, Forest plots and ROC space plot, to ensure optimal visual representation of data, were produced using R (2015) and mada: Meta-Analysis of Diagnostic Accuracy; R package version 0.5.7. (2015) [27] with sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NVP) derived from the available data. A descriptive analysis was also completed using the data from patients whose imaging technique was not concordant with the validation procedure. In line with QUADAS-2 guidance [26], a quality score was not generated due to concerns regarding the use of a summative metric [28].

Results

Of 2,724 papers retrieved, 34 (1997-2016) met the inclusion criteria (Table 1). The level of evidence[25] of the included studies was rated at Level 3 (26/34; 76%) and 4 (8/34; 24%). From QUADAS-2[26] rating, low concern was indicated for applicability with a mixed profile for risk of bias (Table 2).

INSERT TABLE 2: QUADAS-2 Ratings

Participant Characteristics

Total paediatric participants were 353 with an age range of 0.5-19 years (M= 10.79). Information pertaining to gender was available for 218 of the participants with 48% (n= 103) of the participants being female. Handedness data was available for 237 participants. Of these, 83% (n= 197) were described as right handed, 16% (n= 27) left handed and 1% (n= 2) ambidextrous. A full description of participants was not possible due to the quality of reporting.

Concordant and non-concordant cases

Where available, identifiable data indicating concordance (i.e. cases where imaging and validation agreed) were separated (Supplementary Table 1). In total, there were 88 (76%) concordant responses produced by 63 participants. The mean age of these participants was 14.36 years. A full description of participants was not possible due to quality of reporting. Available data indicating non-concordance was extracted (i.e. cases where imaging and validation did not agree) from seven studies [29-35]. In total, there were 28 (24%) non-concordant responses produced by 20 patients with a mean age of 14.93 years. A full description of the 20 was not possible due to quality of reporting. Of the 116 cases of concordance/non-concordance extracted in the retrieved studies, data from eight participants appeared in both concordant and non-concordant groups (7%) [30-32, 34, 35]. Of these eight, the mean age was 16.20 years. A full description was not possible due to quality of reporting.

1. MEG

Seven studies were identified as using MEG [29, 36-41]. One study presented both MEG and fMRI data [42]. No memory related studies were retrieved.

Language

Six studies were identified [29, 36-39, 42] assessing the reliability of MEG in language mapping. Data from [37] are included in [43] and it is unclear how many further patients in this later study were under the age of 18 years. A total of 62 patients between the ages of 4 and 18 years old were identified from the studies.

Language Production

Two studies examined expressive language [38, 42]. The methodologies utilised by the language production studies were: aloud naming of line-drawings of common objects [38] and sub-vocalisation of three letter words [42]. In the former, vocalisation occurred after the stimulus had been removed from the screen in order to avoid muscle artefacts during acquisition. Castillo et al. [38] were able to map expressive language in one patient which was shown to have an atypical, bilateral representation of language. The localisation of eloquent cortex was found to be concordant with the findings of the Electrical Stimulation Mapping (ESM) validation procedure and situated in close proximity to the patient's cortical lesion. Ota et al. [42] also demonstrated 100% concordance with Wada for their three paediatric patients taken from their mixed sample. These patients were deemed to have typical, left-sided language representation. Ota et al. determined a Laterality Index (LI) using the formula (R-L)/(R+L) which was reported in the results section, whereas a similar statistic was not reported in the Castillo et al. study. Cut off scores were similarly absent.

Language Comprehension

Receptive language mapping using MEG was reported in five studies [29, 36,37,41,42]. Van Poppel et al. [36] demonstrated MEG as a viable procedure for passive language mapping in three patients aged 2, 3 and 16 years. Two of the patients described in the study did not meet the age inclusion criteria for this review; however, data were reported for MEG concordance with ESM demonstrated in the 16 year old. A 180-word continuous recognition module consisting of familiar words was presented to the patients. Each patient was allowed to fall asleep naturally or via sedation prior to the mapping procedure. Words were presented one every two seconds. Sources between 250-800 ms post-presentation were utilised to determine laterality and functional language cortex. There were no descriptions in the paper concerning the development or justification of the LI.

Papanicolaou et al [37] compared language lateralisation from MEG with those obtained via Wada and found an 87% rate of concordance with a sensitivity of 0.98 and selectivity of 0.83. Although the study included a mixture of paediatric and non-paediatric patients, it included 19 paediatric patients reported in Hertz-Pannier et al[43]. One of the remaining studies used the same technique as described by Lee et al[29]. The same laterality measure was used but instead of comparing results to an independent measure such as Wada, the aim of the study was to determine to what extent analysis of language laterality paradigms was affected by researcher subjectivity. Eight of 21 individuals were paediatric patients and it was found that there was excellent concordance for language localisation estimates performed in different acquisition sessions and when datasets were evaluated by different raters. Localisations were found consistently in language specific cortex. The authors noted that the strong measures of inter-rater and test-retest reliability indicate that language localisation via MEG was amenable to standardised analysis and interpretation procedures. It should be noted that across all studies, the description of assessment preparation was minimal.

Motor

One study [40] was identified and reported data for two individuals, one of whom was a 16 year old female with 3T MRI revealing a lesion in the left medial parietal lobe, close to the left lower limb S1. Here MEG was used in addition to the specified preoperative evaluation for localisation of the epileptogenic sensorimotor cortical regions. MEG was indicated as providing improved spatial precision with consequent benefit for the patient with a suspected epileptogenic zone near the sensorimotor cortex with seizures frequent enough for ictal MEG.

2. fMRI

26 studies were identified as using fMRI [30-35, 43-63]. One study presented both MEG and fMRI data[42].

Language

In total, 21 studies using fMRI to predict language regions were identified [30-35, 43-47, 49, 52-54, 57-62]. A total of 223 patients participated (age 5 months -19 years). One paper utilised rs-fMRI[57] with another[35] using a passive fMRI paradigm whereby the patients were given an auditory presentation of a children's story and asked to listen whilst keeping their head still and their eyes fixated on a point in the centre of the monitor. In total, 75.5% concordance (n=98) was reported for fMRI with Wada as shown in Table 3. In total, 75.5% (74 of 98) were classified correctly by fMRI against Wada. Sixty percent of responses with left-hemisphere language lateralisation were classified correctly by fMRI compared with 6.12% of responses with bilateral representation. fMRI demonstrated left-sided language representation in 64 (65.3%) of 98 responses.

[Insert table 3: Wada and fMRI results based on left, right and bilateral language representations for all included studies]

Extracted data were dichotomised and used to calculate the PPV and NPV for typical and atypical language lateralisation by fMRI against validation. Results of the bivariate meta-analysis demonstrated a sensitivity value of 0.72 (95% CI 52-86) and a specificity value of 0.60 (95% CI 0.35-0.92). A PPV of 74% (95% CI 61 - 87) for 'typical' fMRI language lateralisation and a NPV of 65% (95 % CI 52 - 78) for 'atypical' lateralisation were obtained. If an example cohort of 100 children and young people were studied, with 50 having typical lateralisation on Wada, this would suggest that fMRI would lateralise language to the 'typical' hemisphere in 37 cases (74%), and lateralise language to the 'atypical' hemisphere in 32.5 cases (64%). Figure 2 depicts point estimate, CI of the best estimate of the average and prediction interval. Forest Plots for sensitivity (Figure 3) and specificity (Figure 4) are presented as supplementary figures.

Figure 2: ROC Space Plot: Sensitivity and specificity of individual studies with CIs and bivariate meta-analysis

[Insert Figure 2]

Supplementary Figure 3: Forest plot of sensitivity values for available fMRI data using a validation method (N=65)

Supplementary Figure 4: Forest plot of specificity values for available fMRI data using a validation method (N=65)

[Insert/ link to Supplementary Figures 3 & 4]

The first study demonstrated the ability of fMRI to map language function in children using a word generation task [42]. Eleven children (9-18 years) were asked to generate words that began with a specific letter presented via intercom. Three cycles were completed with 40 seconds of activation followed by 40 seconds of rest. Words were generated covertly first and if no activation was found, this was repeated using overt word naming. This temporal pattern of activation was correlated with the time series of activation for each voxel and an empirically defined threshold of 0.7 was used to identify activations. No details regarding how this threshold was derived were provided. Regions of interest were defined and an asymmetry index was used to determine hemispheric lateralisation by dividing the number of right-sided pixels by the number of left-sided pixels. Seven patients showed clear activations for covert naming and the remaining four (at the younger end of the cohort) showed activations after overt naming. The inferior frontal gyrus and middle frontal gyrus regions showed the most consistent localising information and in seven patients where dominance was confirmed via Wada or cortical stimulation, there was 100% concordance between these measures and fMRI. The authors noted the large variability of activation size and noise level across individuals; although arbitrarily altering the threshold did not change the lateralisation, it did change levels of significance.

Following this study there were a number of reported examples where language mapping performed via fMRI was concordant with independent measures in the paediatric population. Rutten et al. [44] reported a 14 year old with a tumour in the left inferior frontal gyrus (typically regarded as a crucial region for language production). Four language tasks were performed and although the report does not describe the analysis technique used, the language area identified via electrical stimulation was found to be located 3mm medially in relation to the area defined by fMRI. This case demonstrates that fMRI can be used in the paediatric population to infer regions required for language processing and although the paper provides limited information regarding specific paradigms used or analysis methods, it is clear that clinically relevant information may be gathered.

One retrieved paper focused specifically on how fMRI can be used in the surgical decision making process [49]. Due to brain plasticity, it is very difficult to predict activation patterns in individuals that have sustained a focal brain injury and therefore fMRI is potentially of most use to this population. The paper reports 31 cases where fMRI localisation of language function was discussed with a multidisciplinary surgical team. One case study reported a patient with a lesion in the left inferior frontal gyrus. The language area was found to be dorsal to this region and invasive electrical stimulation revealed speech arrest when this area was stimulated. Surgery was performed which resulted in seizure freedom and no speech or cognitive deficit. In two reported cases, fMRI identified left hemisphere dominance. Therefore, due to the location of cortical lesion, the patients were deemed to be high-risk. One did not proceed to surgery and the other had the region embolised rather than resected. The task used was covert verb generation in response to hearing a concrete noun.

Two papers provide crucial information in the progression towards functional imaging becoming used more routinely[52, 53]. The first investigated receptive and expressive language in 29 children [53]. These patients either had a presumed postnatally acquired disorder (hippocampal sclerosis) or a developmental disorder (focal cortical dysplasia). On a range of language tasks, it became clear that language organisation in patients with an epilepsy was complex creating difficulty in predicting outcomes. This study reported that receptive and expressive language was affected to differing degrees depending on whether the underlying pathology involved frontal or temporal networks. Shurtleff et al. [52] detailed the methods necessary to perform fMRI with very young individuals. Eight children less than eight years were identified, with six of these being five or six years old. Co-operation was facilitated with extensive training by experienced staff and verb generation tasks were practiced overtly until they could be performed covertly. A number of case studies are presented which relate the functional results to the underlying pathology and subsequent intervention. The key finding was that with the appropriate language paradigm, very young children can engage well with fMRI.

Motor

Five original pieces of research were identified [50, 51, 55, 56, 61] and four studies which investigated both motor and language [49, 52, 58, 59]. A total of 40 patients (5-18 years) were included. The majority of studies used finger-tapping tests. A block design was utilised whereby patients tapped at least once with their affected hand and also the unaffected hand; rest periods were interspersed. Few studies reported adequately whether a prompt was used to initiate movement e.g. Liegeois et al[49]. One study that alternated hand and tongue movements, utilised tongue or hand pictures as prompts [50]. If children were unable to engage in hand movements, parents or clinicians would move the hand [49, 52, 61]. The recording of outcomes following fMRI using a motor paradigm varied.

In one example, imaging was considered effective as it indicated that further subdural grid mapping was required. Following this, surgery was successful with no loss of hand function and reduced seizures [48]. Another concluded that motor performance improved following fMRI guided surgery [54]. In the majority of studies, fMRI was found to be accurate and further, invasive procedures were not necessary [49]. The studies concluded motor paradigms were effective and were used with children as young as five with functional age equivalents as low as three years, if pre-scanning training was adequate [51].

Memory

One paper was identified which involved 16 candidates for right anterior temporal lobe resection aged 16-54 years[48]. Two participants (12.5%) were involved aged 16 and 18. The paradigm involved the Roland Hometown Walking Task[64]. In advance of scanning, patients were asked to prepare a map of their hometown including ten destinations that were known well. During scanning, patients were asked to visualise their route. After 30 seconds (when the first destination should have been reached) a baseline task interrupted the route and participants were asked to covertly count in odd numbers beginning with 21. Following this, the control condition was implemented every 30 seconds as consequent destinations were reached. A 1.5T scanner was used and images were corrected for movement. Outside the scanner, the Rey Visual Design Learning Test [65] was implemented to account for non-verbal immediate recall. Based on the Hometown Walking Task, researchers concluded fMRI with a simple retrieval task measured memory function. It acknowledged that the Hometown Walking Task is potentially an inadequately controlled non-specific memory task. The study used pre-defined regions of interest situated over mesio-temporal structures and the number of activated voxels in this region in each hemisphere was used to calculate an asymmetry index. This method was very similar to the laterality indices described previously for both fMRI and MEG lateralisation of language function. No significant memory impairment was identified post-surgery.

Discussion

Retrieved studies indicate evidence that both fMRI and MEG are able to provide information lateralising and localising motor and language functions. A PPV of 74% (95% CI 61-87) for 'typical' lateralisation of language fMRI with validation was demonstrated from available data. The retrieved studies provide evidence that these non-invasive methods are of benefit. However, there is no clear standardised guidance for clinicians regarding which patients are most likely to benefit from a particular modality. Evidence indicates these modalities should not be used as screening tests but should be used to help answer specific questions. For focal lesions this is usually for establishing the relationship of the lesion to the specific eloquent cortex and for mesial temporal epilepsy, assessment of language. Only one retrieved study sought to evaluate memory[48].

Improving Uniformity and Yield

Statistics and Reporting

Volumetric functional imaging tends to use uniform file formats with t-scores, z-scores and dipole locations all able to be visualised using one of the two most popular file types (NIfTI and ANALYZE). This allows data to be compared and transferred from one platform to another, for example importing into image-guided software for neurosurgery. Studies using fMRI to investigate human brain function typically use SPM [66](www.fil.ion.ucl.ac.uk/spm) and FSL [67](http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) to post-process and analyse their data. The retrieved papers vary greatly in their descriptions of analyses used. The variation is more troubling when there are existing metrics of laterality reported in the literature.

Robust statistical thresholding is applied to identify significant activity and the thresholds calculated are adjusted to account for the multiple comparisons problem [68, 69]. Thresholds are used to identify genuine activity and to guard against interpreting non-stimulus-driven responses as being of interest. A threshold applied to data should be objective and any subsequent metrics applied to these areas of activity, such as laterality measures should also be objective. A number of the fMRI studies discussed give sparse details regarding the analyses performed and the thresholds used and focus instead on how the results relate to other independent measures such as electrocorticography or Wada. A number of studies use established software to generate statistical maps but then estimate lateralisation metrics based upon qualitative visual examination [49]. Korman et al [53] provide a discussion of the trade-off between objective identification and the problems this can cause due to variations in anatomy and specific thresholds chosen and thus propose qualitative inspection is a more reliable method by which to establish lateralisation. However, a counter argument is provided [43], where they explicitly consider the effect that thresholds have on the activity seen and inferences made [54]. Most studies perform their analyses at the group level rather than the individual level and thus the effect sizes will be small with Type I and II errors more common for diagnostic scans consisting of a single individual. Therefore, diagnostic mapping of eloquent regions should use all the resources provided by the scientific community in terms of providing objective, robust identification of significant cortical activity.

In MEG, due to the smaller size of the research field in comparison to MRI, there is less consensus both in the specific analyses used and the software used to implement them. All of the retrieved MEG papers use dipole fitting. This is the application of an algorithm which searches for a point-like focal source with a location, orientation and strength that minimises the error between the predicted field from the fitted dipole and the observed field [70]. Dipole fitting is the main analysis tool and the only statistics applied to a dipole estimate are descriptive (typically the goodness-of-fit and correlation value). There is no defined way of inferring statistical significance from a dipole solution and thus the error rate of such an analysis can be difficult to ascertain. Studies which localise function in MEG have moved beyond the dipole fit and now use other analyses such as spatial filtering [71, 72]. Spatial filtering is a data-driven adaptive scanning technique which, unlike dipolar methods, makes no assumptions regarding the number of underlying sources. These methods are used widely and can be subjected to inferential statistical tests [73, 74]. Spatial filtering approaches are now commonplace in MEG investigations of cerebral activity in response to a task; however, despite these advances in methodology and modelling, the dipole fit remains the preferred method for pre-surgical mapping of eloquent cortex in MEG. Although localisation of eloquent regions for research investigations of cortical function has developed more advanced modelling methods and introduced statistical rigour into the process, in a clinical context, recently published guidelines still advocate use of the dipole to perform localisation [75], despite the fact that spatial filtering approaches have been shown to be a robust method of localising such activity [76]. Although there has been an attempt to develop standard practices in the localisation of eloquent brain regions in MEG, there are still large variations in approaches and the methods lag behind the level of statistical inferences which are typically demanded in research studies.

Memory Mapping

Only one retrieved study related to memory mapping [48]. The lack of studies investigating memory is not unique to the paediatric population. In the adult population, there are fewer papers that map memory in epilepsy patients with fMRI [77-80] or MEG [81]. Many of the studies retrieved related to language mapping compare the results to Wada outcomes and highlight the potential that non-invasive functional imaging has for replacing this invasive procedure. However, Wada has a language and memory component and it is the memory component that is of significant interest, particularly for resection to the temporal lobe of the language dominant hemisphere [73, 75].

The type of memory activation task and baseline imaging state effect the extent and location of hippocampal activation. Richardson et al [78] examined verbal memory outcome showing stronger activation on the left side predicted greater decline. However, results across key studies using preoperative hippocampal activation methods have shown inconsistent findings [78, 82-85]. These inconsistencies coupled with technical measurement difficulties, namely signal drop out/macroscopic field inhomogeneity[86] have led to using language lateralisation as a method to predict post-operative memory. Cited support for this approach is a larger region of interest with consequent reduced measurement difficulties; distinct verbal and non-verbal episodic memory networks with different patterns of hemispheric lateralisation and language lateralisation being correlated significantly with verbal memory lateralisation [87]. Binder and colleagues[88] show that the risk of verbal memory decline is more likely to be related to lateralisation of material specific memory networks which are correlated with language lateralisation assessed via contrasted semantic and tone decision tasks and not stimuli yielding episodic memory asymmetry. While these data should perhaps be regarded as preliminary due to small numbers and adult participants, this literature provides guidance for appropriate paediatric protocols.

Paradigm developments for children are required to ensure optimal activation and accurate pre-operative prediction of likely episodic memory decline. As noted, while inconsistent outcomes for hippocampal activation have led to fMRI language lateralisation being promoted to establish pre-operative risk to memory, it must be remembered that no studies have attempted to devise optimal memory activation paradigms for paediatric patients. While this paper does not suggest that Wada has been abandoned too early, if functional imaging techniques are to be a viable alternative in the pre-surgical evaluation of paediatric epilepsy patients, it is necessary to develop protocols that are able to demonstrate concordance with independent measures. Wada is a test that may be failed, providing an indication for likely significant detriment to post-operative memory. The retrieved literature does not provide criteria for failure.

Language Mapping

MEG and fMRI can non-invasively map language function in children and these measures agree with estimates from Wada and electrical stimulation measurements. These are consistent across scan sessions and researchers. Other modalities are available. For example, ECoG is used to localise language eloquent areas for those being considered as potential paediatric epilepsy surgery candidates [89] and consequently these data are used for validation. However, the number of validation studies performed on children is very small and greater rigour for details of stimuli and analysis is required. Many of the MEG studies use similar paradigms, consisting of spoken nouns and a list of target nouns which must be identified. Little published work has been undertaken on optimising language protocols specifically for the paediatric population. One of the greatest challenges for MEG with young individuals is to ensure there is minimal movement. To achieve this, scanning procedures need to remain short whilst still ensuring adequate signal-to-noise.

In fMRI, the standard protocol is to present a letter to the patient via intercom and they are then required to generate words silently beginning with this letter. This technique is shown to work well. However, it may be useful to identify a wider range of language paradigms that are effective. For example, a young patient may have a low phonemic score but a higher semantic naming score, in which case a different language paradigm might be more suitable. These considerations are particularly important given one of the retrieved papers highlighted the different ways the language network is related to the specific type of cortical lesion [53]. The specific implementations should also be unique to each individual. For example, a number of papers use a 30 second 'on-off' design. However, if the patient is able to generate words at a normal rate, a 15 second 'on-off' paradigm would be more appropriate as in the same time there would be twice as many repetitions which greatly enhances the power of the subsequent statistical tests.

Somatosensory and Motor Mapping

One potential contributing factor to the lack of studies on mapping of the motor cortex in MEG and fMRI in paediatric and adult populations is that the paradigms and analyses are simple. Both motor and somatosensory paradigms work effectively for localisation of the central sulcus in an individual and therefore it is a viable alternative to other techniques for patient populations who cannot tolerate other procedures. Motor paradigms were largely uniform across different studies. Some used auditory cues via intercom, whilst others used visual cues. For children where reading is unimpeded, words can be used to cue movement. In younger individuals, coloured pictures, e.g. a cartoon hand on a green background and a cross on a red background, can be used effectively. The responses measured are typically strong and it is possible to monitor if the patient is performing the task. The quickest method of investigating bilateral motor function is to alternate movement of the left and right hands; however, when scanning very young patients, it may be preferable to localise function of the left and right hand independently to prevent the patient from altering the sequence of activation. As with the motor paradigms discussed previously in MEG, despite subtle variations they work well typically and are of short duration. A number of studies describe the scanning of very young children and, although this is time consuming and needs more preparation than adult scanning, it is clearly possible.

Conclusions

Paediatric epilepsies are the most common serious neurological disorders of childhood. Surgery is an effective treatment and in the UK only around 25% of such procedures takes place [9]. fMRI is the predominating tool and all retrieved studies report stimulus-related changes in cerebral blood-flow and oscillatory biomagnetic signals. These methods were also reported to be effective in very young children. Although there were differences across specific protocols used, there were descriptions of a range of approaches which children were both able to tolerate and produce useful signal changes. One notable weakness is the limited number of functional imaging studies, particularly for memory, which focus on the paediatric population. The majority of studies (76%) achieved Level 3 evidence status [25].

Due to the small number of research studies focusing on children, it remains unclear if results from the adult population can be unequivocally extrapolated to children. The numbers reported in this review would be larger if some studies provided comprehensive and consistent information [90]. It is necessary that studies are replicated in entirely paediatric populations. More studies with larger participant numbers and a comparison of paradigms leading to the development of task uniform paradigms are required. Consequently, agreed outcomes allowing prospective collection of data, permitting systematic evaluation coupled with an Individual Participant Data analysis approach may be of benefit [91]. Such approaches have been accomplished previously [92, 93] allowing data combining, planned prospective meta-analysis and sufficient power.

It remains unclear which language and memory tasks produce optimal activation and how this is quantified in a statistically robust manner. If non-invasive functional imaging is to be used routinely in patient populations for pre-surgical evaluation, analyses must be robust, reliable and removed from subjective interpretation [39]. To achieve this, it is crucial that studies are transparent about the specific analyses performed so others may replicate the approach in their locality and more importantly, improve it. Retrieved papers indicate a tendency to be either technical or clinical in their focus i.e. oriented to describing the procedure and analysis in depth with minimal reference to clinical practice, or vice versa. Review of risk for bias via QUADAS-2 indicates the requirement of improvements to study design and reporting. Reported studies need to include enough technical details to allow the stimuli and analyses to be replicated and must also inform clinicians in the field of the relevance the scans have to diagnosis and surgical planning. Presenting concordant aggregated outcome alone is insufficient. As this review shows, a percentage of findings were not concordant with validation (NPV 65% [CI 52 -78] for language fMRI with validation). Non-concordance needs to be understood and managed. A consideration of both helps to ensure selective outcome reporting and analyses are minimised and patient outcomes are optimised [94]. Lack of concordance may be managed clinically through the use of other techniques such as Wada to determine the integrity of contralateral memory and ECoG high-γ modulation to localise language eloquent cortex[89]. There is strong preliminary evidence that fMRI and MEG can be used to lateralise and localise language and motor function in paediatric epilepsy surgery candidates and therefore support treatment decisions.

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Figure 1: PRISMA Diagram

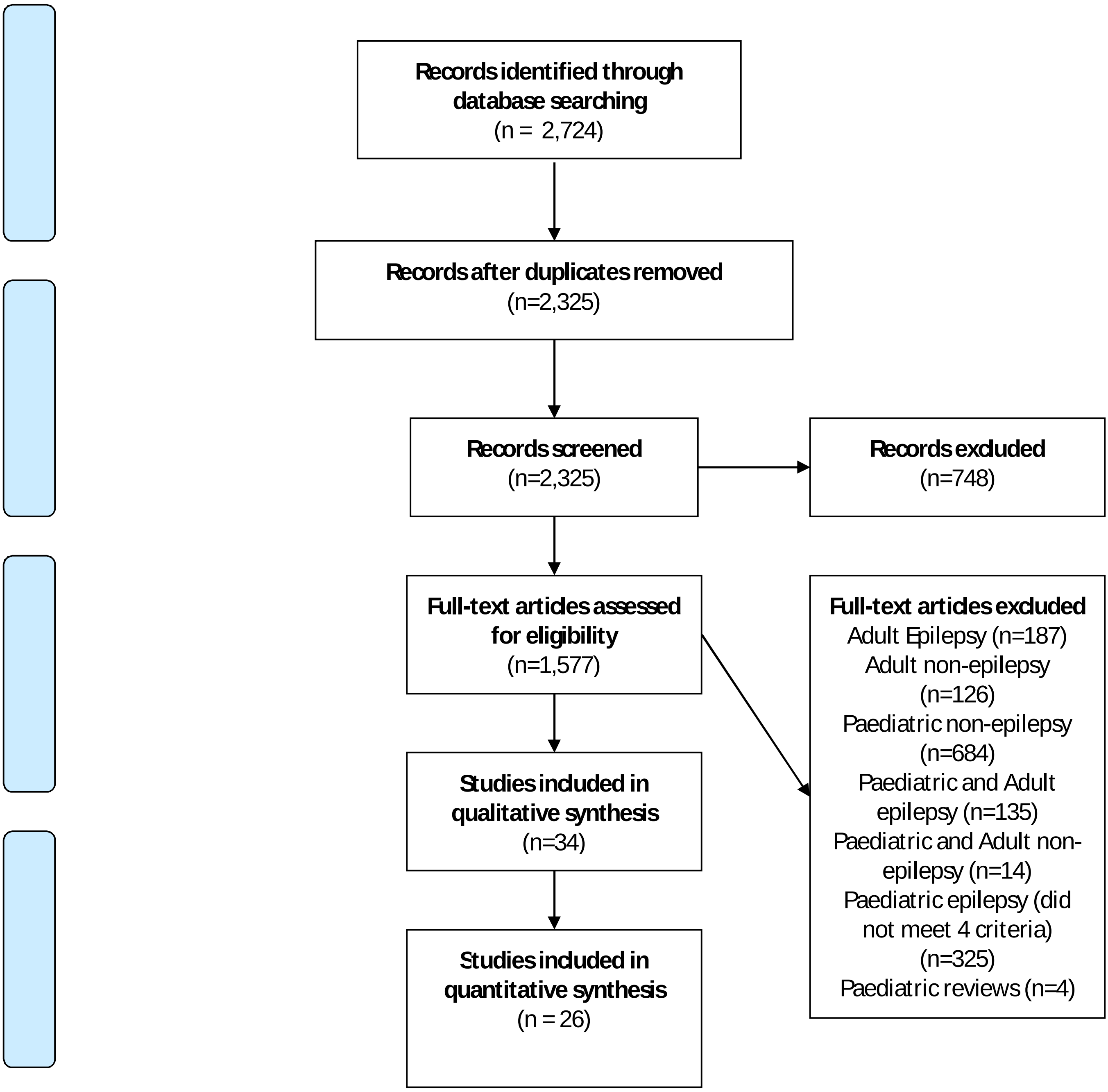

Fig. 2 ROC Space Plot: Sensitivity and specificity of individual studies with CIs and bivariate meta-analysis.

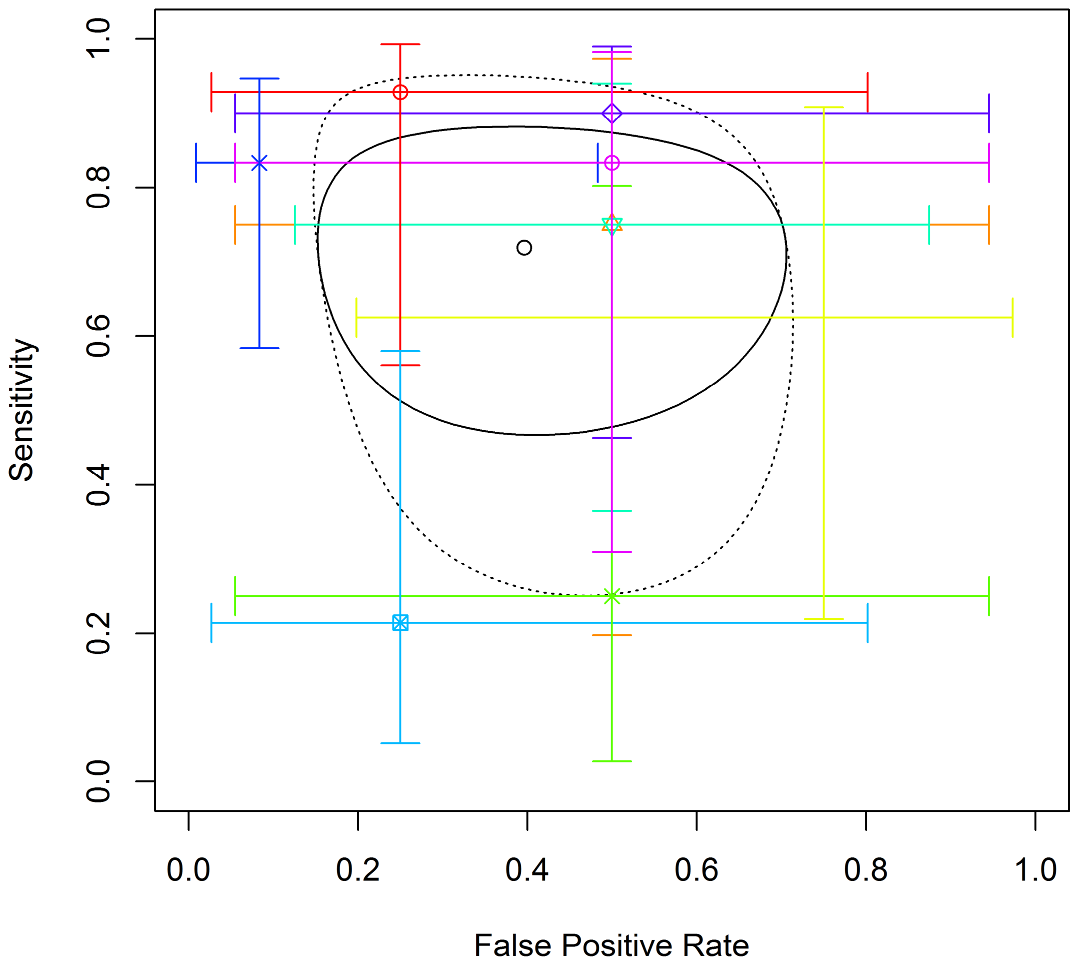

Table 1: All identified studies and characteristics

	Paper	Country of Origin	N (n)	Age range	Imaging (n)	Level of evidence	Imaging task(s)	Validation (n)
1	Hertz-Pannier et al (1997)	USA	11	8.8 - 18	fMRI	3	Language Production	IAT (6); ESM (1)
2	Rutten et al. (1999)	Netherlands	1	14	fMRI	4	Language Production	ioESM
3	Brier et al (2001)	USA	19	8 - 18	fMRI	3	Language Comprehension	IAT
4	Castillo et al (2001)	USA	1	18	MEG	4	Language Production	ioESM
5	Spreer et al (2003)	Germany	4	15 - 17	fMRI	3	Language Comprehension	IAT
6	Adcock et al (2003)	UK	1	15	fMRI	3	Language Production	IAT
7	Sabbah et al (2003)	France	4	9 - 17	fMRI	3	Language Production	IAT
8	Papanicolaou et al. (2004)	USA	19	8 - 18	MEG	3	Language Comprehension	IAT
9	Medina et al. (2005)	USA	7	7.1 - unknown	fMRI	3	Language Production	Clinical Rating
10	Janszky et al. (2005)	Germany	2	16 - 18	fMRI	3	Memory	fMRI
11	Liegeois et al (2006)	UK	31 (7)*	7 - 18	fMRI	4	Motor (2), Language lateralisation (3), Language Production (1), Language Comprehension (1)	ioESM
12	Lee et al. (2006)	USA	8	10 - 17	MEG	3	Language Comprehension	Inter-rater concordance
13	Szaflarski et al. (2008)	USA	28 (1)*	17	fMRI	3	Language Production, Language Comprehension	IAT
14	Arora et al. (2009)	USA	7	12 - 18	fMRI	3	Language Production (6) Language Comprehension (7)	IAT
15	Liu et al (2009)	USA	4	12 - 16	fMRI	3	Motor	ioESM
16	Vitikainen et al. (2009)	USA	2(1)*	16	MEG	4	Motor	nTMS
17	Pilato et al. (2009)	Italy	1	14	fMRI	4	Motor	TMS
18	Shurtleff et al. (2010)	USA	8	5 - 8	fMRI	3	Language Production (4) Motor (7)	ESM, IAT
19	Korman et al. (2010)	USA	29	9 - 18	fMRI	3	Language Production, Language Comprehension	nr.
20	Jones et al. (2011)	USA	59(9)*	8 - 18	fMRI	3	Language Lateralisation	IAT
21	Ota et al. (2011)	Japan	4	14 - 18	fMRI + MEG	3	Language Comprehension	IAT
22	Seo et al. (2011)	USA	14(13)†	3-18	MEG	3	Epileptigenic Foci	iEEG
23	van Poppel et al. (2012)	USA	15(13)*	4 - 16	MEG	3	Language Comprehension	nr.
24	Rodin et al. (2013)	Canada	20	nr.	fMRI	3	Language Production, (7) Language Comprehension (7)	IAT

25	Zhang et al. (2013)	China	7(6)*	7 - 17	fMRI	3	Motor	Clinical Outcome
26	Sommer et al (2013)	Germany	25(3)*	12 - 18	iofMRI	3	Motor	Clinical Outcome
27	Vadivelu et al (2013)	USA	2	4-9	rsfMRI	4	Language lateralisation	Clinical Outcome
28	Genetti et al (2014)	Switzerland	23 (6)*	11-17	fMRI	3	Motor (4), Language Comprehension	hgECoG, ESM
29	Nooraine et al (2014)	India	7 (2)*	11	fMRI	4	Motor (2), Language lateralisation (1)	Clinical Outcome
30	Gelinas et al (2014)	USA	46	7-19	fMRI	3	Language lateralisation	nr.
31	Norrelgen et al (2014)	Sweden	19	8-18	fMRI	3	Language lateralisation	Dichotic listening
32	Suarez et al (2014)	USA	46 (21)*	8-17	Passive fMRI	3	Language lateralisation	ECS(5), IAT (13)
33	Choudhri et al (2015)	USA	56 (17)*	0.5-12.1	pm-fMRI	4	Motor	nr.
34	Sepeta et al (2016)	USA	142 (17)*	6.8-12.8	fMRI	3	Language lateralisation	nr.

*Paediatric data included within adult data; † Paediatric data included with >4 years patient data; fMRI= functional magnetic resonance imaging; IAT= Intracarotid Amobarbital Test; iEEG= intercranial EEG; ioESM= intraoperative Electrocortical Stimulation Mapping; ESM= Electrocortical Stimulation Mapping; nTMS= navigated Transcranial Magnetic Stimulation; TMS= Transcranial Magnetic Stimulation; hgECoG=induced high gamma electrocorticography; nr. = not reported; pm-fMRI= passive motion functional magnetic resonance imaging.

Table 3: Wada and functional MRI results based on left, right and bilateral language representations for all included studies

	Wada		
fMRI	**Left**	**Right**	**Bilateral**
Left	56 (58.33%)	0	1 (1.04; **4.35%**)
Right	1 (1.04%; **4.35%**)	9 (9.38%)	3 (3.15%; **13.04%**)
Bilateral	10 (10.42%; **43.48%**)	4 (4.16%; **17.31%)**	8 (8.33%)

Percentage of responses shown in parentheses (N=96)
Percentage of non-concordant responses shown in bold (N=23)

QUADAS-2 ratings of included studies

Study	Risk of bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index test	Reference Standard
Hertz-Pannier et al (1997)							
Rutten et al. (1999)							
Brier et al (2001)							
Castillo et al (2001)							
Spreer et al (2003)							
Adcock et al (2003)							
Sabbah et al (2003)							
Papanicolaou et al. (2004)							
Medina et al. (2005)							
Janszky et al. (2005)							
Liegeois et al (2006)							
Lee et al. (2006)							
Szaflarski et al. (2008)							
Arora et al. (2009)							

Liu et al (2009)							
Vitikainen et al. (2009)							
Pilato et al. (2009)							
Shurtleff et al. (2010)							
Korman et al. (2010)			N/A	N/A			N/A
Jones et al. (2011)							
Ota et al. (2011)							
Seo et al. (2011)							
van Poppel et al. (2012)							
Rodin et al. (2013)							
Zhang et al. (2013)							
Sommer et al (2013)							
Vadivelu et al (2013)							
Genetti et al (2014)							
Nooraine et al (2014)							
Gelinas et al (2014)			N/A	N/A			N/A
Norrelgen et al (2014)							
Suarez et al (2014)							
Choudhri et al (2015)			N/A	N/A			N/A
Sepeta et al (2016)			N/A	N/A			N/A

= High; = Low; = Unclear; N/A = Not applicable

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