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An algorithmic approach to preoperative studies and patient selection for hemispheric disconnection surgery: a literature review

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ABSTRACT – *Aims.* Hemispheric disconnection surgery (HDS) is one of the most effective surgical options for appropriate candidates with medically-refractory epilepsy (MRE) in whom most or all seizures arise from diffuse areas within a single hemisphere. While there are several well-accepted indications for HDS, there are additional patients who may benefit from HDS. However, there are no standardized recommendations for how preoperative studies should be used to identify appropriate candidates for HDS. We aimed to propose an algorithmic approach for presurgical evaluation in order to guide appropriate implementation of HDS for either cure or palliation of severe MRE in infants, children, and adults. *Methods.* We performed a qualitative review of the literature using PubMed, the Cochrane Library, and Google Scholar to select primary articles addressing imaging modalities used for the presurgical evaluation of patients with MRE being considered for HDS. *Results.* In total, we identified 126 articles that met our inclusion criteria. We propose a framework to guide candidate selection for HDS that incorporates various elements of the clinical presentation, electroencephalographic analysis, and neuroimaging. While this approach still requires prospective validation, the authors feel it is grounded in a synthesis of the best available evidence in the literature and informed by expert opinion. *Conclusions.* HDS is a powerful tool in the armamentarium of experienced multi-disciplinary epilepsy centers to treat patients with severe MRE arising from diffuse areas constrained to a single hemisphere. The under-utilization of epilepsy surgery may be, in part, remedied by establishing evidence-based pathways for presurgical analyses to determine surgical candidacy.

Key words: epilepsy, hemispheric disconnection surgery, hemispherotomy, surgical epilepsy

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Hemispheric disconnection surgery (HDS) is an effective surgical treatment for appropriate candidates with medication-resistant epilepsy (MRE) in whom most or all seizures are thought to arise from diffuse areas within a single hemisphere (Kim *et al*., 2018). While anatomic hemispherectomy (AH) was developed in the early 20th century and may still be favored in certain cases (*e.g*. hemimegalencephaly, Rasmussen's encephalitis, after failed hemispherotomy), most contemporary neurosurgeons have embraced some variation of functional hemispherotomy (FH) for patients with hemispheric epilepsy. FH has also largely replaced hemidecortication, a procedure associated with technical difficulty, blood loss, and at least in one series, lower rates of seizure control (Rangel-Castilla *et al*., 2012; Rasmussen, 1983; Krynauw, 1950; Griessenauer *et al*., 2015). Rather than focus on the nuances of surgical technique, we will hitherto refer to anatomic hemispherotomy, functional hemispherotomy, and hemidecortication collectively as HDS. The foregoing manuscript will therefore seek to provide a systematic framework to evaluate the various components of the preoperative work-up (*e.g*. semiology, brain MRI, PET) in determining candidacy for HDS.

The selection of appropriate candidates for HDS is not standardized and varies between institutions. Thus, we review the literature to elucidate the role of various components of a patient's clinical work-up including neurological exam, seizure semiology, neuropsychological testing, video-EEG (vEEG), and neuroimaging to guide selection of appropriate candidates for HDS. While there are several well-accepted indications for HDS (*e.g*. Rasmussen's encephalitis, Sturge-Weber syndrome, perinatal middle cerebral artery stroke, hemimegalencephaly), other patients without these established indications may benefit from HDS. Thus, a better understanding of the preoperative evaluation can assist neurosurgeons and epileptologists to:

– identify cases of MRE in which the entire hemisphere or much of the hemisphere is involved in seizure generation;

– lateralize seizure activity;

– and inform the patient and family of risks, likely deficits, and expected rates of seizure freedom following surgery.

Methods

We performed a qualitative review of the literature by searching PubMed, Google Scholar, and the Cochrane Library for articles describing various clinical and imaging studies in selecting patients who underwent HDS from 1980 to the present. We also qualitatively reviewed surgical outcomes in this population since quantitative assessment was not possible due to heterogeneity in the literature. Key words included the following: hemispheric disconnection surgery (HDS), functional hemispherotomy (FH), functional hemispherectomy (FHE), anatomic hemispherectomy (AH), hemidecortication, hemispheric epilepsy, epilepsy surgery, medically-refractory epilepsy (MRE), seizure semiology, ictal EEG, interictal EEG, vEEG, brain MRI, PET, SPECT, MEG/MSI, electrical source imaging (ESI), fMRI, Wada test, and neuropsychological evaluation. The reference lists of these articles were also curated to identify relevant studies to this review. Included articles focused on various clinical and imaging studies (*e.g*. MRI, PET, SPECT, MEG) in the presurgical work-up of patients undergoing HDS and associated seizure outcomes. Articles which included patients undergoing repeat HDS due to recurrence were also included. Only human studies written in English were included. Those articles describing multi-lobar resections were excluded from this review. Articles discussing temporal lobe epilepsy, and those illustrating the role of imaging technologies in localizing epilepsy for the purpose of resective surgery were also excluded. Articles were chosen based on their discussion of pre-operative work-up in the decision-making process to proceed with HDS.

Results

We included 126 studies and case reports that focused on various facets of the presurgical evaluation that helped to determine patient candidacy for HDS. Of these studies, 61 studies reported utilizing one or more imaging and/or functional diagnostic studies and their role in selecting patients who underwent HDS. We also reviewed studies that illustrate how adjunctive imaging technologies (*e.g*. PET, SPECT/SISCOM, MEG) may be used to determine surgical candidacy (*table 1*).

Medical history and neurologic examination

Most patients who present for consideration of HDS have frequent (*e.g*. often daily) seizures, hemiparesis, as well as varying degrees of neuropsychological impairment. Invariably, patients who are candidates for HDS have MRE, having failed multiple prior trials of AEDs, and not uncommonly, these patients may have a history of status epilepticus. Hemiparesis classically affects the upper extremities to a greater degree than the lower extremities, and manifests distally (*e.g*. pincer strength) more than proximally. Hemiparesis may be profound or subtle, but the absence of any weakness typically indicates a more focal pathology, and a more selective resection/disconnection should

Table 1. Summary of studies describing the role of imaging modalities in the preoperative work-up for HDS.

Study	Number of patients	EEG	MRI (fMRI/DTI)	PET	MEG	SISCOM
Boshuisen *et al.*, 2010	43	43	43	N/A	N/A	N/A
Carmant *et al.*, 1994	7	7	7	N/A	N/A	7
Carmant *et al.*, 1995	12	12	N/A	N/A	N/A	N/A
Chandra *et al.*, 2008	19	19	19	N/A	N/A	7
Ciliberto *et al.*, 2012	8	8	8	N/A	N/A	N/A
Curtiss *et al.*, 2001	43	43	43	43	N/A	N/A
Doring *et al.*, 1999	28	28	N/A	N/A	N/A	N/A
González-Martínez *et al.*, 2005	18	18	18	18	N/A	N/A
Greiner *et al.*, 2011	54	54	N/A	N/A	N/A	N/A
Groppel *et al.*, 2015	28	28	28	28	N/A	N/A
Hallbook *et al.*, 2010	110	110	110	N/A	N/A	N/A
Hamad *et al.*, 2013	15	15	15	N/A	N/A	N/A
Kiehna *et al.*, 2016	8	8	8 (DTI)	N/A	4	N/A
Kossof *et al.*, 2003	110	110	110	N/A	N/A	N/A
Limbrick *et al.*, 2009	49	49	49	Obtained (number of patients not available)	N/A	Obtained (number of patients not available)
Moosa *et al.*, 2013	186	186	186	186	N/A	N/A
Nelles *et al.*, 2015	34	34	34 (DTI)	N/A	N/A	N/A
Scavarda *et al.*, 2009	8	8	8	N/A	N/A	8
Smith *et al.*, 1991	25	25	25	N/A	N/A	N/A
Soufflet *et al.*, 2004	10	10	10	N/A	N/A	10
Torres *et al.*, 2009	13	13	13	2	13	N/A
Traub-Weidinger *et al.*, 2016	35	35	35	35	N/A	N/A
Wang *et al.*, 2018	25	25	25 (fMRI, DTI)	N/A	N/A	N/A
Wyllie *et al.*, 2007	50	50	50	47	N/A	7

EEG: electroencephalogram; MRI: magnetic resonance imaging; fMRI: functional MRI; PET: positron electron tomography; MEG: magnetoencephalography; SPECT: single-photon emission computed tomography; SISCOM: subtraction ictal SPECT co-registered to MRI; DTI: diffusion tensor imaging (DTI).

be considered. An exception to this may occur in very young children (< six months) with hemispheric involvement on MRI, refractory seizures, and a clinical course suggestive of a catastrophic epileptic encephalopathy - even if focal deficits are difficult to appreciate on examination in such an infant, HDS may still be warranted.

Preoperatively, patients may also exhibit homonymous hemianopsia or other visual field impairments, although in young children or in those with significant

cognitive impairment, formal visual field testing may not be possible. If visual field constriction is not present preoperatively, as may be seen in an individual after perinatal MCA stroke with relative preservation of the optic radiations and occipital cortices, HDS can be expected to result in a homonymous hemianopsia with macular sparing. A new visual field deficit should not be used as a reason to forego HDS in an otherwise appropriate candidate with severe MRE.

Expressive speech and comprehension should be carefully assessed, and if the patient has language skills that can be evaluated, further testing may be required to determine the side of language dominance, especially in patients being considered for left-sided HDS or in patients with acquired epilepsy etiologies. The timing of precipitating insult (*e.g.* perinatal stroke) is also important to establish as a neurological injury occurring earlier may be more likely associated with plasticity and reorganization of eloquent cortices than injury later in life.

In addition to obtaining a thorough history of the precipitating event, the age at seizure onset, and the frequency of seizures, one should be attentive to signs on examination that might indicate that the patient has a syndrome associated with hemispheric epilepsy such as port-wine stains associated with Sturge-Weber syndrome or an enlarged hemisphere with an abnormal gyral pattern, thickened cortex, and enlarged ipsilateral ventricle as seen in hemimegalencephaly (*table 2*). Seizure outcomes in numerous studies have tended to be better in patients with acquired pathologies (*e.g.* perinatal MCA stroke, Rasmussen's encephalitis) compared to those with congenital underlying etiologies (*e.g.* hemimegalencephaly) (Devlin *et al*., 2003; Ciliberto *et al*., 2012; Kim *et al*., 2018). Finally, if hemispheric pathology is suspected and the patient has epileptic encephalopathy or any other features suggestive of congenital pathology, genetic and metabolic testing may be warranted.

A child with infrequent or rare seizures should be monitored with inpatient vEEG or even ambulatory EEG to ensure that nocturnal or subclinical seizures are not being missed. This is especially important in children who seem to be regressing, missing milestones, developing behavioral problems, or show worsening of school performance. It is not uncommon for parents and caregivers to underestimate the seizure burden in children (Benbir *et al*., 2013). Serial neuropsychological testing is advised in all patients with MRE (Wilson *et al*., 2015). A steady decline in behavioral and neurocognitive faculties of affected children can help parents who continue to be reluctant about proceeding with surgery recognize the potentially devastating natural history of MRE.

Language function and testing

The timing, location, etiology of neurological insult causing epilepsy, the age at surgery, quality of preoperative, and baseline language function should each be considered when counseling patients and families on expected postoperative language outcomes. Language mapping utilizing fMRI, Wada testing, MEG, and intra/extra-operative direct cortical stimulation (DCS) is rarely required before proceeding with right-sided HDS, and cannot be performed in infants, preverbal children, or adults with profoundly impaired speech and comprehension (Austermuehle *et al*., 2017; Rolinski *et al*., 2019). On the other hand, identifying the language cortex may be critical in patients with strong baseline verbal skills who had an acquired insult with seizure-onset later in childhood. Early neurological insult promotes increased plasticity in the contralateral hemisphere, and it is thought that a congenital or early-in-life (*e.g.* perinatally-acquired) insult provides enough time for the non-dominant hemisphere to develop language function (de Bode and Curtiss, 2000; Maehara *et al*., 2002; Hamad *et al*., 2013).

Most agree that neurocognitive and language outcomes are maximized if HDS is performed as soon as the patient demonstrates features of hemispheric MRE. At least one group concluded that postoperative language improvement is typically more pronounced in patients with a shorter duration (*e.g.* < two years) of epilepsy prior to surgery (Groppel *et al*., 2015). Meanwhile, the side of surgery remains a controversial topic, and while many studies show that patients who undergo right-sided hemispherectomy experience improved language outcomes compared to those undergoing left-sided hemispherectomy (Dennis and Kohn, 1975; Dennis, 1980; Vargha-Khadem and Polkey, 1992; Stark and McGregor, 1997; Menard *et al*., 2000), there are other reports that show the opposite or no difference between left or right (Smith, 1966; Vargha-Khadem *et al*., 1997; de Bode and Curtiss, 2000). Finally, preserved language may play a role in the timing of definitive HDS of the language-dominant hemisphere in patients with Rasmussen's encephalitis as immunomodulatory therapy has led to cases of prolonged remission (Varadkar *et al*., 2014).

Seizure semiology

Semiology includes clinical observations of the seizure that assist in determining focal or generalized pathology and offers clues to localization and lateralization in the case of focale epilepsy. Despite its many limitations and high rates of interobserver variability, some features of the seizure semiology are reproducible and may be useful in evaluating patients for FH. Semiology features associated with high positive predictive value for post-FH improvement include unilateral clonic

Table 2. Classic MRI and physical examination findings for syndromes in which HDS may be indicated.

Syndrome	Classic MRI findings	Physical examination findings
Rasmussen's syndrome	Swollen cortex with hyperintense T2/fluid-attenuated inversion recovery signals. Scans at later stages of the disease will show progressive atrophy of the affected hemisphere (Bien *et al*., 2002; Varadkar *et al*., 2014; Varadkar and Cross, 2015)	Hemiparesis, hemianopsia, cognitive difficulties (Bien *et al*., 2002; Varadkar *et al*., 2014; Varadkar and Cross, 2015)
Sturge-Weber syndrome	Hyperintense and hypointense white matter abnormalities caused by chronic ischemic changes, in addition to the classic leptomeningeal angiomatosis and hypotrophy of the ipsilateral hemisphere and ventricular enlargement (*Chiron et al*., 1989)	Port-wine stains. Developmental delays and cognitive delays (Chiron *et al*., 1989)
Perinatal ischemic stroke	DWI can show cytotoxic edema within hours of the initial ischemic event. After 1-2 months, the infarcted area will usually reveal tissue loss and cysts (Dudink *et al*., 2009; Lehman and Rivkin, 2014; Taussig *et al*., 2015)	Lethargy, hypotonia, apnea, and hemiparesis (Sehgal, 2012)
Congenital porencephaly	MRI shows cavity with well-circumscribed cystic appearance, encephaloclastic changes, and ventricular enlargement. Hippocampal atrophy and signal abnormalities associated with mesial temporal sclerosis may also be appreciated (Shimizu *et al*., 2012)	Spastic paresis, contractures, hypotonia, cognitive difficulties. Macro- or microcephaly (Shimizu *et al*., 2012)
Other	Diffuse unilateral polymicrogyria (PMG), schizencephaly (often associated with PMG), or diffuse unilateral periventricular nodular heterotopia	N/A

jerking, unilateral dystonic posturing and automatisms with preserved responsiveness, and asymmetric tonic limb posturing (Marks and Laxer, 1998; Elwan *et al*., 2018). Clonic or dystonic arm movements at seizure onset can often be observed and may help implicate the contralateral hemisphere. However, it is not uncommon to have multiple seizure types and rapid secondary generalization (Shukla *et al*., 2002). Patients with generalized semiology or secondary generalization may be more likely to experience recurrent seizures after FH (Hu *et al*., 2016). Thus, semiology can be a critical component of the presurgical analysis, and should be carefully studied by the epilepsy team, to support or contradict the prevailing hypothesis of laterality of the involved hemisphere based on neurological examination, neuroimaging and other elements of the presurgical evaluation.

Neuropsychological examination

Neuropsychological testing is an important component of presurgical evaluation in order to assess verbal memory, intelligence, and other cognitive functions that may be affected by the underlying epilepsy and its comorbidities (*e.g*. anxiety, depression, *etc*.) or may be at risk from proposed operative interventions (Dijkerman *et al*., 2008; Dorfer *et al*., 2015). Neuropsychological evaluation in patients with diffuse unilateral hemispheric involvement is typically varied and requires individualized evaluation (Helmstaedter and Witt, 2012). The most relevant clinical question at hand is determining to what degree the contralateral (unaffected) hemisphere will take over or has already taken over the function of the disease hemisphere (Kim *et al*., 2018). While many studies suggest that the most important predictor of neuropsychological outcomes following HDS is the patient's preoperative baseline condition, improvement in behavior as well as academic performance has also been documented and is likely attributable to resolution and/or reduction in seizure burden (Devlin *et al*., 2003).

Electroencephalography (EEG) (ictal and interictal)

VEEG plays a critical role in determining patient candidacy for HDS, both in lateralizing the epilepsy and in determining whether the electrographic abnormalities are focal or diffuse, but may be less critical in establishing candidacy for HDS than for other types of epilepsy surgery. If the patient has multiple seizure types, bilateral MRI findings, and semiology suggestive of independent seizure onset in the

contralateral hemisphere, a prolonged vEEG study may provide additional information about the laterality (or bilaterality) of seizure onset. When lateralization is not in doubt, a short interictal EEG will typically suffice. Patients who present for consideration of HDS typically have focal interictal abnormalities such as attenuation, slowing, or epileptiform discharges that are seen broadly within the affected hemisphere. Non-lateralizing EEG findings (*i.e.* bilateral or contralateral aka "falsely lateralizing" EEG findings) should not be regarded as a contraindication to HDS when other factors favor proceeding with surgery as postoperative seizure outcomes compare favorably to those patients with EEG findings that lateralize to the abnormal hemisphere (Carmant *et al.*, 1994; Doring *et al.*, 1999; Wyllie *et al.*, 2007; Garzon *et al.*, 2009; Greiner *et al.*, 2011; Elwan *et al.*, 2018).

Lee *et al.* reported post-hemispherectomy seizure freedom rates in 54 epilepsy patients with various etiologies. Of the 42 patients who became seizure-free, 17 had non-lateralizing EEG findings (Lee *et al.*, 2014), with other groups reporting similar findings (Smith *et al.*, 1991; Gonzalez-Martinez *et al.*, 2005; Greiner *et al.*, 2011; Ciliberto *et al.*, 2012; Hu *et al.*, 2016). On the other hand, Carmant *et al.* studied outcomes after HDS in 12 children, and reported that slowing, independent spiking, or ictal discharges over the contralateral hemisphere had a negative impact on postoperative seizure freedom (Carmant *et al.*, 1995). In another study, patients with lateralized onset of seizure on ictal EEG were found to have higher rates of seizure freedom compared to patients with non-lateralized EEG findings (Moosa *et al.*, 2013a). An analysis of 49 HDS patients revealed that those with bilateral ictal and interictal EEG abnormalities had higher rates of seizure recurrence, though this conclusion was not based on statistical significance (Limbrick *et al.*, 2009).

"False lateralization" (ictal or interictal information implicating the contralateral hemisphere at seizure onset) has been documented, most notably in patients who demonstrate a profound degree of hemispheric destruction (*e.g.* post-infectious encephalomalacia, perinatal MCA stroke) and many of these patients can achieve seizure freedom after HDS of the structurally damaged hemisphere (Carmant *et al.*, 1995; Doring *et al.*, 1999; Ciliberto *et al.*, 2012; Wyllie *et al.*, 2007; Garzon *et al.*, 2009;). In large destructive hemispheric lesions, surface EEG electrodes over the affected hemisphere may not detect seizure onset, and the first ictal discharges are instead seen over the contralateral "normal" hemisphere once the seizure has propagated bilaterally. Such patients should not be denied HDS, especially when other elements of the preoperative evaluation (*e.g.* hemiparesis on examination, seizure semiology, neuroimaging) demonstrate concordance.

Magnetic resonance imaging (MRI)

MRI continues to play a critical role in decision-making for epilepsy surgery. The evidence for unilateral hemispheric involvement (*e.g.* atrophy or abnormal cortication) and contralateral hemiparesis found together should lead to serious consideration of HDS candidacy. Classic MRI findings in which HDS is an indicated surgical option are summarized in *table 2*. However, MRI may be normal in some cases or the changes can be subtle (*e.g.* early stages of Rasmussen's encephalitis) (Holec *et al.*, 2016; Nagahama *et al.*, 2017). Increasingly, MR volumetry and MR spectroscopy have shown a role in lateralizing temporal lobe epilepsy (Aitouche *et al.*, 2017), but their application to selection of candidates for HDS has not been established.

MRI abnormalities contralateral to the side of the involved hemisphere are generally thought to be associated with lower rates of seizure freedom after HDS, but as with EEG findings, the significance of bilateral MRI findings is controversial. In a retrospective cohort study of 43 children who underwent HDS, Boshuisen *et al.* found decreased rates of seizure freedom among children with contralateral MRI abnormalities compared to those without contralateral hemispheric lesions (45% vs 88%, respectively; p=0.03) (Boshuisen *et al.*, 2010), and others have corroborated this claim (Moosa *et al.*, 2013a; Moosa *et al.*, 2013b; Ramantani *et al.*, 2013; Villarejo-Ortega *et al.*, 2013; Hu *et al.*, 2016). On the other hand, some studies have failed to demonstrate a significant difference in seizure freedom as a result of contralateral MRI abnormalities and do not consider it to be an independent predictor of outcomes (Hallbook *et al.*, 2010; Hu *et al.*, 2016). This discrepancy is not surprising as not all lesions are epileptogenic and not all epilepsy is lesional. If contralateral MRI abnormalities are seen in a patient with non-lateralizing EEG findings, the possibility that independent epileptogenicity exists in the contralateral hemisphere should be recognized, and while HDS may still be considered, palliation might be a more realistic goal rather than cure.

Functional and adjunctive studies

If the clinical examination, semiology, brain MRI, and vEEG are concordant and all implicate diffuse regions of epileptogenicity and dysfunction within a single hemisphere, further studies may not be required to make a recommendation to proceed with HDS. However, if there is discordance of the aforementioned studies (*e.g.* discordant semiology, multiple seizure types, non-lateralized EEG findings) or if MRI abnormalities are subtle or bilateral, additional studies (*e.g.* PET, SPECT, MEG) may play a role in determining HDS candidacy by helping determine whether all or most of the seizures arise from a single hemisphere. Once the epileptogenic hemisphere is firmly established,

Table 3. Summary of studies looking at imaging techniques and correlation of their findings with hemispherotomy outcomes.

Study	Level of evidence	No. of cases	Procedure	Imaging study	Outcome measured	Follow-up	Outcome
Boshuisen *et al.*, 2010	Level II-2	43	FH	MRI	Seizure freedom and cognitive outcome in patients with contralateral MRI abnormalities	6.9 years (standard deviation: 3.9, range: 1.0–15.7)	Contralateral lesions on MRI were associated with lower rates of seizure freedom (45% vs 88%) and worse cognitive outcomes
Caplan *et al.*, 1993	Level II-2	13	H	PET	Change in non-verbal communication in patients undergoing hemispherectomy	Mean: 15.4 months	Patients undergoing right hemispherectomy with radioactivity in the prefrontal area had positive correlation with change in joint attention
Carmant *et al.*, 1994	Level II-2	7	H	SPECT	Seizure outcomes in patients with unilateral SPECT hypoperfusion	12 months- 4 years	Patients with unilateral SPECT abnormalities had favorable seizure outcomes despite having bilateral EEG or MRI findings
Carmant *et al.*, 1995	Level II-2	12	AH and FH	EEG: ictal and interictal	Post-operative seizure freedom in relation to preoperative EEG	N/A	Seizure freedom correlated with the following findings: "suppression over the abnormal hemisphere, absence of contralateral slowing, absence of generalized discharges and absence of bilateral independent spiking; or by unilateral onset of ictal discharges on invasive intracerebral EEG recording"
Doring *et al.*, 1999	Level II-2	28	H	EEG	Seizure freedom rates and their relation to pre and post-operative EEG in patients with major unilateral hemispheric lesions	N/A	The presence of bilateral EEG abnormalities was high in patients with post-operative seizure freedom and should not preclude surgical work-up

Table 3. Summary of studies looking at imaging techniques and correlation of their findings with hemispherotomy outcomes (*continued*).

Study	Level of evidence	No. of cases	Procedure	Imaging study	Outcome measured	Follow-up	Outcome
Greiner *et al.*, 2011	Level II-2	54	H	EEG	Seizure freedom rates post operatively in patients with lateralizing EEG vs. non-lateralizing EEG	Minimum of 1 year follow-up	EEG non-lateralization did not correlate with poor seizure freedom post hemispherectomy
Hallbook *et al.*, 2010	Level II-2	110	H	MRI	Seizure freedom following hemispherectomy in patients with contralateral MRI abnormalities	12-84 months (median: 24) after surgery	Contralateral MRI abnormalities were not associated with lower rates of seizure freedom when compared to patients with no contralateral lesions (79% vs 83%).
Kiehna *et al.*, 2016	Level II-2	8	Repeat H	DTI	Seizure freedom outcome using Engel classification	Minimum of 2 years of follow-up	5 patients were Engel Class 1. The remaining patients were Engel Class II
Moosa *et al.*, 2013	Level II-2	186	H	PET	Seizure recurrence in patients with bilateral PET findings	5.3 years (±3.3 years)	Presence of bilateral PET abnormalities was associated with higher rates of seizure recurrence (RR = 2.53, 95% CI = 1.02-5.85)
Nelles *et al.*, 2015	Level II-2	34	FH	DTI	Post-operative motor states in relation to DTI mapping of corticospinal tracts	N/A	Fractional anisotropy on DTI was higher in patients who had motor loss following FH compared to those who did not.
Torres *et al.*, 2011	Level II-2	13	H	MEG	Seizure outcome rates in patients with unilateral MEG spikes	N/A	Engel Class I, II, and IV seizure freedom was seen in 10, 2, and 1 patient, respectively
Traub-Weidinger *et al.*, 2016	Level II-2	35	H	PET	Seizure outcome in patients who underwent PET as part of their pre-surgical evaluation for hemispherotomy	39.43 months (range: 12–144)	100% of patients with unilateral 18F-FDG-PET hypometabolism had seizure freedom compared to 75% of those with bilateral hypometabolism

H: hemispherectomy; FH: functional hemispherectomy; AH: anatomic hemispherectomy.

another series of functional studies (*e.g.* fMRI, Wada, MEG, DTI) may help lateralize and localize eloquent brain functions that need to be preserved. A summary of imaging modalities and seizure outcomes across studies is included in *table 3* .

Fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET)

There are numerous surgical epilepsy series in which PET is obtained for all patients as a routine component of the presurgical evaluation (la Fougere *et al*., 2009; Suarez-Pinera *et al*., 2015; Traub-Weidinger *et al*., 2016). Evidence of diffuse hypometabolism of one hemisphere on PET may further bolster the argument to offer a patient HDS while bilateral hypometabolism may serve as a negative prognostic factor (Schur *et al*., 2018). In cases of Rasmussen's syndrome with subtle MRI findings, PET may play a role in seizure lateralization (Chugani *et al*., 1993; Ochoa-Figueroa *et al*., 2012). PET may also help to demonstrate a more focal area of hypometabolism, obviating the need for a more extensive disconnection, which may be especially helpful in infants in whom focal abnormalities may result in generalized EEG patterns (Halac *et al*., 2017). In a study of eight infants with intractable epilepsy of neonatal onset, PET findings helped to determine whether HDS or a more focal, tailored resection was most appropriate (Chugani *et al*., 1993).

While difficult to reliably detect in every case, the presence of bilateral PET abnormalities may influence postoperative seizure freedom but the implication of such findings must be considered in the context of other imaging findings such as MRI, the patient's history, and the neurologic examination (Moosa *et al*., 2013a). In a group of 35 children with MRE, interictal PET was performed prior to HDS. Every patient reported in this series with unilateral PET hypometabolism was seizure-free a year after surgery even if MRI abnormalities were bilateral. Of those with unilateral MRI abnormalities and bilateral PET hypometabolism, 87.5% were seizure-free (Traub-Weidinger *et al*., 2016). In a separate series (Chugani *et al*., 1993), 23 patients with infantile spasms underwent PET as part of their presurgical evaluation. Eight of those 23 patients underwent hemispherectomy. In three patients, PET revealed bilateral areas of hypometabolism, despite unilateral structural abnormalities on MRI. All three patients had persistent seizures post-HDS. The remaining five patients in this series had diffuse hypometabolism of one hemisphere and were seizure-free post-HDS.

Magnetoencephalography (MEG)

Unfortunately, very few studies have specifically addressed the value of MEG in predicting seizure outcomes after HDS. Furthermore, MEG is expensive, requires specialized expertise for interpretation, may be of limited value in the pediatric cohort because of lack of universal sedation protocols, and is typically only available at select academic and high-volume centers in developed countries (Birg *et al*., 2013). In 13 patients evaluated with MEG prior to undergoing peri-insular hemispherotomy, seven of eight patients exhibiting unilateral dipole clusters within the affected hemisphere were seizure-free postoperatively. Of the three patients who had not been completely seizure-free, two had MEG spikes concentrated over the disconnected hemisphere, and one had bilateral MEG spikes (Schwartz *et al*., 2010; Jung *et al*., 2013). Of note, MEG findings did not alter decision-making for patients in this study, despite some patients having MEG results that were discordant with MRI and/or EEG findings (Torres *et al*., 2011). Studies with bigger sample sizes must be performed to further examine the correlation between MEG findings and HDS outcomes. MEG may also be applied to mapping language and motor functions preoperatively, as it has high sensitivity to a wide spectrum of brain signals and the ability to map them to their specific anatomical origins due to its superior temporal resolution (Erdler *et al*., 2000; Baillet, 2017). MEG and Wada studies can assess language lateralization with 80% to 95% accuracy (Burgess *et al*., 2011; Papanicolaou *et al*., 2014). Some have suggested high corncordance between Wada and MEG/fMRI in mapping language and memory (Kemp *et al*., 2018). In addition, MEG has been used with success to map motor and visual function in individuals undergoing evaluation for epilepsy surgery (Kober *et al*., 2001; Ray and Bowyer, 2010; Collinge *et al*., 2017). In patients with recurrent seizures following HDS, MEG may be complementary to vEEG and MRI/DTI studies in determining if recurrent seizures originate from the disconnected or contralateral hemisphere (Kiehna *et al*., 2016).

Single-photon emission computed tomography (SPECT)

While some patients with MRE may have occasional seizures that are difficult to capture, patients who are candidates for HDS often have daily seizures and might be more easily studied with ictal SPECT. Patients with severe unilateral hemispheric epilepsy would be expected to have interictal hypometabolism (as with PET), and increased blood flow to diffuse areas of the affected hemisphere on ictal SPECT. SPECT may also aid with lateralization when MRI, EEG, or semiology findings are unequivocal, and has been studied for various disease states when HDS is being considered. Interictal SPECT has aided lateralization in patients with Sturge-Weber syndrome (SWS), revealing

reduced rates of cerebral blood flow (CBF) in cortical and subcortical areas involving the diseased hemisphere (Chiron *et al*., 1989). A separate series of seven patients undergoing interictal SPECT as part of their work-up for HDS revealed that all six patients who had unilateral hypoperfusion had favorable seizure outcomes following HDS regardless of bilateral findings on ictal scalp EEG and MRI (Carmant *et al*., 1994). Uematsu *et al*. looked at ictal SPECT in nine patients with hemimegalencephaly and found relative hyperperfusion in the affected hemisphere, which was lessened but not totally eliminated post-HDS (Uematsu *et al*., 2010). In Rasmussen's encephalitis, a study of ictal SPECT in eight patients revealed increased areas of focal perfusion in the involved hemisphere in four patients; no patient had increased ictal perfusion within the contralateral hemisphere (Yacubian *et al*., 1997).

Two separate case reports showed continued hypermetabolism in an incompletely disconnected area of frontobasal cortex in patients with continued seizures postoperatively and demonstrated how SPECT can also play a role in considering repeat HDS after failed hemispherotomy. In the first case, targeted stereotactic resection of this residual cortex led to seizure freedom after repeat surgery. In the second case, a patient with right-sided SWS who underwent FH had recurrent seizures. Subtraction ictal SPECT co-registered with MRI (SISCOM) studies revealed right orbito-frontal hyperperfusion. The patient then underwent right orbito-frontal resection and further disconnection of the anterior corpus callosum and was seizure-free after 14 months of follow-up.

Wada testing and functional magnetic resonance imaging (fMRI)

The use of intra-arterial amobarbital testing (IAT) is particularly intriguing in the selection of patients for HDS as this test temporarily inhibits the function of the entire MCA and ACA vascular territories of the injected hemisphere and may be a reliable indicator of post-hemispherotomy speech and motor function. A cohort of six patients undergoing HDS were studied with presurgical IAT; three patients displayed reduced dexterity of fine motor movements during IAT and this correlated in each case with reduced dexterity post-operatively (Fujimoto *et al*., 2017). In a study by Hamer *et al*., all left-hemisphere HDS candidates underwent Wada testing of the abnormal hemisphere (Hamer *et al*., 2000). Bilateral IAT, while critical in temporal lobe epilepsy, is generally avoided in patients with unilateral hemispheric destruction as inactivation of the functional hemisphere often leads to a prolonged period of total unresponsiveness, and inadvertent damage to the intact hemisphere could have catastrophic consequences (Moddel *et al*., 2009). No test is perfect, however, and Loddenkemper *et al*. describe a case of an adult patient who suffered an MVA at the age of five leaving him with left hemispheric encephalomalacia and right hemiparesis. Wada testing was done preoperatively and the patient continued to speak normally following left intracarotid amobarbital injection; nevertheless, HDS was complicated by a new, profound postoperative aphasia (Schulze-Bonhage *et al*., 2004).

Functional magnetic resonance imaging (fMRI) represents a less invasive and less costly technique than IAT which provides a reasonable alternative with comparable accuracy (Sabsevitz *et al*., 2003; Szaflarski *et al*., 2017). In a study that surveyed 82 epilepsy programs worldwide for current clinical practice regarding language fMRI, 100% of these programs reported using fMRI for language lateralization (Benjamin *et al*., 2018). fMRI and Wada display similar accuracy for language lateralization, except in patients with atypical language centers (Janecek *et al*., 2013). Additionally, fMRI allows lateralization and localization of motor, visual, and other eloquent functions (Zhang *et al*., 2015).

Diffusion tensor imaging (DTI)

Evaluation of axonal pathways in the corticospinal tracts (CST) using diffusion tensor imaging (DTI) can be a marker of the integrity of motor function in the affected hemisphere (Nelles *et al*., 2015). The presence of functioning CST in the affected hemisphere may lead to motor deficits following surgery on the hemisphere. DTI therefore can be used for preoperative evaluation in determining patient outcomes with regards to motor function (Mori *et al*., 2002; Nelles *et al*., 2015; Ho *et al*., 2017). The second application of DTI is for patients who have already undergone HDS but continue to suffer from seizures; these patients may benefit from DTI before considering repeat FH, AH, or focal ablation of residual crossing white matter tracts. In a case series of eight patients with recurrent seizures (Kiehna *et al*., 2016), DTI detected residual white matter connecting fibers between the hemispheres and repeat surgery with removal of these connections resulted in seizure freedom in five of these patients; the three remaining patients had Engel Class II outcomes at 24 months of follow-up. In another series of three patients who had recurrent seizures following hemispherotomy, MRI with DTI was obtained for subsequent work-up which revealed remaining connections in the corpus callosum of all three patients. All three patients received a second hemispherotomy to complete the disconnection which was confirmed on follow-up with a second MRI with DTI. Notably, two patients had persistent seizures post-operatively, and in one of those patients, a frontal lobectomy was

needed. Despite complete hemispheric disconnection as confirmed by DTI, not all patients are completely free of seizures postoperatively and this may indicate independent epileptogenicity in the contralateral hemisphere (Bartoli *et al.*, 2018). DTI performed intraoperatively has also been described as a method to identify any remaining connections and allow for the surgeon to complete the disconnection without need for reoperation (Ho *et al.*, 2017; Kim *et al.*, 2017).

Intracranial EEG (icEEG)

Intracranial EEG may play a role in determining the extent of involvement in a diseased hemisphere (*e.g.* to help determine whether HDS versus a more selective, peri-insular disconnection is warranted), lateralizing the side of seizure onset in a patient with multi-focal findings and/or non-lateralizing EEG (*e.g.* tuberous sclerosis), and extra-operative mapping of potentially eloquent cortex in or adjacent to epileptogenic tissue. While noninvasive studies are typically sufficient to identify a candidate and proceed with HDS, icEEG continues to be a powerful tool in the armamentarium to make epilepsy surgery both as safe as possible and as selective as necessary (Thadani *et al.*, 1995).

Timing of surgery

Multiple studies show that the younger the patient and the shorter the duration of their epilepsy, the higher their chances of cure and seizure freedom following HDS (Basheer *et al.*, 2007; Scavarda *et al.*, 2009; Scavarda *et al.*, 2010). In fact, hemispheric disconnection can be considered as early as the first month of life in some cases (Bulteau *et al.*, 2013). In a retrospective study of 61 patients, those who had hemispherectomies before seven years of age had a higher rate of seizure freedom (90%) compared to patients aged 7-16 (73% seizure-free), and patients over the age of 16 (60% seizure-free) (Althausen *et al.*, 2013). However, adult patients may still achieve favorable results if they are well selected for surgery (Cukiert *et al.*, 2009; Althausen *et al.*, 2013). The timing of HDS in patients with Rasmussen's encephalitis is highly individualized and depends on a number of factors including patient age, side of surgery, the frequency and severity of seizures, the rapidity of neurological regression, the effect of immunomodulatory therapy, and baseline neurological functioning (de Bode and Curtiss, 2000; Schur *et al.*, 2018).

HDS in infants

The historic reluctance to perform HDS on infants has largely disappeared due to modern improvements in anesthetic technique (Dorfer *et al.*, 2015), coupled with the rise of FH affording shorter operative times, less blood loss, and fewer major complications as compared to AH (Piastra *et al.*, 2004). Multiple case series report excellent rates of seizure freedom and minimal morbidity and mortality rates in infants undergoing HDS (Gonzalez-Martinez *et al.*, 2005; Honda *et al.*, 2013). Rapid replacement of blood and platelets during surgery, strict control of body temperature, and meticulous surgical and anesthetic technique has remained essential in achieving good outcomes.

Based on a retrospective analysis of 15 infants who received epilepsy surgery between the ages of 1.5 to six months, four infants underwent anatomical and seven underwent functional hemispherotomy. Every patient in this study required a blood transfusion. The rates of seizure freedom were less in this study than in those that looked at slightly older infants (Duchowny *et al.*, 1998). Four patients underwent repeat HDS for recurrent seizures. Based on another series of 18 infants ranging between 3 and 22 months of age, the outcomes of anatomic hemispherectomy, functional hemispherectomy, and modified anatomic hemispherectomy were studied. Thirteen of these patients were seizure-free, four had over 90% reduction in seizure frequency, and one had over 50% reduction in seizure occurrence (Engel Class III). The most significant factor associated with seizure recurrence was found to be incomplete disconnection on follow-up MRI ($p<0.05$) (Gonzalez-Martinez *et al.*, 2005). Overall, carefully selected infants with catastrophic epilepsy may achieve favorable outcomes in terms of seizure freedom which outweighs the risk of blood loss (Peacock *et al.*, 1996; Duchowny *et al.*, 1998; Gonzalez-Martinez *et al.*, 2005). With regards to patients with early infantile epileptic encephalopathies (Ohtahara syndrome), the literature reveals much more favorable outcomes for patients who were treated with epilepsy surgery versus those who received pharmacotherapy (Malik *et al.*, 2013).

HDS in adults

Though HDS has traditionally been a procedure for the pediatric age group, reports in the literature have shown adult patients can be candidates for HDS (McGovern *et al.*, 2019). Carefully-selected adult patients have had excellent outcomes with seizure freedom rates of 75% to 92% following HDS (Cukiert *et al.*, 2009; de Francisco *et al.*, 2009; McClelland and Maxwell, 2007; Liang *et al.*, 2013). With regards to motor outcomes, there have been mixed results reported in the literature. A systematic review of the literature of 90 adult patients who underwent hemispherectomy found that 35% of the patients had improvement in hemiparesis, whereas 21% had worsening of their hemiparesis, but could still ambulate; motor function was stable for about a half of patients after surgery (Althausen *et al.*, 2013; Schusse *et al.*, 2018). Loss of

pincer grasp may occur after HDS in adults, and this should be discussed preoperatively as it may impact quality of life (Stark and McGregor, 1997; Soufflet *et al*., 2004).

Palliative HDS

In special cases where patients have severe and debilitating seizures starting on both sides of the brain but with a clear predominance for one hemisphere, palliative HDS may improve quality of life (QOL), lessen the burden of seizures, and slow neuropsychological decline (Ciliberto *et al*., 2012; Ilyas *et al*., 2014). Families and patients in this situation must be counseled about expectations of surgery. While seizure freedom should always be the goal, significant improvement in seizure burden has been shown to positively impact QOL and development, especially in children (Lupashko *et al*., 2011; Ciliberto *et al*., 2012; Ilyas *et al*., 2014).

Algorithm outlining considerations for HDS

Based on our synthesis of the literature and the collective experience of the authors, we propose an algorithm for the clinical evaluation and treatment indications for HDS (*figure 1*). While this flowchart largely reflects the opinions of the authors and lacks external validation, we hope it can serve as a starting point to guide practitioners who may have limited experience with HDS.

Discussion

To address the profound underutilization of epilepsy surgery, many authors have tried to construct presurgical algorithms that can be implemented to select appropriate candidates for various surgeries (Englot, 2018). Indeed, regarding patient selection for hemispheric surgery, there seems to be no clearly defined standard for which studies should be routinely utilized in preoperative planning. While multi-disciplinary epilepsy teams essentially all rely on neurologic examination, brain MRI, and vEEG, there is significant variability and no universal guidelines for when to obtain PET, SPECT, MR spectroscopy, MEG, fMRI, Wada testing, or DTI. Furthermore, the selection of an infant for hemispherotomy may involve different considerations than in an adult, just as left-sided (dominant) hemispherotomy may pose certain risks to language or memory, that would not be expected with right-sided hemispherotomy. Selection of patients for repeat HDS often involves DTI or thinly cut MRI sequences to facilitate identification of areas of incomplete disconnection (Kiehna *et al*., 2016; Bartoli *et al*., 2018). Finally, while it may be relatively straightforward to identify the need for HDS in a patient with a classic indication (*e.g*. Rasmussen's encephalitis, perinatal ischemic stroke, hemimegalencephaly), the decision to perform hemispherotomy for patients with conditions such as electrical status epilepticus during sleep (ESES), intraventricular hemorrhage (IVH) of prematurity, post-traumatic brain injury (TBI), infection, and subtle or bilateral MRI abnormalities may be significantly more nuanced.

Presurgical studies to select patients for hemispherotomy should be geared toward answering three different but related questions:

– is HDS indicated, or could a less extensive resection/disconnection lead to seizure freedom?

– what is the laterality of the hemisphere involved in generating seizures?

– where on the ipsilateral hemisphere is there residual eloquent cortex, if any?

If the patient has significant hemiparesis on examination with loss of pincer grasp, contralateral destruction of the hemisphere on MRI, an interictal EEG that reveals diffuse spiking, slowing, and attenuation of signals, an ictal EEG that shows ipsilateral onset, and concordant semiology, then the side of the affected hemisphere may not be in question. If, however, MRI findings are subtle or bilateral, semiology is suggestive of multiple, independent seizure foci, and EEG findings are non-lateralizing, then further studies may be indicated before proceeding with HDS. The significance of either bilateral MRI abnormalities or non-lateralized EEG findings, when seen in isolation, is still unclear, but neither should be used as grounds to deny a patient HDS when other factors favor proceeding.

Little has been written about semiology in terms of either patient selection or its influence on the outcome of HDS (Marks and Laxer, 1998; Elwan *et al*., 2018). It is generally assumed that a focal semiology (*e.g*. clonic arm movements contralateral to the affected hemisphere) is another data point that supports pursuing HDS while generalized seizures may portend lower rates of seizure freedom post-hemispherotomy (Carmant *et al*., 1995; Liu *et al*., 2018).

If the lateralization of seizure onset is still in question after obtaining brain MRI and EEG, then PET, ictal SPECT (SISCOM), and/or MEG/MSI may play a role in lateralizing seizure onset. Bilateral PET hypometabolism has been associated with a relatively higher rate of seizure recurrence after HDS, while unilateral hemispheric hypometabolism on PET bolsters the argument to proceed with hemispherotomy and generally is associated with excellent rates of postoperative seizure freedom (la Fougere *et al*., 2009; Ochoa-Figueroa *et al*., 2012; Traub-Weidinger *et al*., 2016). Ictal SPECT is often performed in centers which have these capabilities, either for questionable cases or candidates for repeat hemispherotomy to identify residual areas

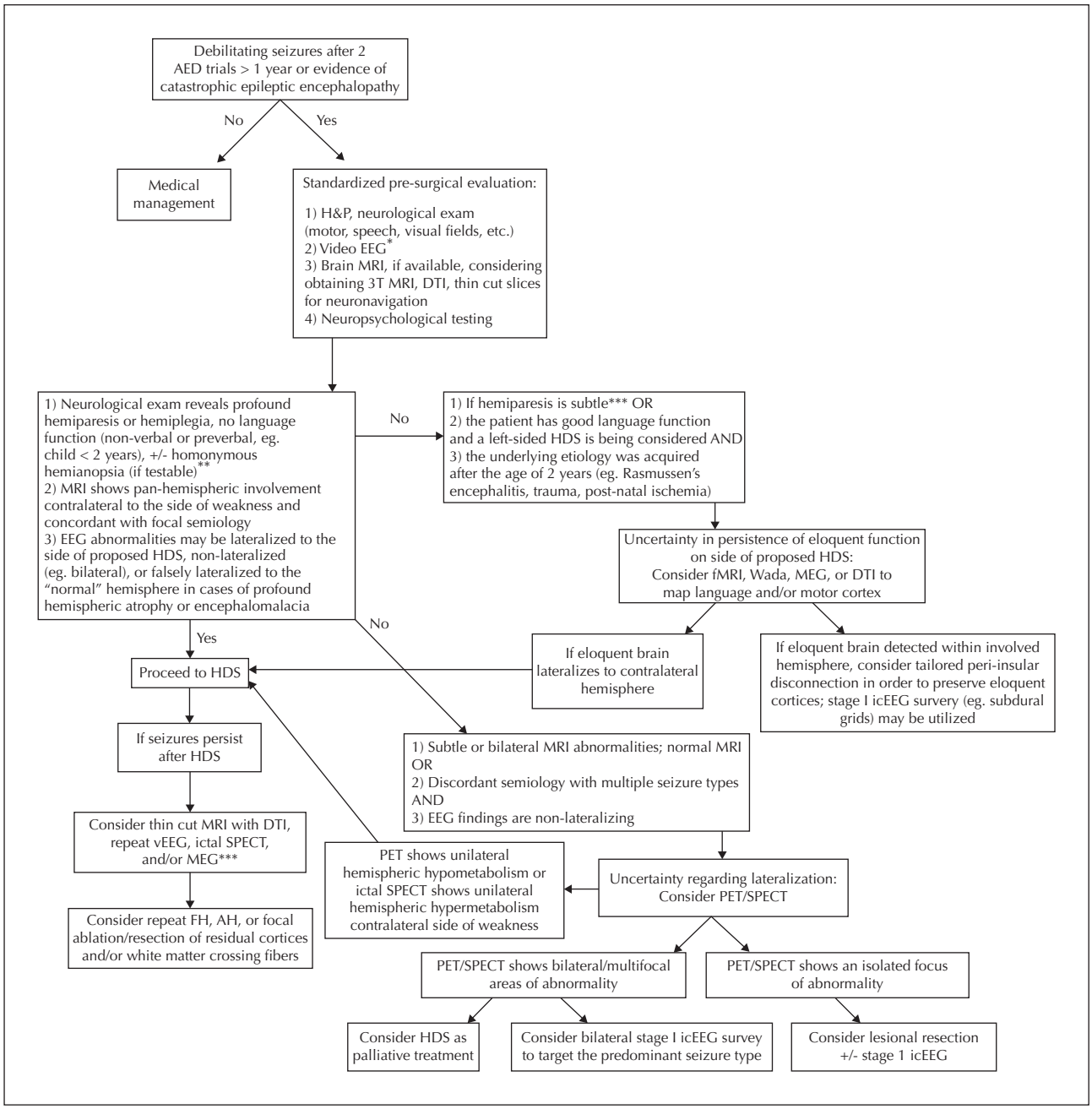

Figure 1. Algorithmic approach for evaluating candidates for hemispheric disconnection surgery (HDS) in patients with medically-refractory epilepsy. *A short interictal EEG may be sufficient especially if there is hemispheric destruction on MRI with appropriate hemi-deficits and semiology suggestive of onset in the affected hemisphere. **Most epilepsy centers do not regard a possible visual field defect as an absolute contraindication to proceeding with HDS in an otherwise appropriate candidate. ***Subtle or non-detectable hemiparesis may occur in infants < six months, but should not be regarded as a contraindication to proceeding with HDS in a situation of catastrophic epileptic encephalopathy. ****Repeat vEEG may be especially helpful in cases with bilateral MRI abnormalities and/or multiple seizure types with semiology implicating the contralateral "normal" hemisphere.

of cortex which continue to cause seizures (Honda *et al*., 2013; Taussig *et al*., 2015). Finally, a few studies have suggested that clustering of spikes based on MEG/MSI studies within the affected hemisphere is associated with higher rates of seizure freedom than in patients who have bilateral MEG clusters, however, the number of patients studied was small and it is difficult to draw firm conclusions (Schwartz *et al*., 2010; Torres *et al*., 2011; Jung *et al*., 2013). MEG has the additional benefit of allowing mapping of motor and language cortex.

It must be said that most of these studies require sedation in children or non-cooperative patients with cognitive dysfunction, and may be difficult to perform. MEG is costly and not widely available even within the United States, and the logistic considerations around ictal SPECT are non-trivial. Electric source imaging (ESI) with high-density EEG should also be mentioned as a tool in the armamentarium of the epileptologist when lateralizing and localizing epileptogenic cortex. Few patients require sedation, application with various electrode nets is relatively easy, and the cost is low, but data analysis is complex and non-intuitive, and requires a certain level of experience and mathematical expertise (Sharma *et al*., 2018). After every non-invasive study, if doubt still lingers as to the lateralization of seizure onset, a bilateral sEEG or subdural strip survey may be considered.

Finally, fMRI, Wada testing, and DTI may play a role in determining the side and localization of eloquent cortex. Especially in left-sided hemispheric surgery, several centers may routinely perform fMRI, Wada, or both to try to localize speech function (Chandra *et al*., 2008; Benjamin *et al*., 2018; Rolinski *et al*., 2019). It has been thought that the timing of insult early in life (*e.g*. perinatal stroke) plays a role in the contralateral relocation of language cortex. Wada testing (*i.e*. IAT) is particularly attractive as this involves the chemical inactivation of the hemisphere in question and allows the examiner to see what additional deficits might be expected after hemispheric disconnection (Hamer *et al*., 2000). However, recent evidence suggests that fMRI and MEG may be comparable to Wada in regard to motor and speech mapping (Papanicolaou *et al*., 2014). Both fMRI and Wada require a certain degree of patient cooperation, which may not be forthcoming in small children or those with cognitive impairments. DTI has been used preoperatively to assess the integrity of corticospinal tracts, and postoperatively to evaluate the completeness of disconnection (Kiehna *et al*., 2016). All these studies are especially helpful in cases where the patient's hemiparesis is subtle or language function is reasonably good; intuitively, these patients have more to lose and therefore should be studied more carefully.

Limitations

While we aim in this review to provide comprehensive recommendations on how to use a neurological examination, semiology, imaging, and functional studies to select patients for HDS, we recognize that any flowchart will involve a gross simplification of what is an inherently complex and nuanced process. The decision of whether or not to proceed with HDS involves a careful balancing of benefits (*e.g*. improvement of seizures, quality of life, and neuropsychological function) against risks (*e.g*. anticipated neurological deficits, surgical complications), from the perspective of both caregivers as well as individual patients and families. The recommendations within this manuscript, while based on an extensive review of the literature, largely represent the opinions and biases of the authors, and lack external, prospective validation.

Conclusion

HDS represents an effective and potentially curative surgical treatment for patients with hemispheric MRE. A better understanding of the presurgical evaluation of HDS candidates, including careful clinical assessment and the use of non-invasive preoperative imaging studies, is critical in this era of underutilization of epilepsy surgery. While the decision to proceed with HDS can often be made on the basis of neurological examination, semiology, brain MRI, and vEEG alone, additional studies may help lateralize seizure onset (*i.e*. PET, SPECT, MEG) and/or identify potential areas of functionality that need to be preserved (fMRI, MEG, IAT, DTI). □

Disclosures.
None of the authors have any conflict of interest to declare.

References

Aitouche Y, Gibbs SA, Gilbert G, Boucher O, Bouthillier A, Nguyen DK. Proton MR spectroscopy in patients with non-lesional insular cortex epilepsy confirmed by invasive EEG recordings. *J Neuroimaging* 2017; 27(5): 517-23.

Althausen A, Gleissner U, Hoppe C, *et al*. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. *J Neurol Neurosurg Psychiatry* 2013; 84: 529-36.

Austermuehle A, Cocjin J, Reynolds R, *et al*. Language functional MRI and direct cortical stimulation in epilepsy preoperative planning. *Ann Neurol* 2017; 81: 526-37.

Baillet S. Magnetoencephalography for brain electrophysiology and imaging. *Nat Neurosci* 2017; 20: 327-39.

Bartoli A, El Hassani Y, Jenny B, *et al*. What to do in failed hemispherotomy? Our clinical series and review of the literature. *Neurosurg Rev* 2018; 41: 125-32.

Basheer SN, Connolly MB, Lautzenhiser A, Sherman EM, Hendson G, Steinbok P. Hemispheric surgery in children with refractory epilepsy: seizure outcome complications and adaptive function. *Epilepsia* 2007; 48: 133-40.

Benjamin CFA, Li AX, Blumenfeld H, *et al*. Presurgical language fMRI: clinical practices and patient outcomes in epilepsy surgical planning. *Human Brain Map* 2018; 39: 2777-85.

Birg L, Narayana S, Rezaie R, Papanicolaou A. Technical tips: MEG and EEG with sedation. *Neurodiagnostic J* 2013; 53: 229-40.

Boshuisen K, van Schooneveld MM, Leijten FS, *et al*. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. *Neurology* 2010; 75: 1623-30.

Bulteau C, Otsuki T, Delalande O. Epilepsy surgery for hemispheric syndromes in infants: hemimegalencepahly and hemispheric cortical dysplasia. *Brain Dev* 2013; 35: 742-7.

Burgess RC, Funke ME, Bowyer SM, Lewine JD, Kirsch HE, Bagic AI. American Clinical Magnetoencephalography Society Clinical Practice Guideline 2: presurgical functional brain mapping using magnetic evoked fields. *J Clin Neurophysiol* 2011; 28: 355361.

Carmant L, Kramer U, Riviello JJ, *et al*. EEG prior to hemispherectomy: correlation with outcome and pathology. *Electroenceph Clin Neurophysiol* 1995; 94: 265-70.

Carmant L, O'Tuama LA, Roach PJ, *et al*. Technetium-99m HmPAO brain SPECT and outcome of hemispherectomy for intractable seizures. *Pediatr Neurol* 1994; 11: 203-7.

Chandra PS, Padma VM, Shailesh G, Chandreshekar B, Sarkar C, Tripathi M. Hemispherotomy for intractable epilepsy. *Neurol India* 2008; 56: 127-32.

Chiron C, Raynaud C, Tzourio N, *et al*. Regional cerebral blood flow by SPECT imaging in Sturge-Weber disease: an aid for diagnosis. *J Neurol Neurosurg Psychiatry* 1989; 52: 1402-9.

Chugani HT, Shewmon DA, Shields WD, *et al*. Surgery for intractable infantile spasms: neuroimaging perspectives. *Epilepsia* 1993; 34: 764-71.

Ciliberto MA, Limbrick D, Powers A, Titus JB, Munro R, Smyth MD. Palliative hemispherotomy in children with bilateral seizure onset. *J Neurosurg Pediatr* 2012; 9: 381-8.

Collinge S, Prendergast G, Mayers ST, *et al*. Pre-surgical mapping of eloquent cortex for paediatric epilepsy surgery candidates: evidence from a review of advanced functional neuroimaging. *Seizure* 2017; 52: 136-46.

Cukiert A, Cukiert CM, Argentoni M, *et al*. Outcome after hemispherectomy in hemiplegic adult patients with refractory epilepsy associated with early middle cerebral artery infarcts. *Epilepsia* 2009; 50: 1381-4.

de Bode S, Curtiss S. Language after hemispherectomy. *Brain Cognit* 2000; 43: 135-8.

de Francisco J, Fernandez S, Carreno M, *et al*. Successful functional hemispherectomy in adult patients with refractory epilepsy. *Neurologia (Barcelona Spain)* 2009; 24: 9-14.

Dennis M. Capacity and strategy for syntactic comprehension after left or right hemidecortication. *Brain Language* 1980; 10: 287-317.

Dennis M, Kohn B. Comprehension of syntax in infantile hemiplegics after cerebral hemidecortication: left-hemisphere superiority. *Brain Language* 1975; 2: 472-82.

Devlin AM, Cross JH, Harkness W, *et al*. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain* 2003; 126: 556-66.

Dijkerman HC, Vargha-Khadem F, Polkey CE, Weiskrantz L. Ipsilesional and contralesional sensorimotor function after hemispherectomy: differences between distal and proximal function. *Neuropsychologia* 2008; 46: 886-901.

Dorfer C, Ochi A, Snead OC, *et al*. Functional hemispherectomy for catastrophic epilepsy in very young infants: technical considerations and complication avoidance. *Childs Nerv Syst* 2015; 31: 2103-9.

Doring S, Cross H, Boyd S, Harkness W, Neville B. The significance of bilateral EEG abnormalities before and after hemispherectomy in children with unilateral major hemisphere lesions. *Epilepsy Res* 1999; 34: 65-73.

Duchowny M, Jayakar P, Resnick T, *et al*. Epilepsy surgery in the first three years of life. *Epilepsia* 1998; 39: 737-43.

Elwan S, Alexopoulos A, Silveira DC, Kotagal P. Lateralizing and localizing value of seizure semiology: Comparison with scalp EEG MRI and PET in patients successfully treated with resective epilepsy surgery. *Seizure* 2018; 61: 203-8.

Englot DJ. A modern epilepsy surgery treatment algorithm: Incorporating traditional and emerging technologies. *Epilepsy Behav* 2018; 80: 68-74.

Erdler M, Beisteiner R, Mayer D, *et al*. Supplementary motor area activation preceding voluntary movement is detectable with a whole-scalp magnetoencephalography system. *Neuroimage* 2000; 11: 697-707.

Fujimoto A, Okanishi T, Nishimura M, Kanai S, Sato K, Enoki H. The Wada test might predict postoperative fine finger motor deficit after hemispherotomy. *J Clin Neurosci* 2017; 45: 319-23.

Garzon E, Gupta A, Bingaman W, Sakamoto AC, Luders H. Paradoxical ictal EEG lateralization in children with unilateral encephaloclastic lesions. *Epileptic Disord* 2009; 11: 215-21.

Gonzalez-Martinez JA, Gupta A, Kotagal P, *et al*. Hemispherectomy for catastrophic epilepsy in infants. *Epilepsia* 2005; 46: 1518-25.

Greiner HM, Park YD, Holland K, *et al*. Scalp EEG does not predict hemispherectomy outcome. *Seizure* 2011; 20: 758-63.

Griessenauer CJ, Salam S, Hendrix P, *et al*. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. *J Neurosurg Pediatr* 2015; 15: 34-44.

Groppel G, Dorfer C, Muhlebner-Fahrngruber A, *et al*. Improvement of language development after successful hemispherotomy. *Seizure* 2015; 30: 70-5.

Halac G, Delil S, Zafer D, *et al*. Compatibility of MRI and FDG-PET findings with histopathological results in patients with focal cortical dysplasia. *Seizure* 2017; 45: 80-6.

Hallbook T, Ruggieri P, Adina C, *et al*. Contralateral MRI abnormalities in candidates for hemispherectomy for refractory epilepsy. *Epilepsia* 2010; 51: 556-63.

Hamad AP, Caboclo LO, Centeno R, *et al*. Hemispheric surgery for refractory epilepsy in children and adolescents: outcome regarding seizures motor skills and adaptive function. *Seizure* 2013; 22: 752-6.

Hamer HM, Wyllie E, Stanford L, Mascha E, Kotagal P, Wolgamuth B. Risk factors for unsuccessful testing during the intracarotid amobarbital procedure in preadolescent children. *Epilepsia* 2000; 41: 554-63.

Helmstaedter C, Witt JA. Clinical neuropsychology in epilepsy: theoretical and practical issues. *Handbook Clin Neurol* 2012; 107: 437-59.

Ho AL, Pendharkar AV, Sussman ES, Casazza M, Grant GA. Diffusion tensor imaging in an infant undergoing functional hemispherectomy: a surgical aid. *Cureus* 2017; 9: e1697.

Holec M, Nagahama Y, Kovach C, Joshi C. Rethinking the magnetic resonance imaging findings in early Rasmussen encephalitis: a case report and review of the literature. *Pediatr Neurol* 2016; 59: 85-9.

Honda R, Kaido T, Sugai K, *et al*. Long-term developmental outcome after early hemispherotomy for hemimegalencephaly in infants with epileptic encephalopathy. *Epilepsy Behav* 2013; 29: 30-5.

Hu WH, Zhang C, Zhang K, Shao XQ, Zhang JG. Hemispheric surgery for refractory epilepsy: a systematic review and meta-analysis with emphasis on seizure predictors and outcomes. *J Neurosurg* 2016; 124: 952-61.

Ilyas M, Sivaswamy L, Asano E, Sood S, Zidan M, Chugani H. Seizure control following palliative resective surgery for intractable epilepsy-a pilot study. *Pediatr Neurol* 2014; 51: 30-5.

Janecek JK, Swanson SJ, Sabsevitz DS, *et al*. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. *Epilepsia* 2013; 54: 314-22.

Jung J, Bouet R, Delpuech C, *et al*. The value of magnetoencephalography for seizure-onset zone localization in magnetic resonance imaging-negative partial epilepsy. *Brain* 2013; 136: 3176-86.

Kemp S, Prendergast G, Karapanagiotidis T, *et al*. Concordance between the Wada test and neuroimaging lateralization: influence of imaging modality (fMRI and MEG) and patient experience. *Epilepsy Behav* 2018; 78: 155-60.

Kiehna EN, Widjaja E, Holowka S, *et al*. Utility of diffusion tensor imaging studies linked to neuronavigation and other modalities in repeat hemispherotomy for intractable epilepsy. *J Neurosurg Pediatr* 2016; 17: 483-90.

Kim GH, Seo JH, Schroff S, Chen PC, Lee KH, Baumgartner J. Impact of intraoperative 3-T MRI with diffusion tensor imaging on hemispherectomy. *J Neurosurg Pediatr* 2017; 19: 63-9.

Kim JS, Park EK, Shim KW, Kim DS. Hemispherotomy and functional hemispherectomy: indications and outcomes. *J Epilepsy Res* 2018; 8: 1-5.

Kober H, Nimsky C, Moller M, Hastreiter P, Fahlbusch R, Ganslandt O. Correlation of sensorimotor activation with functional magnetic resonance imaging and magnetoencephalography in presurgical functional imaging: a spatial analysis. *Neuroimage* 2001; 14: 1214-28.

Krynauw RA. Infantile hemiplegia treated by removing one cerebral hemisphere. *J Neurol Neurosurg Psychiatry* 1950; 13: 243-67.

la Fougere C, Rominger A, Forster S, Geisler J, Bartenstein P. PET and SPECT in epilepsy: a critical review. *Epilepsy Behav* 2009; 15: 50-5.

Lee YJ, Kim EH, Yum MS, Lee JK, Hong S, Ko TS. Long-term outcomes of hemispheric disconnection in pediatric patients with intractable epilepsy. *J Clin Neurol (Seoul Korea)* 2014; 10: 101-7.

Liang S, Zhang G, Li Y, *et al*. Hemispherectomy in adults patients with severe unilateral epilepsy and hemiplegia. *Epilepsy Res* 2013; 106: 257-63.

Limbrick DD, Narayan P, Powers AK, *et al*. Hemispherotomy: efficacy and analysis of seizure recurrence. *J Neurosurg Pediatr* 2009; 4: 323-32.

Liu M, Ji T, Liu Q, *et al*. Generalized seizures presurgically in a cohort of children with hemispherectomy: Predictors and a potential link to surgical outcome? *Seizure* 2018; 58: 101-9.

Lupashko S, Malik S, Donahue D, Hernandez A, Perry MS. Palliative functional hemispherectomy for treatment of refractory status epilepticus associated with Alpers' disease. *Childs Nerv Syst* 2011; 27: 1321-3.

Maehara T, Shimizu H, Kawai K, *et al*. Postoperative development of children after hemispherotomy. *Brain & Dev* 2002; 24: 155-60.

Malik SI, Galliani CA, Hernandez AW, Donahue DJ. Epilepsy surgery for early infantile epileptic encephalopathy (ohtahara syndrome). *J Child Neurol* 2013; 28: 1607-17.

Marks Jr. WJ, Laxer KD. Semiology of temporal lobe seizures: value in lateralizing the seizure focus. *Epilepsia* 1998; 39: 721-6.

McClelland S. 3rd, Maxwell RE. Hemispherectomy for intractable epilepsy in adults: the first reported series. *Ann Neurol* 2007; 61: 372-6.

McGovern RA, Ahsan NVM, Jehi L, *et al*. Hemispherectomy in adults and adolescents: Seizure and functional outcomes in 47 patients. *Epilepsia* 2019; 60: 2416-27.

Menard A, Le Normand MT, Rigoard MT, Cohen H. Language development in a child with left hemispherectomy. *Brain Cogn* 2000; 43: 332-40.

Moddel G, Lineweaver T, Schuele SU, Reinholz J, Loddenkemper T. Atypical language lateralization in epilepsy patients. *Epilepsia* 2009; 50: 1505-16.

Moosa AN, Gupta A, Jehi L, *et al*. Longitudinal seizure outcome and prognostic predictors after hemispherectomy in 170 children. *Neurology* 2013a; 80: 253-60.

Moosa AN, Jehi L, Marashly A, *et al*. Long-term functional outcomes and their predictors after hemispherectomy in 115 children. *Epilepsia* 2013b; 54: 1771-9.

Mori S, Kaufmann WE, Davatzikos C, *et al*. Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. *Magnet Reson Med* 2002; 47: 215-23.

Nagahama Y, Joshi C, Dlouhy B, *et al*. Functional hemispherotomy in Rasmussen syndrome in the absence of classic MRI findings. *Epilepsy & Behav Case Rep* 2017; 7: 24-7.

Nelles M, Urbach H, Sassen R, *et al*. Functional hemispherectomy: postoperative motor state and correlation to preoperative DTI. *Neuroradiology* 2015; 57: 1093-102.

Ochoa-Figueroa MA, Cardenas-Negro C, Allende-Riera A, Martinez-Gimeno E, Desequera-Rahola M, Una-Gorospe J. Role of 18F-FDG PET in the diagnosis of Rasmussen's disease. *Revista Espanola de Medicina Nuclear e Imagen Molecular* 2012; 31: 286-7.

Papanicolaou AC, Rezaie R, Narayana S, *et al*. Is it time to replace the Wada test and put awake craniotomy to sleep? *Epilepsia* 2014; 55: 629-32.

Peacock WJ, Wehby-Grant MC, Shields WD, *et al*. Hemispherectomy for intractable seizures in children: a report of 58 cases. *Childs Nerv Syst* 1996; 12: 376-84.

Piastra M, Pietrini D, Caresta E, *et al*. Hemispherectomy procedures in children: haematological issues. *Childs Nerv Syst* 2004; 20: 453-8.

Ramantani G, Kadish NE, Brandt A, *et al*. Seizure control and developmental trajectories after hemispherotomy for refractory epilepsy in childhood and adolescence. *Epilepsia* 2013; 54: 1046-55.

Rangel-Castilla L, Hwang SW, Al-Shamy G, Jea A, Curry DJ. The periinsular functional hemispherotomy. *Neurosurgical Focus* 2012; 32: E7.

Rasmussen T. Hemispherectomy for seizures revisited. *Can J Neurol Sci* 1983; 10: 71-8.

Ray A, Bowyer SM. Clinical applications of magnetoencephalography in epilepsy. *Ann Indian Acad Neurol* 2010; 13: 14-22.

Rolinski R, Austermuehle A, Wiggs E, *et al*. Functional MRI and direct cortical stimulation: Prediction of postoperative language decline. *Epilepsia* 2019; 60: 560-70.

Sabsevitz DS, Swanson SJ, Hammeke TA, *et al*. Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology* 2003; 60: 1788-92.

Scavarda D, Imada V, Rolland AC, Lortie A, Mercier C, Carmant L. Peri-insular hemispherotomy in children: a single institution experience. *Minerva Pediatrica* 2010; 62: 1-7.

Scavarda D, Major P, Lortie A, Mercier C, Carmant L. Periinsular hemispherotomy in children with stroke-induced refractory epilepsy. *J Neurosurg Pediatr* 2009; 3: 115-20.

Schulze-Bonhage A, Quiske A, Loddenkemper T, Dinner DS, Wyllie E. Validity of language lateralisation by unilateral intracarotid Wada test. *J Neurol Neurosurg Psychiatry* 2004; 75: 1367.

Schur S, Allen V, White A, *et al*. Significance of FDG-PET hypermetabolism in children with intractable focal epilepsy. *Pediatr Neurosurg* 2018; 53: 153-62.

Schusse CM, Smith K, Drees C. Outcomes after hemispherectomy in adult patients with intractable epilepsy: institutional experience and systematic review of the literature. *J Neurosurg* 2018; 128: 853-61.

Schwartz ES, Edgar JC, Gaetz WC, Roberts TP. Magnetoencephalography. *Pediatric Radiol* 2010; 40: 50-8.

Sharma P, Scherg M, Pinborg LH, *et al*. Ictal and interictal electric source imaging in pre-surgical evaluation: a prospective study. *Eur J Neurol* 2018; 25: 1154-60.

Shukla G, Bhatia M, Gaekwad SB, Singh VP, Jain S, Maheshwari MC. The lateralizing significance of version of head and dystonic limb posturing in epileptic seizures. *Neurol India* 2002; 50: 33-6.

Smith A. Speech and other functions after left (dominant) hemispherectomy. *J Neurol Neurosurg Psychiatry* 1966; 29: 467-71.

Smith SJ, Andermann F, Villemure JG, Rasmussen TB, Quesney LF. Functional hemispherectomy: EEG findings spiking from isolated brain postoperatively and prediction of outcome. *Neurology* 1991; 41: 1790-4.

Soufflet C, Bulteau C, Delalande O, *et al*. The nonmalformed hemisphere is secondarily impaired in young children with hemimegalencephaly: a pre- and postsurgery study with SPECT and EEG. *Epilepsia* 2004; 45: 1375-82.

Stark RE, McGregor KK. Follow-up study of a right- and a left-hemispherectomized child: implications for localization and impairment of language in children. *Brain Language* 1997; 60: 222-42.

Suarez-Pinera M, Mestre-Fusco A, Ley M, *et al*. Perfusion SPECT SISCOM and PET (18)F-FDG in the assessment of drug-refractory epilepsy patients candidates for epilepsy surgery. *Revista Espanola de Medicina Nuclear e Imagen Molecular* 2015; 34: 350-7.

Szaflarski JP, Gloss D, Binder JR, *et al*. Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy: Report of the Guideline Development Dissemination and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017; 88: 395-402.

Taussig D, Dorfmuller G, Save J, *et al*. Hemispherotomy for isolated infantile spasms following perinatal ischemic stroke. *Eur J Paediatr Neurol* 2015; 19: 597-602.

Thadani VM, Williamson PD, Berger R, *et al*. Successful epilepsy surgery without intracranial EEG recording: criteria for patient selection. *Epilepsia* 1995; 36: 7-15.

Torres CV, Fallah A, Ibrahim GM, *et al*. The role of magnetoencephalography in children undergoing hemispherectomy. *J Neurosurg Pediatr* 2011; 8: 575-83.

Traub-Weidinger T, Weidinger P, Groppel G, *et al*. Presurgical evaluation of pediatric epilepsy patients prior to hemispherotomy: the prognostic value of (18)F-FDG PET. *J Neurosurg Pediatr* 2016; 25: 683-8.

Uematsu M, Haginoya K, Togashi N, *et al*. Unique discrepancy between cerebral blood flow and glucose metabolism in hemimegalencephaly. *Epilepsy Res* 2010; 92: 201-8.

Varadkar S, Bien CG, Kruse CA, *et al*. Rasmussen's encephalitis: clinical features pathobiology and treatment advances. *Lancet Neurol* 2014; 13: 195-205.

Vargha-Khadem F, Carr LJ, Isaacs E, Brett E, Adams C, Mishkin M. Onset of speech after left hemispherectomy in a nine-year-old boy. *Brain* 1997; 120(1): 159-82.

Vargha-Khadem F, Polkey CE. A review of cognitive outcome after hemidecortication in humans. *Adv Exp Med Biol* 1992; 325: 137-51.

Villarejo-Ortega F, Garcia-Fernandez M, Fournier-Del Castillo C, *et al*. Seizure and developmental outcomes after hemispherectomy in children and adolescents with intractable epilepsy. *Childs Nerv Syst* 2013; 29: 475-88.

Wilson SJ, Baxendale S, Barr W, *et al*. Indications and expectations for neuropsychological assessment in routine epilepsy care: Report of the ILAE Neuropsychology Task Force Diagnostic Methods Commission 2013-2017. *Epilepsia* 2015; 56: 674-81.

Wyllie E, Lachhwani DK, Gupta A, *et al*. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. *Neurology* 2007; 69: 389-97.

Yacubian EM, Marie SK, Valerio RM, Jorge CL, Yamaga L, Buchpiguel C. Neuroimaging findings in Rasmussen's syndrome. *J Neuroimaging* 1997; 7: 16-22.

Zhang CH, Lu Y, Brinkmann B, Welker K, Worrell G, He B. Lateralization and localization of epilepsy related hemodynamic foci using presurgical fMRI. *Clin Neurophysiol* 2015; 126: 27-38.