Transcranial Magnetic Stimulation in Pediatric Epilepsy:

Validation of a Noninvasive, Presurgical Motor Mapping Technique

Presented by:
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Abstract

Background: Transcranial magnetic stimulation (TMS) is a non-invasive technique often used to map the motor cortex in neurosurgical patients. This study aims to evaluate the success of using TMS for pre-surgical motor mapping in a cohort of 13 pediatric patients with medically refractory epilepsy.

Methods: From the prospective institutional database of pre-surgical TMS motor maps (2012 to present), all patients of age <= 18 years with a diagnosis of epilepsy were identified. Thirteen such patients met the inclusion criteria, and their demographic, clinical, and mapping data were extracted.

Results: The median age was 7.5. Ten patients had frontal seizure focus, 3 had a parietal focus, and none had a temporal focus. All patients were on antiepileptic drugs (AEDs) at the time of mapping (3 (23%) patients were taking ONFI (clobazam). 3 (23%) patients were on VIMPAT (lacosamide), and 2 (15%) patients were on KEPPRA (levetiracetam). Ten (77%) patients were on various other AEDs). The median duration of TMS motor mapping was 32 minutes and 34 seconds (19 minutes to 55 minutes). During mapping, patients received an average of 229 (±165) pulses. No provoked seizures were identified during mapping. All patients were able to complete the mapping session without significant discomfort. Nine (69%) patients were mapped successfully, and 4 (31%) were not mapped successfully. All patients underwent surgical resection, and the median Engel outcome score was Engel Class I (±0.69).

Conclusions: TMS is a safe, well-tolerated, and effective method for mapping the motor cortex in pediatric patients with epilepsy. TMS is a valuable modality for mapping precisely the anatomic location of the motor system in the pre-surgical pediatric epilepsy population. As such, it helps to facilitate pre-surgical planning, offers valuable prognostic information, and may

shorten intra-operative mapping times, thus reducing the risks intrinsic to prolonged surgical cases.

1. Introduction

In neurosurgical procedures, a general guiding principle is to remove as much diseased tissue as possible while preserving the patient's function. In pediatric epilepsy, this tenet is of particular importance, as the causative lesions are rarely malignant, thus making post-operative neurological deficits difficult to justify. Epilepsy surgery has thus been an opportunity for neurosurgeons and neurophysiologists to developed and refine a variety of techniques to interrogate and map out eloquent areas, such as motor cortex, within the human brain (Najib et al., 2011). In current neurosurgical practice, direct cortical stimulation (DCS) is the gold standard method for motor mapping and has been widely implemented and accepted as the best technique for preserving critical cortical structures during surgery.

However, DCS is not without its risks: it has a 5.4% risk of precipitating seizure in adults (Ulkatan et al., 2017). Given that the pediatric brain generally has a lower seizure threshold than the adult brain, it is likely that the seizure rate is higher in children. Furthermore, children in the operating room are under heavy doses of anesthesia and thus stronger electrical currents are needed to stimulate the motor cortex. Additionally, since many of the neurons in the pediatric brain are unmyelinated, it is necessary to utilize stronger currents to obtain a response. As a result, electrical stimulation can be particularly dangerous in this population, which is already seizure-prone. Moreover, DCS is inherently invasive; it can only be performed intraoperatively. DCS results must therefore be incorporated into the surgical plan in real-time and cannot be used to inform pre-operative family conversations or surgical planning.

It is for these reasons that transcranial magnetic stimulation (TMS), a non-invasive modality that offers pre-surgical functional motor maps, has become increasingly recognized. Historically, TMS was used therapeutically for psychological and psychiatric disorders such as

medication-resistant depression and schizophrenia (Horvath et al., 2011). However, a growing body of evidence has demonstrated that navigated TMS offers highly accurate motor maps and compares favorably to other noninvasive modalities such as fMRI and MEG (Krings et al., 2001; Picht et al., 2009; Krieg et al.,2012; Tarapore et al., 2012). These data, combined with multi-center reports documenting the safety of TMS-based motor mapping (Tarapore et al., 2015) culminated in the Navigated TMS Protocol (2017), a standardization of the protocols surrounding TMS-based motor mapping. The protocol report concludes by recommending the use of nTMS in neurosurgical pre-operative practice, but it also states a need for more research supporting the reliability of this technique (Krieg et al., 2017).

Despite the widespread acceptance of TMS techniques in the adult population, there are few reports of motor mapping in the pediatric epilepsy population. One study published in 2013 evaluated 13 adult patients with focal epilepsy to compare the nTMS motor cortical representation of hand and arm muscles with intraoperative DCS results. The study concluded that nTMS is a reliable tool to locate the motor cortex in epileptic patients (Vitikainen et al., 2013). Another study demonstrated successful TMS-based language mapping in a mixed pediatric-adult population but does not report motor mapping results (Lehtinen et al., 2018).

In this study, we seek to evaluate the success of using TMS for pre-surgical motor mapping in a cohort of pediatric patients from our institution with a diagnosis of medically refractory epilepsy. We describe the demographic and clinical characteristics of the population. We also thoroughly characterize the stimulation parameters, and report on the tolerability and complications associated with the study. In so doing, we aim to identify which parameters, if any, may be associated with successful TMS motor mapping.

2. Methods

This study was approved by the UCSF Institutional Review Board. All research was conducted according to the Declaration of Helsinki. This study reflects a single institution dataset that was gathered prospectively and analyzed retrospectively. Patients were identified at the time of care for possible inclusion in the study by a pediatric neurosurgeon (KIA). All included patients had a clinical diagnosis of medically refractory epilepsy and were being considered for operative management of the same. Patients were subsequently referred for pre-surgical mapping with navigated TMS, and were again assessed by the principal investigator (PET) as to their appropriateness for undergoing TMS. Patients with poorly controlled seizure, dangerous seizure semiology (i.e. prepensity for respiratory arrest), or continuous seizure manifestation were excluded from the study. A full list of the inclusion and exclusion criteria can be found in the Workshop Guidelines for TMS Motor mapping (Krieg SM et al., 2017).

Once patients had been appropriately screened, informed consent was obtained from the legal guardian of the patient. The procedural workflow and details were provided to the legal guardian at this time and, if possible and appropriate, to the patient as well. All concerns were addressed and questions answered. A baseline clinical assessment was performed, including the patient's level of pain, prior to initiation of mapping. Navigated TMS-based motor mapping was then performed as described later in this section.

2.1 Demographic and Clinical Data

Patient demographic and clinical data was recorded. Data included, but were not limited to, date of birth, age at time of study, gender, type of epilepsy, location of focus, antiepileptics on board at the time of procedure, complications, seizure frequency outcomes (according to the

ILAE/Engel classification system), duration of mapping, and whether an MRI with tractography (diffusion tensor imaging, or DTI) was performed.

To quantify the parameters of the motor-mapping session, we recorded multiple relevant parameters for each successful stimulus: number of stimuli, range of attempted stimuli (%), max stimulator output (%), peeling depth (mm), E-field max value (V/m), amplitude (uV) for each muscle group, period of latency (ms) for each muscle group, and the stimulus intensity (%). Movements were measured through surface electromyography (EMG) electrodes. A motor evoked potential (MEP) was defined as a stimulus that evokes a repeatable response in a target muscle group: abductor digiti quinti (ADQ), abductor pollicis brevis (APB), orbicularis oris (OO). MEPs were considered in the study results if their latency period was 10 ms - 50 ms, and internally consistent within a single muscle group (+/- 5ms). An example MEP can be seen in Figure 1.

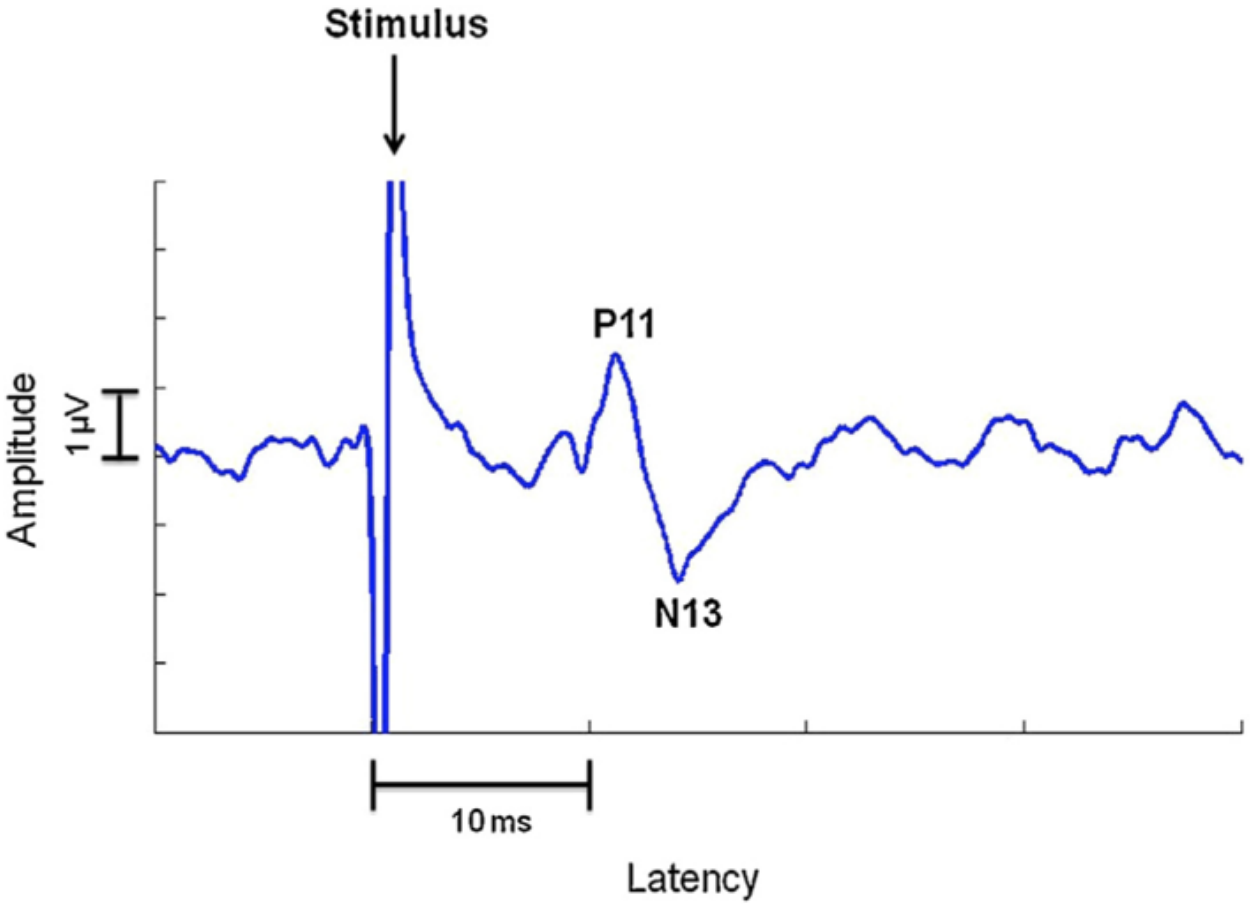

Figure 1: Electromyograph with a successful stimulus (10 ms latency)

During the mapping procedure, patients were monitored continuously by two attending neurosurgeons (KIA, PET). Any complications or side effects during the procedure were noted. As per established guidelines, any demonstration of prodromal signs or symptoms (i.e. reported aura, muscle twitching or increasing spontaneous EMG activity) would have resulted in the procedure's immediate suspension and appropriate assistance being given to the patient.

2.1 Magnetic resonance imaging (MRI)

Prior to undergoing TMS, every patient underwent a high-resolution MRI scan using a 3 Tesla unit. This MRI usually included a T1-weighed, 3D spoiled gradient-recalled echo sequence with a 34 msec TR, 3 - 8-msec TE, and 30° flip angle, as well as a T2-weighted 3D fast spin-echo

sequence with a 3 second TR, and 105 msec TE. The slice thickness was 1.5 mm for both sequences with a 256 x 256 x 128 matrix and a 260 x 260-mm field of view, which included the nasion, preauricular points, and external fiducial markers. The MRI scans were used for navigation within the TMS system based on anatomical landmarks.

2.2 Mapping Procedure

The protocol for navigated TMS-based motor mapping has been previously described, and was performed as recommended in the published Workshop Guidelines (Kreig SM et al., 2017). Studies were performed using the Navigated Brain Stimulation system (Nexstim Oy, Helsinki, Finland).

Motor cortex mapping was started at 110% resting motor threshold (RMT). However, if there was difficulty in obtaining MEP at a given stimulator setting, the stimulator output was increased in increments of 10% RMT until satisfactory MEPs were obtained. Likewise, if a given stimulator output elicited discomfort, the stimulator output was lowered in 10% RMT increments until stimulation was tolerable. In the first pass, the complete hemisphere was mapped using a grid pattern with 1cm raster. Perirolandic regions, the proposed region of resection, and any region exhibiting an MEP on first pass were subsequently mapped in higher definition using a grid with 5mm raster and at least 3 iterations.

2.3 Optimization for the Pediatric Patient

TMS-based motor mapping in the pediatric patient presents a unique set of challenges. In particular, pediatric patients can become restless and have difficulty sitting still, which is critical to obtaining high-quality EMG data. Thus, efforts were taken to ensure the comfort (and the

stillness) of the study subjects during mapping. The youngest patients were mapped while sleeping, if possible. Older patients were encouraged to sit on a parent's or caregiver's lap and were given electronic devices with favorite movies to divert their attention (Figure 2). Frequent breaks were offered, and care was taken to assess the subject's responses continually during mapping.

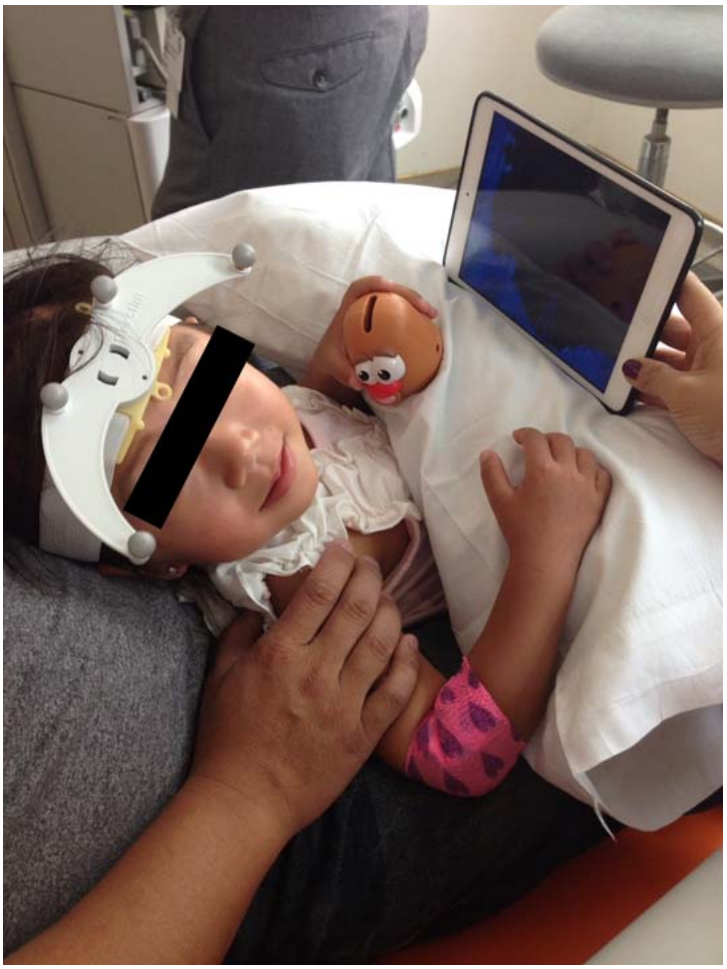

Figure 2: Patient on caregiver's lap, with an electronic device

It was found that securing the reference arc using a circumferential headband was the best-tolerated method; adhesive stickers affixing the reference arc to the forehead were frequently dislodged by the patient, both accidentally and intentionally. Similarly, we found that

reinforcing EMG surface electrodes with large, colorful children's stickers helped ensure that the leads remained safely in place for the duration of the study.

2.4 Data Analysis

Continuous variables with normal distribution were presented as mean (+/- SD); those with non-normal distribution were presented as median (+/- SD). Means testing between continuous variables was performed using t-test or ANOVA, as appropriate. Comparisons between categorical variables were performed using chi-square analysis. All data was stored and tabulated in Excel (Microsoft Co, Seattle, WA). Statistical calculations were conducted in STATA 15.1 (StataCorp LLC, College Station, TX). Statistical significance was determined based on a p-value < 0.05.

3. Results

3.1 Demographics

The study population included a total of 13 patients between the ages of 0-17. The median age was 7.5 years old. Eight (57%) patients identified as male and 5 (38%) identified as female. All 13 (100%) patients were diagnosed with medically refractory epilepsy. A MRI with DTI was performed in all 13 (100%) patients.

3.2 Clinical Characteristics

At the time of TMS motor mapping, 2 (15%) patients were not taking antiepileptic drugs (AEDs). The most common AEDs were Onfi and Vimpat with 3 (23%) patients each. Two (15%) patients were taking KEPPRA (levetiracetam). Ten (77%) patients were on other AEDs. The complete list of AEDs is included in the complete patient dataset (Appendix 1). The anatomic locations of epileptic foci were widely distributed in our patient population. Five (38%) of our patients had a right frontal epilepsy; 5 had left frontal lobe epilepsy. The left parietal lobe contained the seizure focus in 2 (15%) patients while the right parietal lobe contained the seizure focus in 1 patient (8%).

We also classified the seizure freedom outcomes for each patient in terms of ILAE/Engel classification system. Seven (54%) patients were classified as Engel class 1, 3 (23%) were Engel class 2, 1 (7.7%) was Engel class 3, and none were Engel class 4. Six (46%) patients were classified as ILAE class 1, 1 (7.7%) patient was ILAE class 2, 1 (7.7%) patient was ILAE class 3, and 3 (23%) patients were ILAE class 4.

3.3 Mapping Parameters

The median peeling depth was 16.25 mm (7.6 to 21.8 mm). The median stimulation intensity was 60% of stimulator output (45% to 100%) and the median E-field max value was 128 V/m (115.5 to 214 V/m). The median duration of examination was 32 minutes and 34 seconds (19 minutes to 55 minutes). The average number of pulses for each examination was 229 pulses (± 165). This data is represented in Table 2.

3.4 Complications and Other Diagnoses

There were no complications related to TMS mapping. One patient had a right foot drop following surgical resection of her epileptic focus. [see Appendix 1: Complications]. Many patients had other preexisting diagnoses such as hemiparesis, ADHD, tuberous sclerosis, behavioral disorder, perinatal infarct, and a skull defect.

3.5 *Overall Success*

Navigated TMS-based motor mapping was successfully completed in all patients. Useful motor maps were achieved in 9 patients (69%); in the remaining 4 patients (31%), although they completed the mapping successfully, usable results were not generated. Mean successful stimulus latencies were calculated for each muscle group in each of the 9 successful patients. These data are available in Figure 3. The average age of successful patients is 11.1 (± 1.79) and that of unsuccessful patients is 3.0 (± 1.53); age, however, was not a significant determinant of success, although it did display a trend in that direction (t-statistic = 1.74; p=0.094). Of the 4 patients who failed, all were male. Again, sex was not a significant predictor of success, but displayed a trend toward significance (X^2 = 2.44; p=0.057). Finally, each of the 4 patients who

failed mapping had frontal seizure focus (X^2 = 1.73; p=0.188). These data are depicted in Table 4.

4. Discussion

TMS is a promising modality for pre-surgical, non-invasive localization of eloquent motor cortex in the pediatric patient with medically refractory epilepsy. In this study, we report the results of a single institutional cohort of 13 consecutive patients. We found that, in a majority of patients, TMS was capable of mapping the eloquent motor cortex. Increasing age and female gender demonstrated a trend toward successful mapping, but neither variable was statistically significant. To our knowledge, this is the first such reported series in the English language literature. Although further study is warranted, it is highly suggestive that TMS-based pre-surgical motor mapping is a valuable modality in this patient population.

4.1 Principal Findings

Overall, in our cohort, the success rate for TMS-based motor mapping was approximately 70%. Although we were successful in the majority of our patients, the success rate is lower than that of adult cohorts, which have been reported at >99% (Picht T, 2014). It is therefore of interest to determine which parameters are most responsible for the failure rate, and whether those parameters may be optimize to improve the success of nTMS motor mapping going forward.

4.2 Factors that Correlate with a Successful Study

In analyzing the unsuccessful cases, we found associations with multiple demographic and clinical parameters. Perhaps the most interesting correlation (and the strongest) was with age. We hypothesized that it would be more difficult to map the motor cortex of extremely young patients (i.e. less than 3) because, in these patients, the majority of the corticospinal neurons are unmyelinated. TMS depends on the principle of induction to generate an electrical current in the target neuron; induction, in turn, depends on a changing magnetic field interacting with an insulated conductor. Without myelin, the immature neuron is largely uninsulated, and thus the inductive mechanism on which TMS depends would be less effective than in a mature, myelinated neuron. Using a finite-element analysis model, Syeda et al (Hadimani, 2017) demonstrate exactly this result, that stimulation threshold increases discretely as the myelin sheath decreases. It should be noted, however, that although the threshold increases, it is not infinite: in fact, the same study demonstrates that even unmyelinated neurons can be successfully activated with safe (albeit increased) levels of stimulation.

It is not known whether there exists a particular age threshold at which nTMS would no longer be an effective modality for motor mapping. Analysis of our series suggests a strong correlation between younger patients and unsuccessful mapping. Furthermore, we can say with confidence that patients aged 3 years and below are highly unlikely to yield a successful study. Although our oldest unsuccessful map took place in a 7-year-old, after further investigation into his specific case, we believe that this failure was due in part to severe behavioral issues that prevented him from sitting still for more than a few minutes at a time. As a result, achieving reliable EMG results on his study was extremely difficult and contributed significantly to the failure of his study.

Another variable that seemed to have an association with study success was, surprisingly, patient sex. This association has not been previously reported in the TMS-based motor mapping literature. We are extremely cautious in its interpretation for three reasons: First, because of the small sample size within this study; second, because the finding was not statistically significant; finally, there is no physiological explanation for this difference. In the psychiatric literature, it has been reported that repetitive TMS is more effective in improving the symptoms of schizophrenia in women than in men (Huber et al., 2003); however, there is little reason to believe that this finding applies as well to our study cohort, and further study with larger cohorts is needed.

Notably, we also found a lack of association between certain clinical factors and a successful study. Presence of an AED, for example, did not seem to correlate with a successful study, nor even did particular AEDs have an association with RMT. This finding suggests that the reduction in neuronal excitability (which is the desired effect of an AED) does not necessarily translate into an increased RMT. That being said, there were a wide variety of AEDs and ages represented in our population, and a much larger cohort would be necessary to characterize the effect of these AEDs across a range of ages.

Another important finding is the lack of association between location of focus and study success. Although all the patients with a failed study had a frontal focus, there were even more patients with frontal foci who had a successful study. Moreover, there was no association between proximity of the lesion to peri-Rolandic cortex and study success. Given that nTMS-based motor mapping is of greatest interest in patients with lesions in peri-Rolandic cortex, it is valuable to know that mapping studies in these patients have a high probability of success.

4.3 Specific Considerations in the Pediatric Population

As is often the case in the pediatric population, a number of specific considerations bear mentioning when conducting navigated TMS-based motor mapping. First, as previously discussed, is the issue of stimulator thresholds in the immature brain. RMT was notably higher than in adult populations, with median RMT being 60% of stimulator output. In some cases, mapping was performed at 100% stimulator output, which is extremely rare in adults. No patient found the stimulations to be unpleasant, and at no point did a patient request that the stimulator output be decreased despite continual encouragement from the team to share feelings of discomfort. This tolerability of the study is consistent with other published reports on single-pulse TMS in the adult population (Tarapore et al., 2015 and Tarapore et al., 2012) , which is tolerated exceedingly well and rarely results in patient complaint.

On a related note, we cannot over-emphasize the importance of creating and maintaining a safe, comfortable, and supportive environment for patients and their families through the entire mapping experience. In our experience, a successful study started well before the patient entered the TMS suite. Careful preparation of the caregivers, including a description of the study, its importance, the sensations associated with it, and its risks and benefits, was performed in the clinic. Once a family chose to participate, they were brought back some days later for the TMS study, and again offered a full explanation of the study, as well as its risks and benefits. Only then were the patient and caregivers brought into the TMS suite for the study itself.

Within the TMS suite, great attention was paid to maintaining a child-friendly environment. Harsh lighting and unnecessary electronic or medical equipment were avoided, and child-friendly posters were placed on the walls. Favorite videos were typically offered on a personal video device, and caregivers were encouraged to sit with their children for additional

reassurance. Stuffed animals, stickers, balloons, and favorite toys frequently played a role as well. In the case of infants and toddlers, if at all possible, caregivers were encouraged to allow the patient to fall asleep, as motor mapping requires no active participation from the patient. We feel that our 0% dropout rate was due in large part to these efforts, which are easily reproduced.

4.4 Limitations

The main limitation of our study was a small sample size (n=13 patients). As a result, our attempts to determine significant predictors of study failure met with limited success. With further study, however, and greater patient numbers, we are confident that the trends we identified in our series will be definitively proven (or disproven). Another important limitation is the heterogeneity of demographic and clinical characteristics within our patient population. Pediatric epilepsy is not a single diagnosis; rather, it is a collection of dozens of diseases, each of which may be manifested across a variety of anatomic locations and patient ages. Future studies with greater numbers will hopefully have the ability to cull homogeneous subgroups from within the greater population, and more accurately characterize the role of navigated TMS-based motor mapping within these subgroups. It is our hope that future meta-analyses with greater numbers will be better equipped to answer such questions; for this reason, we have included the granular raw data set in our Appendix 1.

4.4 Future Directions

This study suggests many future directions of investigation. It would be of great interest to quantify the effect of navigated TMS-based motor maps on patient outcomes: effect on surgical time, frequency of complications, and overall seizure freedom may all be affected by this pre-

surgical study. Additionally, it may be helpful to quantify the discomfort of navigated TMS in a more systematic fashion, as standard techniques such as the Visual Analog Scale are less useful in the very young patient. In future studies, we hope to see reports of larger, multi-center patient cohorts that may conclusively determine the effect of age on study success, and even determine a low-end threshold below which motor mapping is futile. As stated previously, we have included our complete dataset in this report to aid in future meta-analyses, and we strongly encourage future publications in this field to do the same.

4.5 Conclusion

In conclusion, our research shows that it is possible to use nTMS to map the motor cortex in pediatric patients with refractory epilepsy. Our overall success rate was 69%, and patients who failed mapping were most likely too young and, as a result, had neurophysiology that was poorly suited to TMS. Navigated TMS-based motor maps were not affected by the anatomic location of the epileptic focus. RMT was typically higher than in adult populations. All patients were able to tolerate the study to its completion, and no patient complained of discomfort during mapping that required reduction in stimulator output. Navigated TMS-based motor mapping is a valuable tool in the pre-surgical management of pediatric patients with refractory epilepsy.

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Appendix I - Dataset

Table A: Demographic and Clinical Characteristics

Patient	Date of Study	Age at time of study	Sex	Type of epilepsy	Other Diagnoses
A	9/13/2012	4	Female	Epilepsy (HCC)	none
B	11/8/2012	12	Female	medically refractory epilepsy	none
C	4/30/2015	17	Male	refractory epilepsy	hemiparesis, nephrolithiasis, hematuria, foot deformity
D	6/18/2015	8	Male	refractory epilepsy	ADHD
E	6/18/2015	8 months	Male	refractory epilepsy (possibly due to a tumor)	tuberous sclerosis
F	10/1/2015	5	Female	refractory epilepsy	none
G	1/21/2016	13	Male	refractory epilepsy	none
H	5/5/2016	16	Male	refractory epilepsy	none
I	6/30/2016	10	Female	Epilepsia partialis continua (HCC)	none
J	5/26/2016	7	Male	focal epilepsy and executive dysfunction in the setting of known frontal perinatal stroke	behavioral disorder
K	8/23/2018	2	Male	refractory epilepsy	none
L	1/10/2019	15	Female	refractory epilepsy	perinatal infarct
M	3/27/2012	3	Male	localization-related focal partial epilepsy	skull defect, behavioral disorder

Table B: Clinical Characteristics

Patient	Location of Focus	Antiepileptics on board at time of mapping	Complications
A	focal cortical dysplasia of left frontal lobe in supplementary motor area	VIMPAT (lacosamide)	right foot drop

B	right frontal lobe	TRILEPTAL (oxcarbazepine), TOPAMAX (topiramate), ATIVAN (lorazepam)	none
C	left paracentral lobule lesion	ONFI (clobazam)	none
D	right parietal lobe	ONFI (clobazam) + ZONEGRAN (zonisanide) + ATIVAN (lorazepam) + APTIOM (eslicarbazepine) +VIMPAT (lacosamide) + KLONOPIN (clonazepam)	none
E	right posterior paracentral lobule and bilateral frontal/temporal lobes	KEPPRA (levetiracetam) + SABRIL (vigabatrin)	none
F	right frontal cortical dysplasia	LAMICTAL (lamotrigine)	none
G	left frontoparietal	VIMPAT (lacosamide), KEPPRA (levetiracetan), ATIVAN (lorazepam), FYCOMPA (perampanel)	none
H	right frontal lobe	ONFI (clobazam), DEPAKOTE (divalproex), FELBATOL (felbamate), ATIVAN (lorazepam), TRILEPTAL (oxcarbazepine)	none
I	frontal insular cortical dysplasia	TEGRETOL (carbamazepine), LAMICTAL (lamotrigine), ATIVAN (lorazepam), ONFI (clobazam), DEPACON (valproate)	none
J	right frontal cortex	ATIVAN (lorazepam)	none
K	right frontal cortex	none	none
L	left parietal occipital	TEGRETOL (carbamazepine), ONFI (clobazam), DIASTAT ACUDIAL (diazepam), ATIVAN (lorazepam)	none
M	left frontal cortex	none	none

Table C: Clinical Characteristics. The registration time for each patient was 15:00 minutes.

Patient	**Seizure freedom outcomes**		**Duration of Examination**	**DTI (Y/N)**	**RMT (%)**	**Peeling Depth (mm)**	**Number of Pulses**	**Successful?**
	Engel Class	ILAE Class	Total Duration					
A	I	I	0:38:59	Yes	40	13.4	191	Yes
B	I	I	0:20:32	Yes	50	16.1	160	Yes
C	I	II	0:33:01	Yes	40	19.8	375	Yes
D	III	IV	0:40:06	Yes	50	18.2	413	Yes
E	II	III	0:54:17	Yes	40	9.7	209	No
F	I	I	0:19:11	Yes	40	7.6	92	Yes
G	II	IV	0:28:52	Yes	50	17.6	210	Yes
H	II	IV	0:55:55	Yes	45	21.8	637	Yes
I	N/A	N/A	0:32:34	No	35	19.5	350	Yes
J	I	I	0:25:42	yes	45	15.5	152	No
K	I	I	0:20:03	yes	51	11.5	46	No
L	TBD	TBD	0:35:35	yes	45	18.9	235	Yes
M	I	I	0:21:22	yes	41	16.4	88	No

Appendix II - Supplemental Tables and Figures

Table 1: Clinical/Demographic Variables. The values for clinical and demographic variables in the study patient population are noted in this table.

Table 1:	Value	Frequency
Clinical/Demographic Variables		
Total	13	
Male	8	62%
Female	6	46%
Age (median)	7.5	58%
Age (range)	0-17	
DTI (Yes)	13	100%
DTI (No)	0	0%
Diagnosis		
medically refractory epilepsy (intractable epilepsy or pharmaco-resistant epilepsy)	13	100%
Location of Focus		
left frontal	5	38%
left parietal	2	15%
right frontal	5	38%
right parietal	1	8%
Antiepileptics on Board at time of Mapping		
ONFI (clobazam)	3	23%
VIMPAT (lacosamide)	3	23%
KEPRA (levetiracetam)	2	15%
other	10	77%
none	2	15%
Seizure Freedom Outcomes		
Engel class 1	7	54%
Engel class 2	3	23%
Engel class 3	1	7.7%
Engel class 4	0	0.0%
ILAE class 1	6	46%
ILAE class 2	1	7.7%
ILAE class 3	1	7.7%
ILAE class 4	3	23%

Engel Score (median, standard deviation)	1	0.69

Table 2: Stimulus Parameters. The median and average stimulus parameters tabulated from each patient are noted.

Table 2:	median	standard deviation
Stimulus Parameters		
Duration of examination	0:32:34	0:12:13
E-field max value (V/M)	128.00	46.62
Stimulus Intensity	60%	19%
Average Number of Pulses	229	165
Peeling Depth (mm)	16.25	4.77

Table 3: Outcome. The overall binary outcome for our study is listed in this table.

Table 3:	Value	Frequency
Outcome		
Overall Success		
Yes	10	77%
No	3	23%

Table 4: Why no? This table describes factors that may affect the success of nTMS in a pediatric patient.

Table 4: Why No?	**Overall Success**		**Statistical Test**	**p-value**
Variable	Yes (n=10, 77%)	No (n=3, 23%)		
Age (mean, SD)	11.1 (1.79)	3.0 (1.53)	t-statistic = 1.74	0.110
Gender			chi squared = 2.44	0.118
Male	5	3		
Female	5	0		
Location of focus			chi squared = 1.73	0.188
frontal	6	3		
parietal	4	0		

Figure 3: Overall Success. The overall success for our study is noted in this pie chart. N=9 patients were successful and n=4 patients were not.

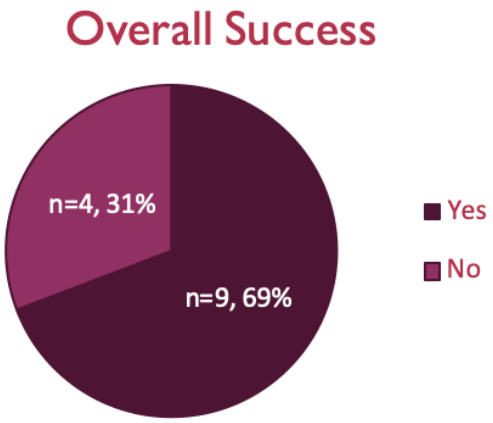

Figure 4: Mean Successful Stimulus Latency for each muscle group. For each of the 9 patients, we noticed a repeatable stimulus latency between 10-30 ms.