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High-resolution electric source imaging for presurgical evaluation of tuberous sclerosis complex patients

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HIGHLIGHTS

- Patient-history-based and video-based semiology poorly localize the epileptogenic zone in tuberous sclerosis patients.
- High resolution electric source imaging is more often concordant with the epileptogenic zone compared to ictal EEG.
- High resolution electric source imaging positively impacts clinical management in 50% of patients.

ABSTRACT

Objective: We retrospectively assessed the localizing value of patient-history-based semiology (PHS), video-based semiology (VS), long-term monitoring video electroencephalography (LTM-VEEG) and interictal high resolution electric source imaging (HR-ESI) in the presurgical workup of patients with tuberous sclerosis complex (TSC).
Methods: Data from 24 consecutive TSC surgical candidates who underwent both HR-ESI and LTM-VEEG was retrospectively collected. PHS and VS were analyzed to hypothesize the symptomatogenic zone localization. LTM-VEEG and HR-ESI localization results were extracted from the diagnostic reports. Localizing value was compared between modalities, taken the resected/disconnected area of surgical patients in consideration. HR-ESI's impact on the epileptogenic zone hypothesis and surgical workup was evaluated.
Results: Semiology, interictal EEG, ictal EEG and HR-ESI were localizing in 25%, 54%, 63% and 79% of patients. Inter-modality concordance ranged between 33–89%. In good surgical outcome patients, PHS, VS, interictal EEG, ictal EEG and HR-ESI showed concordance with resected area in 1/9 (11%), 0/9 (0%), 4/9 (44%), 3/9 (33%) and 6/9 patients (67%). HR-ESI positively impacts clinical management in 50% of patients.
Conclusions: In presurgical evaluation of TSC patients, semiology often has limited localizing value. Presurgical work-up benefits from HR-ESI.
Significance: Our findings may advice future presurgical epilepsy workup of TSC patients with the ultimate aim to improve outcome.

Abbreviations: AMT-PET, α[^{11}C]-methyl-l-tryptophan-positron emission tomography; DTI, diffusion tensor imaging; ECoG, electrocorticography; EEG, electroencephalography; EZ, epileptogenic zone; GRID, intracranial GRID EEG; HR-ESI, high resolution electric source imaging; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MSI, magnetic source imaging; MUSIC, multiple signal classification; PHS, patient-history-based semiology; SEEG, stereo depth EEG; sLORETA, standardized low-resolution brain electromagnetic tomography; SPECT, single photon emission computed tomography; TSC, tuberous sclerosis complex; VS, video-based semiology.

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1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder with multiple hamartomas that manifest most commonly in the skin, retina, heart, kidney and brain. In the central nervous system TSC gives rise to cortical tubers that may cause neurological symptoms, including epilepsy and neurodevelopmental disorders such as autism and intellectual disability. Early seizure onset and poor seizure control are related to the level of neurodevelopmental deficit (Vingerhoets 2006; Teutonico et al. 2008). With anti-seizure medication adequate seizure control may be achieved but studies show high variability in the number of patients in whom seizure freedom is achieved (17–100%) (van der Poest Clement et al. 2020). For medically intractable epilepsy patients surgery is considered and postoperative seizure freedom can be achieved in 55–65% of cases (Jansen et al. 2007; Fallah et al. 2013; Specchio et al. 2021).

The cornerstone of feasibility of epilepsy surgery is accurate localization of the epileptogenic zone (EZ), which is defined as the area of cortex that is necessary and sufficient for initiating seizures and which needs to be removed (or disconnected) for complete elimination of seizures (Luders, Burgess, and Noachtar 1993). Unfortunately, in TSC patients multiple potentially epileptogenic lesions (i.e. tubers) are scattered throughout the brain. Not all tubers contribute to epilepsy and removal of a single or of a few tubers may render a patient seizure-free. The challenge is therefore to identify the epileptogenic tuber(s) involved in seizure generation. Even with functional neuroimaging techniques such as $\alpha[^{11}C]$-methyl-l-Tryptophan-Positron Emission Tomography (AMT-PET) it remains challenging to distinguish epileptogenic from non-epileptogenic tubers, apart from the fact that the tracer is not available in most facilities (Rubi et al. 2013).

As a result, the presurgical workup of TSC patients is different from that in most patients with other etiologies; it aims to identify the single epileptogenic lesion among many, rather than attempting to visualize a lesion and determine its concordance with semiology and electroencephalography (EEG) findings. For most etiologies, long-term video-EEG monitoring (LTM-VEEG) is the center-piece neurophysiological evaluation in EZ identification (Kobulashvili et al. 2018). In TSC patients, focality in interictal or ictal EEG has been found predictive of good surgical outcome (Zhang et al. 2013; Fallah et al. 2013). Still, using ictal EEG to localize the seizure onset zone, related to an epileptogenic tuber, may be problematic. Tubers may show abnormal, diffusive connectivity with other tubers and perituberal cortices and propagated ictal rhythms are often indistinguishable from seizure onset (Yu et al. 2019; Kannan et al. 2016). Thus, renewed interest has surged for interictal electric source imaging (ESI), particularly because in surgical TSC candidates dominant interictal foci often remain unaltered over long periods of time (Jansen et al. 2005).

With high resolution interictal electric source imaging (HR-ESI) locations of underlying source currents are estimated using 64 or more scalp EEG electrodes (HR-EEG) and subsequently combined with structural high-resolution magnetic resonance imaging (MRI). Prospective studies have shown that HR-ESI accurately estimates the EZ in the presurgical epilepsy workup of lesional and non-lesional epilepsy surgery candidates (Megevand et al. 2014; Brodbeck et al. 2011; Feng et al. 2016; Mouthaan et al. 2019).

A comparison of LTM-VEEG and HR-ESI findings in the presurgical work-up of TSC patients has not yet been performed. In this retrospective cohort study we selected patients who underwent both LTM-VEEG and HR-ESI and assessed the localizing value of each modality in the presurgical workup. We analyzed the lobar co-localization of semiology taken from patient or relatives (patient history-based semiology, PHS) with video-based semiology (VS) from LTM-VEEG. We compared the localizing value of ictal and interictal EEG data from LTM-VEEG with HR-ESI. Furthermore, we assessed the localizing value of the modalities by using the ultimate gold standard, which is the resected area in seizure-free patients. Finally, we evaluated the impact of HR-ESI on the EZ hypothesis, its clinical consequences and how this translated to positive surgical outcome.

2. Methods

2.1. Patients

We retrospectively collected clinical data from consecutive patients with a definite diagnosis of TSC who underwent both HR-ESI and LTM-VEEG as part of epilepsy surgery evaluation between 2011–2019. The Dutch epilepsy surgery program consists of a national collaboration between the University Medical Center Utrecht (UMCU) and two other Dutch epilepsy institutes (ACE Kempenhaeghe/MUMC, Heeze; SEIN, Heemstede). The UMCU is a nationally and internationally (EpiCARE) endorsed expertise center for patients with rare and complex epilepsies. We have approximately 200 children and 500 adults with TSC in active clinical care, some of whom will undergo an epilepsy surgery diagnostic workup, based on clinical criteria. We collected demographic information, including sex, age, as well as epilepsy related characteristics, such as age at seizure onset, seizure frequency, seizure semiology, and epilepsy treatment. Initial pre-operative evaluation included semiology, 3T MRI and LTM-VEEG. If in subsequent multidisciplinary team meetings focus localization was uncertain, a second stage evaluation was performed including HR-ESI and in some patients interictal and ictal Single Photon Emission Computed Tomography (SPECT), or magnetoencephalography (MEG). When indicated, subsequent functional evaluation was done with Wada testing, functional MRI, or diffusion tensor imaging (DTI). Patients that were considered eligible for surgery underwent disconnection or resection including intra-operative tailoring with Electrocorticography (ECoG).

At the time of data collection, patients had been either operated, rejected for surgery, presurgical workup was ongoing, or patients had been withdrawn from workup. No informed consent was required under Dutch law for this retrospective observational study on available and pseudonymized data from routine clinical care.

2.2. Semiology

PHS and VS from LTM-VEEG were extracted from medical records separately. Two independent clinical neurophysiologists from two centers with each at least 15 years of experience within the field (FL, AC), were instructed to hypothesize the symptomatogenic zone location from either modality (Luders 1999). Seizure descriptions were presented in a randomized fashion blinded for the source of the description (i.e. PHS or VS). Discrepancies between reviewers were resolved in an organized meeting to achieve consensus and obtain final results.

2.3. LTM-VEEG

Continuous video and simultaneous 21–32 channel EEG was recorded. Electrodes were positioned according to the 10–10 system or to the 10–20 system with additional coverage of lateral frontal and/or temporal regions. Patients were recorded for at least 21 hours up to 2 weeks, sometimes preceded by tapering of medication. If multiple LTM-VEEG recordings were performed in a patient, the recording with recorded ictal epileptic activity that

was closest to the date of the HR-ESI was selected. Interictal focus, or foci, and the presumed ictal onset zone were extracted from the LTM-VEEG report that was written by the clinical neurophysiologist at the time of evaluation. In case of multifocal interictal activity, localization of the predominant focus –defined as the focus that showed a prominent high spike frequency among other foci – was also extracted from the report.

2.4. HR-ESI

High resolution EEG was recorded using a 85-channel EEG electrocap (BioSemi Mark-6, Brainstar system 4.0) from 2011-2013 and an 84-channel TinCap custom (Easycap) from 2013 onwards both using a LTM 128 amplifier with SystemPlus Evolution software (Micromed). Electrode positions relative to the skull were registered by using a magnetic tracking device (Polhemus, Colchester, VT, U.S.A.). Spontaneous activity was recorded during a 40–60 minute session, sometimes after sleep deprivation. Interictal epileptic spikes were visually marked and subsequently inspected for their spatiotemporal consistency by an automatic clustering program according to Van 't Ent et al. (Van 't Ent et al. 2003). Spikes from each cluster were averaged and standard deviations were calculated. Clusters showing a standard deviation smaller than one-third of the spike maximum, were considered consistent (Agirre-Arrizubieta et al. 2009). Only consistent clusters were selected for forward modeling using individual patient 3D T1 MRI with CURRY 7.0 software (Compumedics, Victoria, Australia). Inverse solution was applied using two algorithms: multiple signal classification (MUSIC) and standardized low-resolution brain electromagnetic tomography (sLORETA). Clusters showing consistency between the two inverse solutions were considered representative of a focal source and formed the net-result of the source localization. Clusters showing inconsistency between MUSIC and sLORETA were rejected because of the invalidity of a focal assumption. The source location was extracted from the reports written by the physicist involved in the source imaging procedure at the time presurgical workup.

2.5. Data analysis

Anatomical location results of modalities – PHS, VS, interictal EEG (LTM-VEEG), ictal EEG (LTM-VEEG), HR-ESI – and the resected area were defined by lateralization and lobar localization. Lateralization was defined as: left, right or midline. Lobar regions were defined as: frontal (including fronto-central), central, temporal, parietal (including parieto-central) and occipital. A result was considered multifocal in case of bilateral localizations or multiple unilateral localizations in different lobes. A result was considered non-localizing if the modality showed an unclear focus or suggested a deep non-localizing focus.

2.5.1. Localization concordance

Localization of modalities was evaluated for their lobar concordance with each other (inter-modality) and with the resected or disconnected area in patients who underwent surgery. Concordance was expressed in terms of:

1- Concordant: sources co-localized in the ipsilateral lobe
2- Discordant: sources localized contra-laterally or in different ipsilateral lobes
3- Indeterminate: either one of the modalities was non-localizing or multifocal
4- Partially concordant: (a) one source localized in midline and the other to the left/right in the same lobar region (e.g. midline parietal with right parietal); (b) one source localized in the border region between lobes and the other source in one of the lobes (e.g. parieto-occipital with parietal); or (c) in case of multiple resected areas, the source localized in only one of the resected areas (e.g. a right parietal focus with right parietal and central resection)

A fronto-central or parieto-central localization was considered to be concordant with frontal and parietal localizations respectively. A central localization that was unknown to be on the parietal or frontal side was considered concordant with a fronto-central or parieto-central location and partially concordant with a frontal or parietal localization. Data was analyzed descriptively and presented as proportions of concordance levels and surgical outcome within patient groups.

2.5.2. Impact of HR-ESI on epilepsy surgery workup

The impact of HR-ESI on the diagnostic epilepsy surgery workup was assessed by reviewing multidisciplinary meeting records. We collected the hypothesized EZ formulated during the initial pre-operative evaluation (prior to evaluation of HR-ESI results) and the newly defined EZ hypothesis that was formulated (after review of HR-ESI results) during the subsequent second multidisciplinary meeting. If hypotheses were not in the minutes of the meeting records, the study authors attempted to formulate hypotheses by means of deduction using the available diagnostic information. Patients were excluded from this analysis if HR-ESI was performed prior to the first multidisciplinary meeting or if new information from other diagnostics was discussed in the second meeting. In these cases we deemed the newly formed hypothesis biased and not a representative for HR-ESI's impact on clinical management.

Details of the HR-ESI results, with respect to tuber correspondence or intra-lobar/sublobar location, were extracted from medical records to evaluate the basis of a hypothesis change. We then classified the level of EZ hypothesis modification as follows:

1. EZ discarded: the old hypothesis was considered unreliable and the new information not sufficient to constitute a novel hypothesis
2. EZ enlarged: the new hypothesis encompassed a wider region surrounding the old hypothesis
3. EZ unaffected: the hypothesis was unaltered due to non-contributing HR-ESI results
4. EZ confirmed: the old hypothesis was confirmed by contributing HR-ESI results
5. EZ narrowed: the new hypothesis encompassed a more targeted region of the old hypothesis
6. EZ changed: the hypothesis was changed to a different lobar region
7. EZ generated: the old hypothesis was non-localizing, HR-ESI resulted in a new localizing hypothesis

Subsequently, we noted the decisions – for additional (non)invasive testing or neurosurgical procedures – made in the second multidisciplinary meeting. In patients who underwent surgery the impact of HR-ESI on the clinical management was based on the EZ modification, whether the HR-ESI source was part of the resected area and the surgical outcome. Clinical contribution of HR-ESI was categorized as critically valuable, critically misguiding, opposing, positively supportive, negatively supportive, disruptive, indeterminate (Fig. 1).

3. Results

3.1. Patient characteristics

Twenty-four patients (16 male) were included in this study. Median age at seizure onset was 0.5 years (range 0.08–12 years).

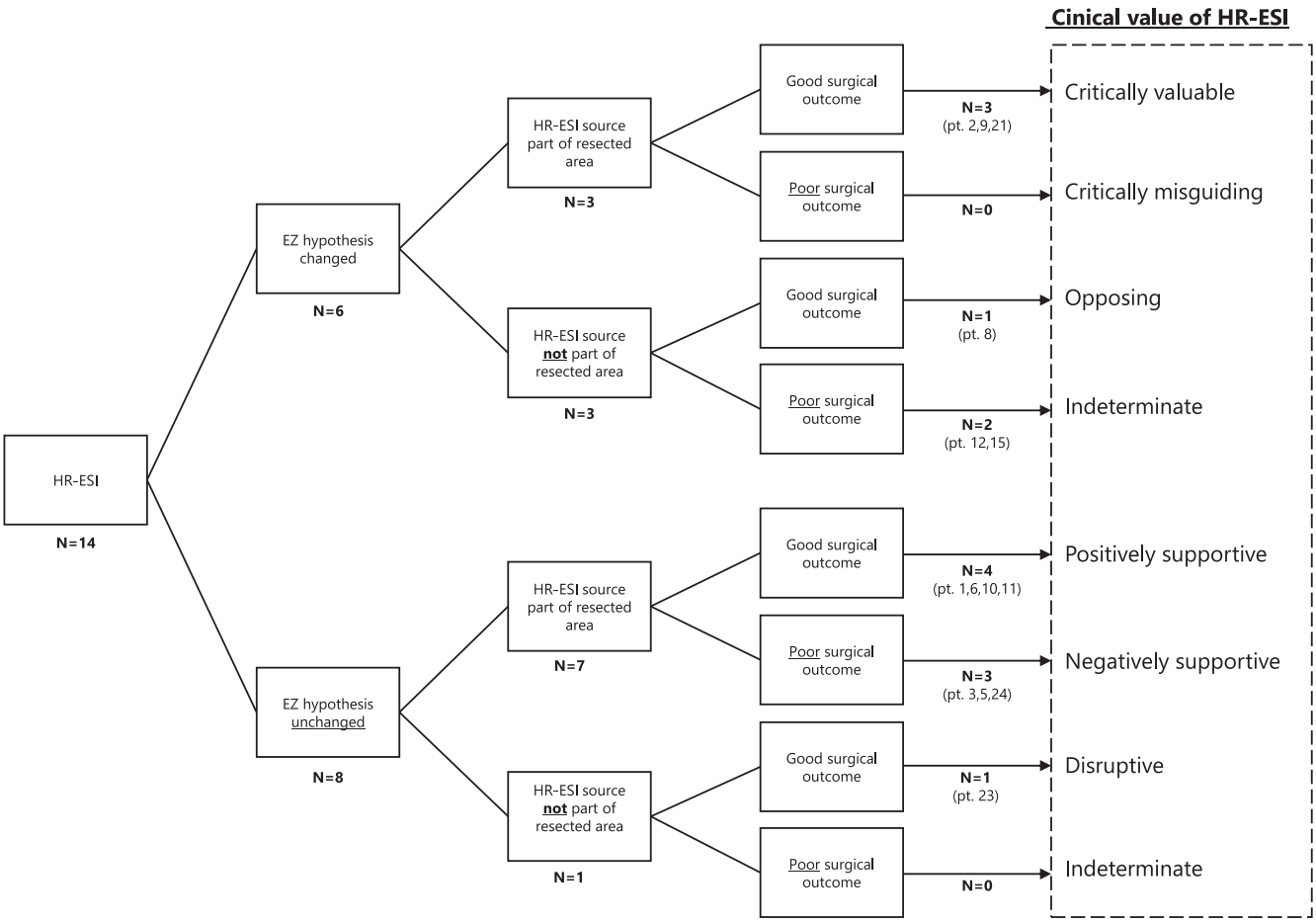

Fig. 1. Framework and results for clinical value evaluation of HR-ESI. Pt.: patient; HR-ESI: high-resolution electric source imaging; EZ: epileptogenic zone; Good surgical outcome: Engel 1; Poor surgical outcome: Engel 2–4.

Median age at the start of presurgical evaluation was 5 years (range 1–35 years). Seizure types at the start of presurgical workup were focal epileptic spasms in seven, other focal motor in seven and focal non-motor seizures in eleven patients. Three patients had two or more types of seizures (Supplementary Table S1). Sixteen patients had daily seizures, four patients had daily to weekly seizures, three patients had weekly seizures and one patient monthly seizures.

3.2. Presurgical workup

Median time between recording of LTM-VEEG and HR-ESI was 4 months (range 1–24 months). Non-invasive ancillary or repeated tests were performed in seven patients: SPECT in three, MEG in two and repeated LTM-VEEG in two. Four patients (4/24, 17%) were rejected for surgery: in three, workup did not result in a clear and consistent EZ hypothesis; in one, stereo depth EEG (SEEG) was considered but contra-indicated as the child was too young. Additionally, 4/24 patients (17%) were withdrawn from further surgical workup of whom three were withdrawn due to seizure reduction and in one patient parents decided to cancel further investigations. One patient is still awaiting planned ECoG-guided surgery. Thus, at the time of data collection, a total of fifteen patients had undergone surgery. In 14/15 patients (93%) surgery was guided by ECoG. Additional presurgical intracranial EEG monitoring with SEEG was performed in two and with grid electrodes in four children. Median follow up was 12 months (range 4–73 months). Good outcome (Engel 1, assessed at the end of follow up) was achieved in 9/15 patients (60%).

3.3. Semiology

PHS was presumed localizing to a single (unilateral) lobar region in 6/24 (25%) patients. In none of the subgroup of seven patients with epileptic spasms, localization was achieved. In 6/24 patients (25%) it was only possible to either lateralize to a hemisphere, or to localize to a lobar region but with uncertain lateralization. Clinical seizures were captured on video during LTM-VEEG in all patients. VS was presumed to localize to a single (unilateral) lobar region in 6/24 patients (25%). For the subgroup of patients with epileptic spasms localization was achieved in 1/7 (14%) patients versus 5/17 patients (29%) with other seizure types. In 5/24 (21%) VS was only able to localize to the temporal or frontal lobe with uncertain lateralization.

In patients with both localizing ictal EEG and localizing PHS, PHS was concordant in one out of three patients. This patient also showed concordance with interictal EEG, HR-ESI and resected area (patient 9). There were no patients showing concordance between VS and other modalities. In six patients both PHS and VS were non-localizing and in only one patient PHS and VS were both localizing to the same unilateral lobar region. In this particular patient however ictal EEG and HR-ESI localized to the contra-lateral parietal lobe and surgery in this area resulted in good outcome after 7 months (patient 6; see Supplementary Table S2).

3.4. LTM-EEG

Ictal EEG was available in all patients. Clinical seizures showed simultaneous – not necessarily concordant – seizure activity in all

patients. Number of seizures ranged from 2 to 16 (median 7). Mean LTM-VEEG duration was 67 hours (range 21–100 hours). In four patients no information on anti-seizure medication reduction was registered. In 12 of 20 patients (57%) dosage was decreased before and during recording.

Interictal EEG localized to a single lobe in 13/24 patients (54%). In 10/24 patients (42%) multifocal interictal EEG abnormalities were recorded. In six of these patients multifocal EEG suggested a predominant unilateral focal area. In the remaining patient interictal EEG was non-localizing. With respect to patients with epileptic spasms interictal EEG localized in 2/7 patients (29%) which was lower than in patients with other seizure types (12/17, 71%).

Ictal EEG was localizing in 15/24 patients (63%) and non-localizing in 7/24 patients (29%). In the remaining two patients multifocal sources were seen (patient 18, 7) (Supplementary Table S2). For the subgroup of patients with epileptic spasms ictal EEG localized in 4/7 patients (57%) compared to 11/17 patients (65%) with other seizure types.

In patients with both localizing ictal EEG and localizing interictal EEG, inter-modality concordance was found in 8/9 patients (89%) and partial concordance in the remaining patient. In patients with multifocal interictal EEG showing a predominant unilateral focus and a localizing ictal EEG, concordance was found in one half and partial concordance in the other half of patients (patient 1, 10, 17, 19).

3.5. HR-ESI

HR-ESI recording duration was scheduled for 60–120 min (dependent on patient cooperation). Interictal epileptic activity was observed in all but one patient. This patient had indistinct spikes that could not be differentiated from artefacts. HR-ESI localized to an unilateral single lobe in 19/24 (79%) of patients. HR-ESI was bilaterally multifocal in 4/24 patients (17%) (Supplementary Table S2). In patients with epileptic spasms HR-ESI was localizing in 4/7 (57%) compared to 15/17 (88%) patients with other seizure types. Fig. 2 shows an example of a HR-ESI result in a patient with a left frontal focus.

In patients with both localizing interictal EEG and HR-ESI, intermodality concordance was seen in 7/10 (70%) and partial concordance in 2/10 patients (20%). Intermodality concordance between ictal EEG and interictal HR-ESI was seen in 7/13 patients (54%), partial concordance in 4/13 (31%).

From the six patients with multifocal interictal EEG showing a predominant unilateral focus one was concordant with HR-ESI (17%), three were partial concordant (50%), one was discordant, and in the remaining patient HR-ESI was multifocal.

3.6. Localization concordance with resected area and surgical outcome

Concordance with the resected area was seen in one patient for PHS and in none for VS (Table 1a&b). Both interictal and ictal EEG were concordant with resected area in 5/15 patients (33%) compared to 9/15 patients (60%) for HR-ESI. Partial concordance was seen in 2/15 (13%), 5/15 (33%) and 2/15 patients (13%) for interictal EEG, ictal EEG and HR-ESI. Nine patients (60%) had good surgical outcome with median follow up of 9 months (range 4–73). Median follow up in poor surgical outcome patients was 19 months (range 7–39).

In the patients with good surgical outcome, PHS, interictal EEG, ictal EEG and HR-ESI were concordant with the resected area in 1/9 (11%), 4/9 (44%), 3/9 (33%) and in 6/9 patients (67%). Partial concordance was seen in 1/9 (11%), 4/9 (44%) and 1/9 patients (11%).

In poor outcome patients, concordance with resected area was seen in 1/6 (17%), 2/6 (33%) and 3/6 patients (50%) for interictal, ictal EEG and HR-ESI respectively. Partial concordance was seen in 1/6 patients (17%) for each modality.

When excluding non-localizing and multifocal test results, concordance with the resected area in patients with good surgical outcome was seen in 4/5 (80%) for interictal EEG and 3/7 patients (42%) for ictal EEG. Partial concordance was seen in 1/5 (20%) and 4/7 (58%) of patients. HR-ESI maintained the same concordance rate due to absence of non-localizing or multifocal results in this subgroup.

In patients showing concordance with resected area, good outcome was achieved in 4/5 (80%), 3/5 (60%), 6/9 (67%) for interictal, ictal EEG and HR-ESI respectively. Partial concordance had good outcome in 1/2 patients (50%) for interictal EEG and HR-ESI and in 4/5 (80%) for ictal EEG. Discordance had good outcome in no patients for interictal EEG and ictal EEG and in all patients for HR-ESI. In the case of an indeterminate concordance level, good outcome was seen in 4/6 (67%) and 2/2 patients (50%) for interictal EEG and ictal EEG, and in none for HR-ESI.

3.7. Impact of HR-ESI on epilepsy surgery workup

Three patients were excluded from this analysis (Supplementary Table S3). In one patient the MRI result – a nearby transmantle sign – was included in post-HR-ESI hypothesis as decided in the second multidisciplinary meeting (patient 24). In patient 12, HR-ESI was indicated prior to review of LTM-VEEG results and both results were simultaneously reviewed during the multidisciplinary meeting. In patient 20 LTM-VEEG was performed after evaluation of HR-ESI results.

In the remaining 21 patients HR-ESI modified the hypothesized EZ in eleven (52%), in four of whom HR-ESI discarded the presumed EZ. HR-ESI did not change the hypothesis in 10/21 patients (48%): in eight HR-ESI confirmed the hypothesis and in two HR-ESI was not contributory and the EZ remained unaffected. After HR-ESI evaluation in the second multidisciplinary meeting 9/21 patients (43%) proceeded directly to surgery, 10/21 (48%) underwent additional testing and 2/21 (10%) were directly rejected for surgery. In most patients in whom HR-ESI confirmed the EZ (6/8, 75%), it was decided to directly proceed to surgery. In the other two patients additional testing was performed (Table 2).

Of the 21 patients included in the analysis, fourteen underwent surgery. In 7/14 patients (50%) HR-ESI contributed positively to the presurgical decision making process. In three, this contribution was critically valuable suggesting that without HR-ESI they would not have been operated and become seizure free. In 5/14 (36%) patients HR-ESI contributed negatively to the presurgical workup but this was never considered critically misguiding (Fig. 1).

4. Discussion

In this retrospective cohort study including 24 TSC patients, we evaluated the localizing value of HR-ESI in the presurgical workup and compared this with semiology and LTM-VEEG results. HR-ESI was more often localizing compared to semiology, interictal EEG and ictal EEG (79% versus 25%, 54% and 63%). When localizing, interictal and ictal EEG have a high inter-modality concordance (89%), while HR-ESI was concordant with interictal and ictal EEG in 70% and 55% of patients respectively. Inter-test concordance for semiology was poor and was seen in only one patient. Localization was achieved less often in patients with epileptic spasms, especially using semiology and interictal EEG and to a lesser degree using ictal EEG and HR-ESI.

Concordance with resected area was best for HR-ESI. In seizure-free patients, HR-ESI is more often concordant (67%) with resected than ictal EEG (33%) while ictal EEG is more often partially concordant than HR-ESI (44% versus 11%). However, non-localizing and multifocal test results were seen often with interictal and ictal

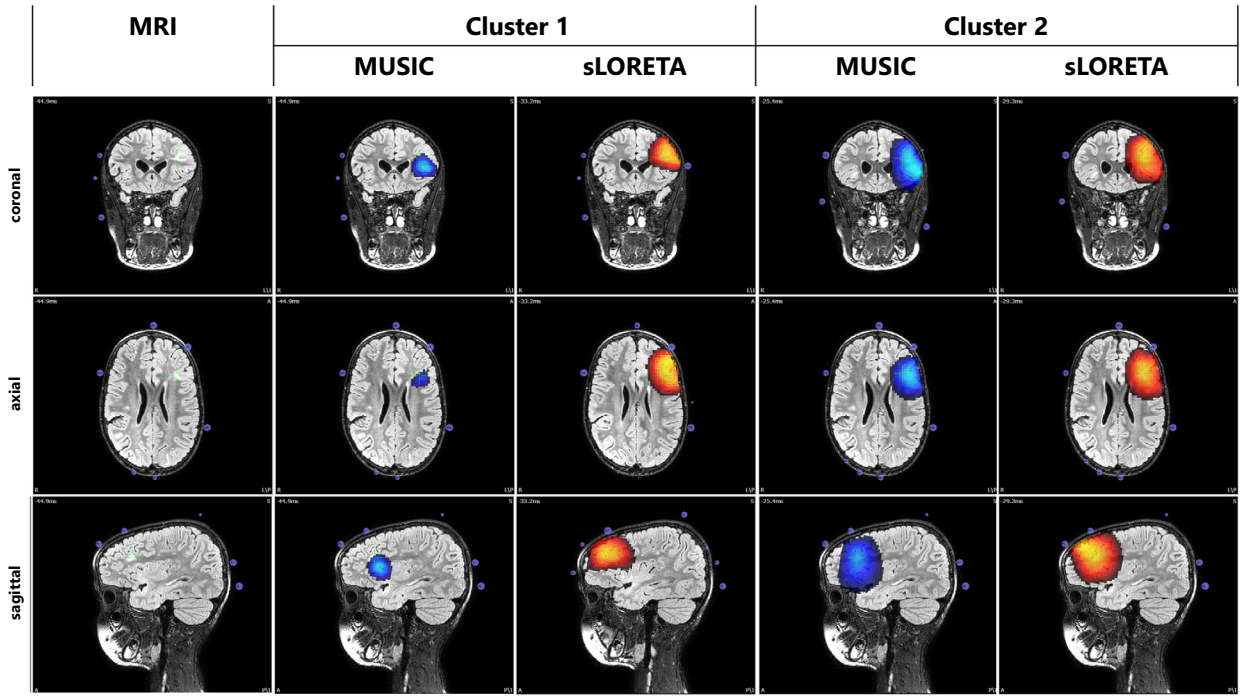

Fig. 2. HR-ESI results from patient 3 indicating a left frontal focus. HR-ESI: high resolution electric source imaging; MUSIC: multiple signal classification; sLORETA: standardized low-resolution brain electromagnetic tomography. Fluid attenuated inversion recovery (FLAIR) MRI shows multiple bilateral subcortical tubers. A large tuber is located in the left fronto-lateral region (marked with crosshair). HR-ESI resulted in two spike clusters. MUSIC and sLORETA results for each cluster are depicted by blue and red blobs and were all located in or near the tuber region with varying spatial accuracy. Interictal EEG was multifocal by showing bilateral frontal and temporal activity with a predominant left fronto-temporal focus. Ictal EEG suggested a widespread left fronto-centro-parietal focus. Resection of two tubers in the left frontal area resulted in seizure freedom (Engel 1a) at 13 months follow up.

Table 1

A. Modality concordance with resected area per surgical patient.

Patient	PHS	VS	Interictal EEG (LTM-VEEG)	ictal EEG (LTM-VEEG)	HR-ESI	Surgical outcome
1	indet	indet	indet	pc	c	Good
2	indet	indet	c	c	c	Good
3	d	indet	indet	pc	c	Good
4	d	indet	pc	indet	d	Good
5	d	indet	c	indet	c	Good
6	d	d	indet	pc	pc	Good
7	indet	indet	indet	pc	d	Good
8	indet	d	c	c	c	Good
9	c	indet	c	c	c	Good
10	indet	d	indet	c	c	Poor
11	indet	indet	pc	pc	pc	Poor
12	indet	indet	indet	indet	c	Poor
13	indet	indet	d	d	indet	Poor
14	indet	d	c	c	c	Poor
15	indet	indet	d	indet	indet	Poor

B. Modality concordance with resected area of all surgical patients.

Modality		PHS		VS		Interictal EEG (LTM-VEEG)		Ictal EEG (LTM-VEEG)		HR-ESI	
Surgical outcome		Good	Poor	Good	Poor	Good	Poor	Good	Poor	Good	Poor
Level of concordance	Concordant	1	0	0	0	4	1	3	2	6	3
	Partially Concordant	0	0	0	0	1	1	4	1	1	1
	Discordant	4	0	2	2	0	2	0	1	2	0
	Indeterminate	4	6	7	4	4	2	2	2	0	2

PHS: patient-history based semiology; VS: video-based semiology: LTM-VEEG: long term monitoring video electroencephalopgraphy; HR-ESI: high-resolution electric source imaging. Surgical outcome: Good (Engel 1), Poor (Engel 2–4). c: concordant; pc: partially concordant; d: discordant; indet: indeterminate.

EEG and excluding these from the calculation affected the concordance rate by increasing this to 80% for interictal EEG, and 42% for ictal EEG while not altering the concordance rate for HR-ESI.

When HR-ESI results were discussed in the second multidisciplinary meeting, it had a strong impact on epilepsy surgery workup by modifying or confirming the hypothesized EZ in 52% and 38% of

Table 2
Number of patients with HR-ESI related EZ modification and resulting clinical consequences.

EZ modification	Clinical consequence					*Total (%)*
	Rejected	Additional non-invasive testing	Additional non-invasive testing and invasive testing	Additional invasive testing	Proceed to surgery	
EZ discarded	2	1	-	1	-	4 (21%)
EZ enlarged	-	-	2	-	-	2 (10%)
EZ unaffected	-	1	-	-	1	2 (10%)
EZ confirmed	-	1	-	1	6	8 (38%)
EZ narrowed	-	-	-	2	1	3 (14%)
EZ changed	-	-	-	-	1	1 (4%)
EZ generated	-	-	-	1	-	1 (4%)
Total (%)	2 (10%)	3 (14%)	2 (10%)	5 (24%)	9(43%)	21 (100%)

EZ: epileptogenic zone.

patients respectively. In 50% of patients HR-ESI positively impacts presurgical decision making process; in three this was critically valuable to achieve seizure freedom.

Video-based semiology has been reported to be often subtle in TSC patients but investigations into the localizing value of semiology in surgical TSC patients have not been performed yet (Savini et al. 2018). History-based seizure semiology classification often agreed with video-based seizure semiology classification in general epilepsy surgery cohorts (Hirfanoglu et al. 2007). However, correct localization in focal epilepsy is lower for PHS than for VS; showing 20–38% PHS concordance versus 50–56% VS concordance when using seizure conference conclusion or non-invasive diagnostics as reference standard (Beniczky et al. 2012; Kim et al. 2015). In 77% of seizure-free patients VS co-localized with resected area on lobar level (Elwan et al. 2018).

Our data did not confirm a superior localizing value of VS over PHS. Fundamentally, seizure semiology is an interpretation that is dependent on the experience and recall of the observer (Tufenkjian and Luders 2012). It solely reflects symptomatogenic zone activation, which may only be part of – or even not be included in – the EZ. Seizures arising from different EZ could activate the same symptomatogenic zone or vice-versa (Tufenkjian and Luders 2012). The complex and numerous brain abnormalities involved in TSC and our center's liberal inclusion criteria (i.e. poorly localizing semiology and non-localizing epileptic spasms) for presurgical evaluation, might govern the poor localizing accuracy of semiology reported here. Also, our population consisted mostly of young patients – sometimes with cognitive disabilities – who are often unable to communicate their symptoms to caretakers. Semiology in the context of EZ identification in determining surgical candidacy in TSC might be considered of limited value.

In a previous small study on HR-ESI for EZ identification, all five postoperative seizure-free TSC patients had the HR-ESI source maximum included within the resected area though all poor outcome patients HR-ESI was partially concordant (Kargiotis et al. 2014). The authors used a higher number of electrodes (i.e. 128–256 electrodes) and concordance was determined post-operatively using post-operative MRI and unblinded for surgical outcome (Kargiotis et al. 2014). In a selection of patients in whom ESI changed the clinical management, a 67% sensitivity and 50% specificity was demonstrated when taking resected area and the postoperative outcome as reference standard (Foged et al. 2020). This compares to our demonstrated concordance in 67% of good outcome patients and in 50% patients of poor outcome patients (Foged et al. 2020).

A meta-analysis on LTM-VEEG by Kobulashvili and coworkers reported a sensitivity of 70% -based on complete and partial concordance – that compares to our 78% (partial) concordance rate in our good surgical outcome group (Kobulashvili et al. 2018). A comparative analysis between ictal EEG and magnetic source imaging (MSI), the magnetic counterpart of HR-ESI, demonstrated superior sensitivity of interictal MSI over ictal EEG (100% versus 56%) in predicting the resected area in six seizure-free TSC patients (Wu et al. 2006).

A prospective study showed a clinical management plan change in 34% of 82 consecutive TSC patients based on new and non-redundant information from ESI (Foged et al. 2020). The used classification of new non-redundant information compares to our outcome of EZ modification that showed an HR-ESI-related change of the EZ in 11/21 patients (52%). Change of management is however difficult to assess retrospectively; additional non-invasive testing could still have been performed even without HR-ESI result. This could explain the high proportion of EZ modification in our cohort.

Many patients had multifocal interictal epileptiform EEG abnormalities, but a predominant unilateral focus was often identified. Unexpectedly, we found predominant foci and the ictal EEG in all patients with localizing ictal EEG to be at least partially concordant. This supports what earlier studies demonstrated; surgical candidates with TSC have dominant and consistent interictal epileptogenic foci over the course of many years that are often concordant with the ictal onset zone (van der Heide et al. 2010; Jansen et al. 2005). A dominant interictal EEG focus as surrogate for the region of ictal onset, combined with HR-ESI findings, may be favored for localization purposes over ictal EEG recordings.

The finding of multifocal HR-ESI results in two patients with unifocal interictal LTM-VEEG appears counter-intuitive (patient 17, 13). However, when reviewing the diagnostic reports of the individual patients, HR-ESI captured bilateral interictal activity that was previously not seen during interictal LTM-EEG (patient 13). In patient 17, interictal LTM-EEG was concluded as a midline central focus although it regularly showed bilateral spread. This spread was registered in the HR-ESI resulting in a multifocal source estimate. Inter-observer differences may have resulted in dissimilar classification and selection of interictal epileptic discharges for localization purposes.

Unexpectedly, the localizing results from the individual diagnostic tests did not always reflect the resected area, and seizure-outcome did not always relate to the degree of concordance or discordance of different presurgical investigations as was seen in patient 14, 4 and 7. This displays that studying localizing accuracy of the presurgical epilepsy workup is challenged by specific nuances and the selected geometric level of co-localization (i.e. lobar or sub-lobar) involved in a complex clinical decisional process.

Our study included only data from official diagnostic reports. We anticipated that the evaluation of diagnostics results in light of other clinical and diagnostic information, which is common in presurgical multidisciplinary meetings, could potentially introduce bias. We found in some patients that initial diagnostic reports were

in disagreement with the evaluation by the multidisciplinary team. In patient 12 the LTM-VEEG official report concluded an unclear localization, while the team agreed on a right frontal focus which was included into the surgical plan. Unfortunately, in this patient surgery resulted in poor outcome. In another patient (patient 7) the team concluded that the bilateral multifocal interictal EEG, as concluded in the official report, actually showed two consistent foci of which one supported partly the equivocal left temporal ictal EEG localization. The left temporal lobe was subsequently selected as area to be resected which resulted in a good postsurgical outcome.

This study has several limitations. First, there is a patient selection bias. Patients undergoing HR-ESI are more likely to have inconclusive or non-congruent presurgical workup results and should be considered as a population with difficult to localize seizures. Second, lower localization value of LTM-VEEG relative to HR-ESI may be partially the result of LTM-VEEG's contribution to an inconclusive workup. Yet, we had a non-localizing ictal EEG in 7/24 patients (29%) that is in reasonable agreement with a non-localization rate of 22% found in a large series of TSC patients (Savini et al. 2018). To minimize bias, we selected only LTM-VEEG's with seizure data and included HR-ESI results even with artefacts or without epileptic activity. Third, due to the retrospective nature of this study, the reporting epileptologists and physicist were not fully blinded for the clinical history, seizure semiology and MRI data during the review of HR-ESI and LTM-VEEG. The two experts analyzed semiology based on descriptions taken from the charts blinded for other data. This always lacks finesse. Fourth, the lobar co-localization is affected by differences in size and shape of brain lobes; the larger frontal lobe likely to be more often concordant than the smaller occipital lobe. Therefore, we presented partially concordant results separate from concordant results as a lobar concordance level may be considered already liberal. Alternatively, measures such as Euclidean distance or surface overlap between source localization and resected area are more objective but are difficult to establish in the non-ESI modalities studies here, such as standard LTM-VEEG and semiology. Nevertheless, partially concordant results may still be clinically valuable in the context of other imaging modalities. Fifth, source localization based on LTM-VEEG data was not part of standard practice. It is recognized that ictal ESI provides additional localizing information over interictal ESI (van Mierlo et al. 2020). More diagnostic potential may be reached when source localization is performed on the collected interictal and ictal EEG from LTM-VEEG (van Mierlo et al. 2017; Sharma et al. 2018). Sixth, the selection criteria for spike clusters used for source localization were largely based on strict signal quality standards that do not necessarily correlate with the epileptic tuber. Moreover, altered intracranial geometry and tuber-specific conductivity may violate some assumptions of the forward model that may cause a small localization error. An alternative approach might be to constrain source solutions to perituberal regions while simultaneously allowing a more liberal acceptance regarding signal quality (Peters et al. 2020). Seventh, our reference standard – the resected area in seizure free patients – has its limitations. Seizure recurrence may be caused by incomplete resection – due to eloquent area vicinity – or it may be explained by newly evolved epileptogenic tissue (Knowlton et al. 2008; Vadera et al. 2013). To increase sample size we included all operated patients regardless of postoperative follow-up duration. The concept of the epileptogenic zone is based on a focal assumption, yet it is increasingly acknowledged that epilepsy also behaves as a complex network (Jehi 2018). For TSC specifically, focal seizures and interictal epileptiform discharges may arise in the centre of epileptogenic tubers, propagating to the tuber rim, perituberal cortex and other (epileptogenic) tubers (Kannan et al. 2016; Ma et al. 2012; Major et al. 2009). Epileptic activity may also start independently from different tubers (Bauman et al. 2005; Jacobs et al. 2008). Complex and widespread epileptic zones and networks have also been demonstrated by various methodologies and biomarkers such as EEG-functional MRI (Jacobs et al. 2008) and high frequency oscillations (Okanishi et al. 2014). These zones are sometimes located with spatial distance from spike topography (Jacobs et al. 2008). Tuber locations associated with epileptic spasms show functional connection to the globi pallidi and cerebellar vermis (Cohen et al. 2021). Thus, removal of the cortical tuber (tuberectomy) alone may not be sufficient to interrupt the complex epileptic network completely. Surgical failure may not necessarily rule out epileptogenicity of resected tissue but is also no proof that non-resected source estimates are epileptogenic (Rikir et al. 2017). Lastly, our small sample size prevented statistical analysis and computation of reliable sensitivity and specificity. A larger cohort is needed for more robust and reliable outcomes.

5. Conclusions

This study demonstrates that HR-ESI is more often localizing compared to semiology, interictal EEG and ictal EEG in presurgical evaluation of TSC patients. Semiology has limited localizing value. Interictal and ictal EEG have often non-localizing and multifocal test results that impact the overall localization value of these methods. HR-ESI is more concordant with proven epileptogenic zone, with ictal EEG being more partial concordant. HR-ESI has a predominantly positive impact on clinical management without ever being critically misguiding. Presurgical workup of TSC might benefit from less emphasis on semiology and more on HR-ESI results. Employing HR-ESI initial presurgical workup modality might complement LTM-VEEG results by improving localization accuracy, guiding ancillary (non)invasive testing or confirming the EZ hypothesis when there is hesitance to undertake surgery. Future studies should prospectively explore the added value of HR-ESI early in the presurgical epilepsy evaluation of TSC patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.09.020.

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