



Neuropsychological outcomes after resection of cortical sites with visual naming associated electrocorticographic high-gamma modulation

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ABSTRACT

Background: Language mapping with high-gamma modulation (HGM) has compared well with electrical cortical stimulation mapping (ESM). However, there is limited prospective data about its functional validity. We compared changes in neuropsychological evaluation (NPE) performed before and 1-year after epilepsy surgery, between patients with/without resection of cortical sites showing HGM during a visual naming task.

Methods: Pediatric drug-resistant epilepsy (DRE) patients underwent pre-surgical language localization with ESM and HGM using a visual naming task. Surgical decisions were based solely on ESM results. NPE difference scores were compared between patients with/without resection of HGM naming sites using principal component (PC) analysis. Follow-up NPE scores were modeled with resection group as main effect and respective pre-surgical score as a covariate, using analysis of covariance.

Results: Seventeen native English speakers (12 females), aged 6.5–20.2 years, were included. One year after epilepsy surgery, first PC score increased by (mean \pm standard deviation) 14.4 ± 16.5 points in patients without resection, whereas it decreased by 7.6 ± 24.6 points in those with resection of HGM naming sites ($p = 0.040$). This PC score represented verbal comprehension, working memory, perceptual reasoning (Wechsler subscales); Woodcock-Johnson Tests of Achievement; and Peabody Picture Vocabulary Test. Subsequent analysis showed significant difference in working memory score between patients with/without resection of HGM naming sites (-15.2 points, 95% confidence limits -29.7 to -0.7 , $p = 0.041$).

Conclusion: We highlight the functional consequences of resecting HGM language sites, and suggest that NPE of DRE patients should include comprehensive assessment of multiple linguistic and cognitive domains besides naming ability.

1. Introduction

Electrical cortical stimulation mapping (ESM) remains the gold standard for pre-surgical localization of brain function with intracranial electrodes. However, concerns about its safety, neurophysiologic validity, and application in children have led to the development of an alternate method based on task-related high-gamma modulation (HGM) in electrocorticograph (ECoG) spectra (Aungaroon et al., 2017; Lachaux

et al., 2012; Zea Vera et al., 2017). HGM associated with language tasks, has been shown to have physiological validity based on correlation with neuronal firing rates and blood-oxygen-level-dependent responses, and, clinical validity compared to ESM using a variety of language paradigms (Arya et al., 2017, 2018b, 2015; Lachaux et al., 2007; Nakai et al., 2017; Wang et al., 2016). A recent meta-analysis including data from 15 studies found HGM mapping to be a good classifier of ESM language sites with high specificity (Arya et al.,

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2018a). Despite accumulating evidence for validity of HGM language mapping, its adaptation in clinical practice, either as a substitute or a supplement to ESM, has remained challenging due to paucity of data for corroboration with post-operative outcomes. A few studies have reported language impairment after resection of HGM language sites, and suggested that the resected number of HGM electrodes lying within the canonical language areas can help predict the need for post-operative speech therapy (Cervenka et al., 2011, 2013; Kojima et al., 2013a,b). However, there is no prospective data about the impact of resecting HGM language sites, including those outside the conventional anatomic language areas, on changes in neuropsychological outcomes, which arguably provide the most comprehensive biomarker of the functional impact of neurosurgery. In this prospective study, we have compared the changes in neuropsychological function from pre-surgical evaluation to at least 1-year after epilepsy surgery, between groups of pediatric patients with and without resection of cortical sites showing HGM during a visual naming task.

2. Methods

2.1. Patient population

Drug-resistant epilepsy (DRE) patients with intracranial electrodes implanted for extra-operative monitoring, since April 2012, were eligible. We included patients who underwent language mapping with both ESM and HGM, and neuropsychological evaluation (NPE) before and at least 1-year after their epilepsy surgery. Parental informed consent was obtained, with additional assent from patients over 10 years of age. Clinical information along with details of non-invasive (phase I) and invasive (phase II) pre-surgical evaluations were obtained from the patients' records for study purposes. The study was approved by the institutional review board (IRB #2012-0791).

2.2. Language localization with ESM and HGM

Methods for language mapping with ESM and HGM used at the study institution have been described in our previous publications and are only briefly summarized here (Arya et al., 2017, 2018b, 2015; Aungaroon et al., 2017; Zea Vera et al., 2017). Subdural electrodes made of platinum-iridium alloy embedded in silicone elastomer, with 2.5 mm exposed contacts (Auragen, Integra Neurosciences, Plainsboro, NJ), were used to record extra-operative ECoG. ESM was performed by stimulating pairs of adjacent electrodes with 50 Hz, bipolar, 500 μ s pulses, in trains lasting 5 s, using incremental current strengths until a functional response or a burst of evolving after-discharges (ADs) was seen, or the instrument limit was reached. The selection of electrodes, sequence of stimulation, and functional end-points were individualized for each patient by the clinical team. A picture naming task was used for ESM; and aphasia, paraphasic errors, or anomia due to orofacial sensorimotor interference with speech were regarded as indicative of language function in the cortex underlying the stimulated electrode pair (Arya and Crone, 2018; Zea Vera et al., 2017).

For analysis of HGM, ECoG signals were recorded during a 5 min baseline period of quiet wakefulness, and then during a visual picture naming task. For HGM mapping, pictures identical to those used for ESM, were each displayed for 3500 ms, with 2500 ms inter-stimulus interval, repetitively for 5 min (50 trials), after requesting the patient to name them aloud. Our ECoG processing was based on the signal modeling for real-time identification and event detection (SIGFRIED) approach (Schalk et al., 2008). From the autoregressive Gaussian mixture model fitted to the baseline data, the likelihood of 70–150 Hz power modulation during the visual naming task, relative to the baseline, was estimated at each electrode. This was quantified as a normalized Euclidean distance and the statistical significance of HGM at each electrode was determined with paired *t*-test corrected for the total number of channels in a given patient. Significant HGM associated with visual

naming were then plotted on cortical models derived from patient's pre-operative brain magnetic resonance imaging (MRI) and electrode locations derived from post-implant computed tomographic (CT) scans (Arya et al., 2017, 2018b). Neurosurgical decisions about the resection were made purely on the basis of ESM, and HGM mapping results were not used for clinical purposes.

2.3. Neuropsychological evaluation (NPE)

Neuropsychological tests were administered by a qualified psychometrist, supervised and interpreted by a pediatric neuropsychologist, preoperatively, and at least 12 months postoperatively. The standard clinical battery included the age-appropriate version of the Wechsler Intelligence Scale for Children (WISC), or the Wechsler Adult Intelligence Scale (WAIS); Woodcock-Johnson Tests of Achievement, Revision 3 (WJ-III); Boston Naming Test (BNT); A Developmental NEUROPSYCHOLOGICAL Assessment, version 2 (NEPSY-II); and the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV). Standardized scoring procedures were used to obtain standard scores with a mean of 100 and a standard deviation of 15; and, in the case of the Boston Naming Test, z-scores were obtained based on age-related normative data provided in the test manual (Goodglass et al., 2001). Cerebral hemispheric dominance for language function was decided based on the results of functional MRI, obtained as a part of pre-surgical evaluation. If functional MRI could not be obtained in any patient, then left hemisphere was regarded to have essential language function, irrespective of the handedness (Kojima et al., 2013b).

2.4. Measurement of resection volume

Since neuropsychological outcomes after epilepsy surgery have been shown to be associated with the size of resection, it was regarded as an important potential confounder (Sherman et al., 2011). We ascertained the volume of cerebral tissue resected in each patient by co-registering pre- and post-operative brain imaging using a neuro-navigational suite (Brainlab, Westchester, IL). After co-registration, the resection was segmented as a 3-dimensional object and volumetric measurements were made.

2.5. Statistical analysis

The groups of patients with/without resection of electrodes with naming-associated HGM were compared for relevant clinical variables using Wilcoxon (continuous) and Fisher exact (categorical) tests. Raw difference scores (RDS) for NPE subscales were calculated for each patient by subtracting the score obtained before surgery from that obtained 1-year or later after surgery. Since multiple NPE subscales were acquired for each patient, we first performed a principal component analysis (PCA) to obtain composite scores derived from linear combinations of all NPE subscales. This addressed the concern for multiple comparisons and minimized information loss. For PCA, WISC and WAIS scores were treated as identical. Although, only < 7% of the data was missing in the matrix used for PCA, we performed multiple imputation using regularized iterative PCA algorithm, which avoids overfitting and is statistically conservative (Josse et al., 2011). The number of principal components (PCs) was selected based on the proportion of cumulative attributable variance. Composite scores were then derived for each patient from the factor loadings for individual PCs. These composite scores were compared between patients with and without resection of cortical sites showing HGM during visual naming. To account for possible between-group imbalances in pre-surgical scores, and possible correlation between follow-up and pre-surgical scores, type I analysis of covariance (ANCOVA) models were fitted for each NPE subscale with follow-up score as the dependent variable, resection of HGM naming electrodes as the main effect, and pre-surgical NPE score as a covariate. NPE subscales found to have significant association with resection of

HGM naming sites on ANCOVA, adjusted for pre-surgical score(s), were tested for group differences in RDS using Tukey's tests. Lastly, post-hoc ANCOVA models were also fitted to explore if the relationship between resection of HGM naming sites and NPE RDS or PCs, was influenced by age, sex, seizure freedom, resection including the mesial temporal lobe (MTL), surgery involving the language dominant hemisphere, and the resection volume. A non-directional p-value ≤ 0.05 was considered significant for all tests. R version 3.4 was used for all analyses (R core team, 2017).

3. Results

Seventeen patients (12 females), aged 6.5 to 20.2 years (mean \pm standard deviation 13.1 ± 4.7) were included. Of these, 10 patients were right handed, 6 were left handed, while 1 patient was ambidextrous. All patients were native English speakers. A mean of 84 electrodes (± 22) were implanted for extra-operative ECoG in these patients. Twelve patients were implanted with subdural electrodes on the left hemisphere, while 5 had a right-sided implant. One year after the surgery, 12/17 (70.6%) of the patients were seizure free. The groups of patients with and without resection of cortical sites showing naming-associated HGM did not differ in terms of these variables (Table 1). Language lateralization was available from functional MRI in 13/17 (76.5%) patients. Although a higher proportion of patients with resection of HGM language electrodes underwent resections including MTL (6/9 vs. 4/8) and dominant hemisphere surgeries (6/9 vs. 3/8), the differences were not significant. Also, the mean brain resection volume was comparable between patients with (20.7 ± 12.3 ml) and without (18.0 ± 13.8 ml) resection of HGM naming sites ($p = 0.61$). Additional details including localization of seizure-onset zone, subdural electrode coverage, and topography of ESM and HGM have been published earlier (Arya et al., 2017).

3.1. Composite scores obtained from PCA

The composite score derived from first PC increased by 14.4 (± 16.5) points in patients without resection, whereas it decreased by 7.6 (± 24.6) points in patients with resection of HGM naming sites ($p = 0.040$, Table 2). This first composite score represents an aggregate of WISC/WAIS subscales (verbal comprehension, perceptual reasoning, and working memory); PPVT-IV; and WJ-III. The composite scores derived from PC2 and PC3 did not show significant differences between the groups of patients with and without resection of HGM naming sites. The second composite score predominantly represents FSIQ and BNT, while the third composite score represents the passage comprehension subscale of WJ-III and semantic word generation subtask of NEPSY-II. An orthogonal bi-plot of PC1 and PC2 scores for all patients verified these observations, and showed a trend for subscales of WISC/WAIS, NEPSY-II, and WJ-III to differentiate patients with and without

resection of HGM naming sites, though the confidence ellipses overlapped (Fig. 1). Further, the association between composite score derived from PC1 and the resection of HGM naming sites was not significantly affected by age, sex, seizure freedom, resection including MTL, surgery involving the language dominant hemisphere, or the resection volume (Table e1).

3.2. Follow-up NPE subscale scores

ANCOVA models for follow-up NPE subscale scores showed significant association with respective pre-surgical scores (Table 3). Adjusting for these associations, follow-up scores for perceptual reasoning and working memory subscales of WISC/WAIS; and, passage comprehension and letter-word identification subscales of WJ-III, showed significant association with resection of HGM naming sites. On exploring differences in RDS for these subscales, all 4 scores showed a decline in patients with resection of HGM naming sites (Table 4). In particular, working memory showed a difference of -15 points (95% CI -29.7 to -0.7 , $p = 0.041$) in mean RDS between patients with and without resection of electrodes with naming-associated HGM. Perceptual reasoning (-9.0 , 95% CI -19.3 to 1.3 , $p = 0.081$) and letter-word identification (-6.8 , 95% CI -14.3 to 0.8 , $p = 0.076$) also showed similar trends but did not achieve statistical significance.

4. Discussion

This study found that resection of HGM language sites was associated with poorer neuropsychological outcomes after epilepsy surgery. This difference was most prominent for working memory which improved after surgery in patients without resection of HGM naming sites, compared to a decrease in patients who had resection of these sites, with a 15 point difference (Tables 3 and 4). Perceptual reasoning and letter-word identification also showed similar trends but did not attain statistical significance. These findings were also substantiated by a 22 point difference in the first composite score derived from PCA representing multiple WISC/WAIS subscales, PPVT-IV, and WJ-III (Table 2). Hence, our study supports that although ESM has been a time-honored method to make clinical decisions for epilepsy surgery, it may be imperfect, and resection of language sites detected by HGM mapping, may have important functional consequences.

We have validated earlier smaller reports of decline in language function and/or NPE after resection of HGM language sites. In a cohort of 11 adults who had resective epilepsy surgery, 7 demonstrated post-operative language deficits not anticipated by ESM (Cervenka et al., 2013). In 4/7 of these patients, the resection included HGM naming sites, and was associated with poorer performance on Hopkins verbal learning test, verbal fluency, and in 1 patient, transcortical motor aphasia. The authors reported auditory description naming to be more predictive of post-operative deficits than visual naming. Another study

Table 1

Characteristics of the patient sample and comparison of clinical variables between groups of patients with and without resection of cortical sites showing ECoG high-gamma modulation during visual naming.

	Overall sample	Not resected	Resected	Effect estimate* (95% confidence limits)	p-value
Number of patients	17	8	9		
Age (years, mean \pm SD)	13.1 ± 4.7	15.1 ± 3.8	11.2 ± 4.8	$-0.87 (-1.95, 0.22)$	0.101
Gender (female, male)	12, 5	7, 1	5, 4	$5.06 (0.35, 313.62)$	0.294
Number of electrodes (mean \pm SD)	84 ± 22	87 ± 22	82 ± 22	$-0.19 (-1.23, 0.84)$	0.440
Handedness (right, left or atypical)	10, 7	4, 4	6, 3	$1.92 (0.19, 21.62)$	0.637
Hemisphere (left, right)	12, 5	5, 3	7, 2	$0.50 (0.03, 6.18)$	0.620
Surgery in dominant hemisphere (n, %)	9 (52.9%)	3 (37.5%)	6 (66.7%)	$3.09 (0.32, 37.60)$	0.347
Resection included MTL (n, %)	10 (58.8%)	4 (50.0%)	6 (66.7%)	$1.92 (0.19, 21.62)$	0.637
Seizure free at 1-year (n, %)	12 (70.6%)	6 (75.0%)	6 (66.7%)	$0.68 (0.04, 8.48)$	0.999
Resection volume (ml, mean \pm SD)	19.4 ± 12.7	18.0 ± 13.8	20.7 ± 12.3	$0.19 (-0.84, 1.23)$	0.606

(ECoG electrocorticographic; MTL mesial temporal lobe; SD standard deviation; *represents standardized mean difference [Hedge's g] for continuous variables and odds ratio for categorical variables).

Table 2

Composite scores derived from principal component analysis of the neuropsychological measures evaluated before and one-year after epilepsy surgery compared between groups of patients with and without resection of visual naming related ECoG high-gamma modulation cortical sites. First three principal components (75.0% cumulative explained variance) are presented along with their factor loadings.

	Composite scores	Not resected (mean ± SD)	Resected (mean ± SD)	p-value
	PC1	14.40 ± 16.50	-7.64 ± 24.56	0.040 (*)
	PC2	-6.88 ± 10.70	-6.22 ± 27.66	0.949
	PC3	4.08 ± 9.21	0.45 ± 8.53	0.414
Proportion of Variance		61.8%	14.7%	7.5%
Cumulative Proportion		61.8%	76.5%	84.0%
Factor loadings				
WISC-IV/ WAIS-IV	Verbal comprehension	0.381 [#]	-0.234 [#]	0.373
	Perceptual reasoning	0.388 [#]	0.180	-0.198 [#]
	Working memory	0.326 [#]	-0.178	0.150
	Processing speed	0.307	-0.187	-0.202 [#]
	Full scale IQ	0.166	-0.598 [#]	0.072
PPVT-IV		0.342 [#]	0.211	0.178
Boston naming test		0.077	0.545 [#]	-0.035
NEPSY-II	Word generation (semantic)	0.146	0.313 [#]	0.645 [#]
	Word generation (phonemic)	0.264	0.218 [#]	-0.137
Woodcock-Johnson III	Passage comprehension	0.335 [#]	0.033	-0.477 [#]
	Letter-word identification	0.388 [#]	0.014	-0.136

(ECoG electrocorticographic; IQ intelligence quotient; NEPSY-II A Developmental NEuroPSYchological Assessment; PC principal component; PPVT Peabody Picture Vocabulary Test; SD standard deviation; WAIS Wechsler Adult Intelligence Scale; WISC Wechsler Intelligence Scale for Children; [#] top 50 centile factor loadings).

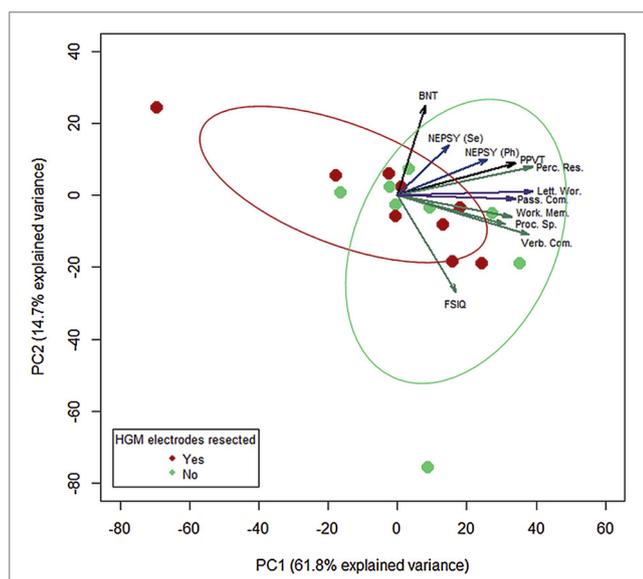


Fig. 1. Bi-plot with first two PCs along orthogonal axes showing that patients with and without resection of HGM naming sites are best differentiated by subdomains of the WISC/WAIS, WJ-III, and NEPSY-II. The length of the arrows represents the factor loadings of the neuropsychological subdomains in the PC space.

[BNT: Boston Naming Test; FSIQ: Full scale intelligence quotient; HGM: high-gamma modulation; Lett. Wor.: Letter-word identification (WJ-III); NEPSY-II: A Developmental NEuroPSYchological Assessment (version 2, Se: semantic word generation, Ph: phonemic word generation, blue arrows); Pass. Com.: Passage Comprehension (WJ-III); PC: principal component; Perc. Res.: Perceptual Reasoning (WISC/WAIS); PPVT: Peabody Picture Vocabulary Test (4th edition); Proc. Sp.: Processing Speed (WISC/WAIS); Verb. Com.: Verbal Comprehension (WISC/WAIS); WAIS: Wechsler Adult Intelligence Scale (4th edition, dark green arrows); WISC: Wechsler Intelligence Scale for Children (4th edition, dark green arrows); WJ-III: Woodcock-Johnson Tests of Achievement (revision 3, purple arrows); Work. Mem.: Working memory (WISC/WAIS)]

identified post-operative deficits in verbal memory in 3/4 bilingual patients, with isolated deficits in their second language (English) in 1 case, which were predicted by HGM but not ESM (Cervenka et al.,

2011). In a Dutch speaking cohort, 6/8 patients had resection of HGM language sites, with aphasia on follow-up in 2/6 patients (Bauer et al., 2013). Other anecdotal reports include expressive aphasia after resection of premotor and inferior Rolandic HGM auditory naming sites (Kojima et al., 2012); and aphasia (no formal testing), and impaired naming and verbal memory in 1 patient each following resection of HGM picture naming sites (Sinai et al., 2005). Another pediatric patient showed a decline in semantic fluency, visual confrontation naming, and everyday linguistic abilities 2 months after resection of HGM language sites, which progressed to substantial decline in the ability to make semantic associations, receptive language skills, and working memory 1 year following surgery (Korostenskaja et al., 2014).

The usual neurosurgical practice is to avoid resection of anatomic language areas including Broca’s area (pars triangularis and opercularis of the dominant inferior frontal gyrus), inferior peri Rolandic (orofacial motor) cortex, and Wernicke’s area (posterior third of dominant superior temporal gyrus, sometimes also including supra-marginal gyrus), and ESM language sites, unless there is a considerable overlap with seizure-onset zone and the potential risk of language deficit is clearly outweighed by the likelihood of favorable seizure outcome(s), and the patient/family is willing to accept those risks. While this strategy may often protect against overt naming deficits, our study suggests that there may be deficits related to higher-order cognitive processing of language, when HGM sites outside these anatomic language areas are resected. At a group level, this is supported by our observation that resection of HGM naming sites did not result in significant deterioration in FSIQ and BNT, but rather in WISC/WAIS, NEPSY-II, and WJ-III subscales representing interpretative and integrative aspects of language in addition to the perceptive-expressive domains (Tables 2–4; Fig. 1). In individual patients, resection of HGM naming sites, which were ESM – and/or outside the anatomic language areas, was associated with poorer NPE outcomes (Fig. 2). Hence, it may perhaps be more ecologically valid to think about functional specialization rather than hemispheric dominance since human language represents a complex cognitive task involving multiple networks in both hemispheres which participate in different subroutines of language processing (Chang et al., 2015).

Our study found change in working memory to be significantly affected by the resection of HGM naming sites. The working memory subtest of WISC/WAIS measures the ability to hold and manipulate

Table 3

Analysis of covariance models with follow-up score for respective neuropsychological subscales as the dependent variable, resection of HGM naming electrodes as the main effect, and pre-surgical score for the same subscale as a covariate.

		HGM electrodes resection	Pre-surgical score	Interaction term
		p-values		
WISC-IV/ WAIS-IV	Verbal comprehension	0.102	< 0.0001	0.340
	Perceptual reasoning	0.029*	< 0.0001	0.865
	Working memory	0.035*	0.001	0.252
	Processing speed	0.065	0.004	0.601
	Full scale IQ	0.673	0.001	0.930
PPVT-IV		0.368	< 0.0001	0.116
Boston naming test		0.925	< 0.0001	0.996
NEPSY-II	Word generation (semantic)	0.357	< 0.0001	0.217
	Word generation (phonemic)	0.253	0.058	0.505
Woodcock-Johnson III	Passage comprehension	0.014*	< 0.0001	0.313
	Letter-word identification	< 0.0001*	< 0.0001	0.621

(HGM high-gamma modulation; IQ intelligence quotient; NEPSY-II A Developmental NEuroPSYchological Assessment; PPVT Peabody Picture Vocabulary Test; WAIS Wechsler Adult Intelligence Scale; WISC Wechsler Intelligence Scale for Children; * ≤ 0.05).

Table 4

Selected mean raw difference scores analyzed with respect to resection of electrodes showing high-gamma modulation during visual naming.

		Difference in mean RDS* (95% confidence limits)	p-value**
WISC-IV/ WAIS-IV	Perceptual reasoning	-9.0 (-19.3, 1.3)	0.081
	Working memory	-15.2 (-29.7, -0.7)	0.041
Woodcock-Johnson III	Passage comprehension	-2.7 (-14.2, 8.8)	0.627
	Letter-word identification	-6.8 (-14.3, 0.8)	0.076

(RDS raw difference score; WAIS Wechsler Adult Intelligence Scale; WISC Wechsler Intelligence Scale for Children; *represents the difference in mean RDS between groups with and without resection of electrodes having naming-associated high-gamma modulation; **represents p-value adjusted for multiple comparisons using Tukey's honest significant difference).

verbal information in the short-term memory (Wechsler, 2014). A conceptual model of working memory proposes a central executive which is interdependently linked to visuospatial sketchpad and phonological loop subdomains, themselves mediated via an episodic buffer (Baddeley, 1992; Linden, 2007; Muller and Knight, 2006). The visuospatial sketchpad integrates ventral occipito-temporal stream mediating object recognition, and dorsal occipito-parietal stream which enables spatial operations. The phonological/articulatory loop also has 2 components including phonological short-term store localizing to inferior parietal cortex, and sub-vocal rehearsal process relying on Broca's area, supplementary sensorimotor cortex, and cerebellum (Linden, 2007; Muller and Knight, 2006). We hypothesize that resection of HGM sites within or adjacent to these cortical locations may have been responsible for observed difference in working memory in our study (Fig. 2). We used a visual naming task which, though not designed to test the

nuances of working memory systems, involves multiple language sub-routines including semantic, lexical, and phonological processes (Hamberger, 2015). Neuropsychological studies in adults with temporal lobe epilepsy have shown that word finding or naming difficulties in such patients are likely due to interference with post-semantic processing (Helmstaedter et al., 2003; Seidenberg et al., 1993). Clinically, patients with DRE experiencing naming difficulties can often still describe the item they are unable to name, implying successful semantic retrieval; and can sometimes provide the first phoneme, number of syllables, or syllabic stress of the name, indicating partial access to lexical and phonological information (Helmstaedter et al., 2003; Miozzo and Caramazza, 1997; Miozzo and Hamberger, 2015). Since we included a mixed sample of pediatric DRE, our findings probably suggest that chronic DRE may adversely affect language networks, even outside the areas defined by conventional neuroanatomy and/or ESM;

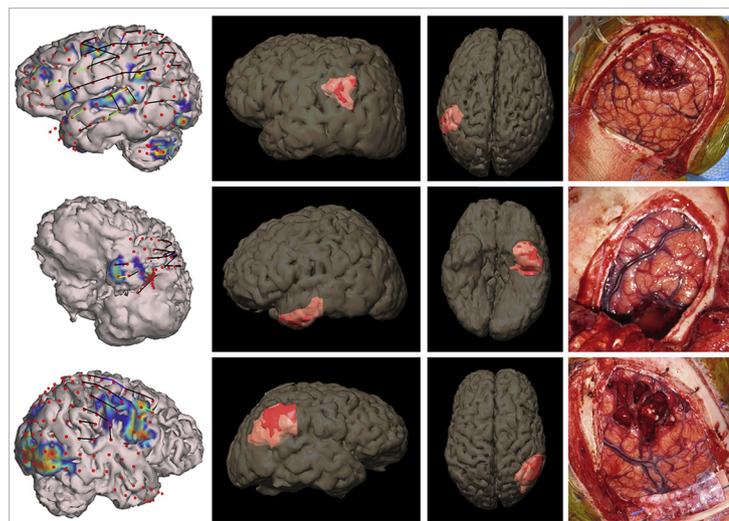


Fig. 2. Cortical surfaces derived from patient's brain MRI showing electrode locations (red dots); ESM results (green lines: orofacial sensorimotor speech interference, yellow lines: aphasia, black lines: no naming dysfunction); and visual naming related HGM (left panel). Also shown are co-registered pre- and post-operative brain imaging with 3D resection objects (middle 2 panels); and post-resection intra-operative photographs (right panel). Illustrative examples with resection of HGM + language sites in left supra-marginal gyrus and inferior peri-Rolandic cortex (top, Δ WM 3, Δ FSIQ -9, Δ PC1 -0.6); left anterior basal temporal and temporal pole (middle, Δ WM -4, Δ FSIQ -5, Δ PC1 -12.4); and right parietal lobe (bottom, Δ WM -3, Δ FSIQ -2, Δ PC1 -2.8). [Δ change (post-operative score - pre-operative score); 3D 3-dimensional; ESM electrical stimulation mapping; FSIQ full-scale intelligence quotient; HGM high-gamma modulation; MRI magnetic resonance imaging; PC principal component; WM working memory; electrodes placed over the ventral temporal-occipital surface are projected over cerebellum for visualization]

and that NPE of these patients should be comprehensive and include multiple functional tests in addition to the assessment of naming ability.

At present, epilepsy surgery decisions incorporate only ESM results for functional localization, in a majority of centers. Although our study makes a good case for continued evaluation of NPE consequences of resecting HGM + ESM – electrodes to better inform neurosurgery, it has some unavoidable limitations. Changes in language or NPE outcomes before and after epilepsy surgery depend on several variables, including seizure recurrence/frequency after surgery, anti-seizure medications, localization of the seizure-onset zone, and the anatomy of resection. Also, the topography of HGM depends on the tasks used for language mapping, and methods used for signal analysis (Arya et al., 2018a). In particular, it will be desirable to evaluate the effect of different thresholds of an HGM metric (for example, trial-averaged power change) on post-operative NPE. However, in our present implementation of HGM analysis, only a binary significance was obtained for each electrode (Arya et al., 2017, 2018b). A small sample size also precluded incorporating these variables and the proportion of HGM naming sites that were resected, in a predictive model. However, we did not find a significant impact of age, sex, seizure freedom, resections including MTL, surgery in the language dominant hemisphere, or the resection volume, on the association between NPE outcomes and resection of HGM naming sites. Finally, not all the HGM naming sites that were resected, were tested by ESM in our study, since ESM was driven by clinical factors.

5. Conclusion

We found resection of HGM language sites to be associated with significantly worse post-operative working memory. We also showed that NPE of children with DRE should incorporate comprehensive evaluation of multiple cognitive and linguistic domains besides naming ability. Recently, results of multiple functional imaging and mapping modalities were incorporated using a machine learning approach to generate a predictive model for post-operative BNT scores in a small ($n = 11$) patient population (Babajani-Feremi et al., 2018). In future, we believe that use of more homogeneous methods for intracranial neuro-signal acquisition and analysis, incorporation of disease and patient specific variables, and use of predictive algorithms in large multi-center samples will ultimately drive a change in practice.

Authors' contributions

Study concept: RA, JAW, DFR, and KDH. Study design: RA, JAW, AWB, DFR. Data acquisition: RA, CR, JLL, DM, JAW, HMG, HF, DFR, FTM, AWB, KDH. Computational methods for signal and image processing: JAW, RA, JLL, LR, JB, CS, HF, DFR, NEC. Statistical analysis: PSH, RA, CR. First draft: RA. Critical review for content and approval: all authors

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as a part of her summer research internship at the study institution. JAW currently works for DRW Holdings (Chicago, IL) as a senior programmer. DM and DFR have retired from their positions at the study institution. Signal processing was performed using a derivative of SIGFRIED algorithm developed by Dr. Schalk's lab, which is covered under appropriate end user license. One of the panels in Fig. 2 is reproduced with permission from an earlier publication by the same group.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eplepsyres.2019.01.011>.

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