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Persistent uncrossed corticospinal connections in patients with intractable focal epilepsy

Harper L. Kaye [a,b], Roman Gersner [a,b], Aaron D. Boes [c], Alvaro Pascual-Leone [d], Alexander Rotenberg [a,b,d,*]

[a] Neuromodulation Program, Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Boston, MA, USA
[b] F.M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, MA, USA
[c] Neuromodulation Program, Division of Pediatric Neurology, Department of Pediatrics, University of Iowa, Iowa City, IA, USA
[d] Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Department of Neurology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA

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ABSTRACT

Corticospinal connections may be bilateral at birth, but a predominantly unilateral and crossed pattern develops by the toddler years. Acquired injury can alter the normal development of laterality such that uncrossed corticospinal connections persist, particularly if the injury is early in life and involves the motor system. Whether other developmental insults, such as childhood epilepsy, affect the development of crossed laterality in the motor system is unknown, although this topic has relevance for understanding the broader impact of epilepsy on brain development. Accordingly, in a cohort of children with intractable focal epilepsy, we tested by neuronavigated transcranial magnetic stimulation (nTMS) whether childhood epilepsy is associated with persistent uncrossed corticospinal connections. Specifically, we hypothesized that in contrast to early-life neuroclastic corticospinal tract injury that induces preservation of uncrossed corticospinal connections in the contralesional hemisphere, uncrossed corticospinal connections will be preserved in the epileptic hemisphere where the corticospinal tract is intact, but overstimulated by ongoing seizures and epileptic interictal discharges. Motor cortex mapping was performed by nTMS as part of a clinical presurgical evaluation, and the analysis was limited to patients with radiographically intact motor cortices and corticospinal tracts. Given that foot motor cortex representation is often bilateral, we focused on the lateralization for the tibialis anterior muscle cortical motor representation and its relation to the seizure focus. We demonstrate preserved uncrossed corticospinal connections for the tibialis anterior region of the hemisphere affected by the epilepsy. These findings indicate a pathologically preserved immature motor lateralization in patients with epilepsy and suggest that developmental processes associated with hemispheric lateralization are affected by epilepsy.

1. Introduction

Cortical stimulation studies provide insight into normal neurophysiological changes that occur during motor system maturation, particularly with respect to the development of crossed and uncrossed corticospinal motor pathways. Maturation of the corticospinal tract typically progresses from bilateral projections of the motor cortices at birth to a predominately unilateral crossed projection by the toddler years, where the right motor cortex controls the left body and the left motor cortex controls the right body [1–3]. While corticospinal connections are overwhelmingly crossed in children after the toddler years, sometimes uncrossed connections remain in older children and adults, particularly for the foot [4]. Better motor function is associated with strictly crossed control of limb movement, with poor motor function more likely to be associated with uncrossed or bilateral innervation [5].

Studies of normal development of motor system laterality have laid the groundwork for understanding deviations from the normal pattern. Unilateral injury to the motor system early in development is associated with preserved uncrossed corticospinal connections in the spared hemisphere. The functional role of these uncrossed corticospinal connections in motor recovery is not known, but published reports indicate that uncrossed corticospinal projections that normally regress or prune during infancy persist after injury [1]. Whether these persistent uncrossed corticospinal projections aid in recovery or negatively impact motor performance is not fully understood, but improved functional recovery seen with early-life motor system lesions may reflect robust bilateral

Abbreviations: APB, abductor pollicis brevis; EEG, electroencephalogram; EMG, electromyography; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; MEP, motor evoked potential; nTMS, neuronavigated transcranial magnetic stimulation; rMT, resting motor threshold; TA, tibialis anterior; TA-R, right tibialis anterior; TA-L, left tibialis anterior.

* Corresponding author at: Neuromodulation Program, Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, 300 Longwood Avenue, Fegan 9, Boston, MA, USA.
E-mail address: alexander.rotenberg@childrens.harvard.edu (A. Rotenberg).

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motor innervation in the neonatal period such that preserved uncrossed corticospinal projections compensate for the injured side [5].

While many studies have investigated the laterality of the motor system after focal acquired injury such as stroke [6,7], how a developmental disorder like childhood epilepsy without any gross lesion of the motor system affects motor development and specifically the development of corticospinal laterality is unknown. This topic is important as it may provide insight into the biology of cortical development and lateralization more broadly in the cerebral cortex in patients with focal epilepsy. Here, we evaluate motor cortex laterality using navigated transcranial magnetic stimulation (nTMS), a method for focal noninvasive cortical electrical stimulation where small intracranial electrical currents are generated by a powerful extracranial fluctuating magnetic field. nTMS is an FDA-approved method for presurgical mapping of the motor cortex that is safe, well tolerated, and comparable in spatial resolution to fMRI [8,9] and the current gold standard of intraoperative motor mapping by direct current stimulation cortical stimulation [1].We thus test whether and where uncrossed corticospinal projections persist in children with intractable focal epilepsy who are without structural corticospinal lesion. Specifically, we hypothesized that in contrast to early-life neuroclastic corticospinal tract injury that induces preservation of uncrossed corticospinal connections in the contralesional hemisphere, uncrossed corticospinal connections will be preserved in the epileptic hemisphere where the corticospinal tract is intact, but overstimulated by ongoing seizures and epileptic interictal discharges.

2. Materials and methods

Study participants were children with intractable epilepsy being evaluated for resective epilepsy surgery, who underwent functional motor mapping by nTMS. Our inclusion criteria required the following: (1) focal, unilateral seizures, as assessed by EEG and seizure semiology; (2) absence of MRI lesion in the region of the motor cortex or corticospinal tract; and (3) preserved uncrossed tibialis anterior representation in only one hemisphere. For patients who met these criteria (Table 1), we evaluated whether the uncrossed muscle representation was on the same side as the epileptic focus. Verbal and written consent was obtained from each patient's parent or legal guardian prior to stimulation.

Patients also underwent presurgical neuropsychological testing administered by a clinical neuropsychologist with specialized training in pediatric epilepsy. Scores were obtained from the Grooved Pegboard Task, designed to assess fine motor performance for both the dominant and nondominant hand. Fine motor deficit was defined as a patient's performance being equal to or greater than two standard deviations below the mean of the normative population sample [10].

Intellectual functioning was assessed using one of the following measures: Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition, Wechsler Intelligence Scale for Children-Fourth Edition, Wechsler Intelligence Scale for Children-Fifth Edition, or Wechsler Adult Intelligence Scale-Fourth Edition [11–14].

Table 1
Summary of patients with ipsilateral corticospinal tract connectivity in only one hemisphere, who met the predefined criteria (Fig. 1, red outline; n = 21): (1) age at time of visit; (2) sex; (3) age of first reported seizure; (4) seizure onset zone; (5) underlying etiology; (6) seizure semiology as defined by the International League Against Epilepsy 2017 criteria; (7) seizure frequency classified by more than one seizure per day, less than one seizure per day but multiple seizures a week/per month, and one to two seizures per year; (8) presence or absence of a fine motor deficit in the dominant hand; (9) metrics of patient verbal IQ; and (10) nonverbal IQ.

Age (yrs)	Sex (F/M)	Handedness (R/L/A)	Age of seizure onset (yrs)	Seizure onset zone	Etiology	Semiology at onset	Frequency	Fine motor deficit? (Y/N)	Verbal IQ	Nonverbal IQ
1	F	R	0	Right frontal	FCD	Focal motor	>Daily	N/A[a]	N/A[a]	N/A[a]
5	M	L	1	Left frontal	FCD	Focal motor	>Daily	Y	66	65
7	F	R	3	Left parietal	Stroke	Focal motor	>Daily	N	76	97
7	M	R	6	Right insular	FCD	Dyscognitive	>Daily	N	108	112
8	F	R	4	Left posterior frontal, parietal, temporal	MCD	Focal sensory	Weekly to monthly	Y	86	103
9	F	R	8	Right frontal temporal	Rasmussen's encephalitis	Focal motor	>Daily	Y	111	94
10	M	A	0	Right temporal	TSC2	(1) Focal sensory; (2) focal motor	>Daily	Y	50	49
10	M	L	4	Left frontoparietal	Stroke	Focal motor	>Daily	Y	62	57
11	F	R	5	Left parietal	FCD	Focal sensory	Weekly to monthly	Y	102	117
11	F	R	0.75	Right temporal	Unknown	(1) Dyscognitive; (2) focal motor	>Daily	N	100	97
12	M	L	0	Left mesial	Stroke	Focal motor	Weekly to monthly	Y	111	105
12	F	R	1.5	Right frontal	Unknown	Focal motor	>Daily	Y	89	98
13	M	R	9	Right temporoparietal junction	Unknown	(1) Dyscognitive; (2) focal sensory	Weekly to monthly	N	63	77
13	M	R	1.2	Right posterior temporal	Unknown	Dyscognitive	>Yearly	Y	121	112
15	M	R	6	Right frontoparietal	Unknown	Focal motor	>Daily	N	59	64
16	M	L	10	Left temporal lobe	Stroke	(1) GTC; (2) dyscognitive	Yearly	N	64	53
17	M	R	10	Right frontotemporal	Stroke	Dyscognitive	Weekly to monthly	N	114	88
17	F	R	4	Right frontal medial	Stroke	Focal motor	Weekly to monthly	Y	94	91
17	M	A	11	Right temporoparietal	Stroke	Dyscognitive	Weekly to monthly	Y	105	109
18	F	R	12	Left temporal	Nonlesional; unknown	(1) Focal motor; (2) GTC	Weekly to monthly	N	100	92
18	F	L	0	Right frontoparietal	Unknown	Sensory aura[b]	>Daily	Y	132	105

Abbreviations: years (yrs), female (F), male (M), right handed (R), left handed (L), ambidextrous (A), presence of fine motor deficit (Y), absence of fine motor deficit (N), focal cortical dysplasia (FCD), multiple focal cortical dysplasias (MCD), tuberous sclerosis complex-type II (TSC2), generalized tonic–clonic (GTC).

[a] Neuropsychological evaluation preformed ~14 month post-nTMS visit.

[b] Sensations of light headedness.

The review of medical records was approved by the Boston Children's Hospital Internal Review Board (IRB-P00020115).

Between the two patient groups, verbal and nonverbal IQs were compared by Students *t* test, unpaired. Chi squared comparisons of proportions between the two groups for handedness, sex, age of seizure onset, seizure frequency, semiology at onset, proximity of affected lobe to M1, and fine motor deficit were performed to identify any significant contributory factors.

2.1. Neuronavigated TMS

Each patient's MRI was converted to a three-dimensional head surface and brain reconstruction using Nexstim 4.3 software (Nexstim, Finland). Surface EMG electrodes were placed on the right and the left abductor pollicis brevis, deltoid, and tibialis anterior muscles. A ground electrode was placed on the underside of the right forearm. With single pulse nTMS, stimuli were applied at scalp sites overlying the motor cortex, while motor evoked potentials (MEPs) were recorded bilaterally from the abductor pollicis brevis, deltoid, and tibialis anterior by surface electromyography. The nTMS unit was operated using a figure-of-eight coil with frameless stereotaxy. Resting motor threshold (rMT), operationally defined as the minimum machine output necessary to elicit a response from the abductor pollicis brevis, contralateral to the stimulated hemisphere, of 50 μV, on ≥50% of trials, was determined using Nexstim guidance software. Tibialis anterior MEPs were obtained by stepwise increase in stimulation intensity from abductor pollicis brevis rMT such that >50-μV tibialis anterior MEPs were elicited in 100% of trials. rMT determination and motor mapping were performed separately in each hemisphere.

2.2. Analysis

Each patient's MRI and clinical data were reviewed by the research team (HK, AR). Those subjects who met inclusion criteria were sorted into two categories: (1) bilateral tibialis anterior motor cortex representation ipsilateral to seizure focus and (2) bilateral tibialis anterior motor cortex representation contralateral to seizure focus. Proportions of total were compared by chi squared analysis.

3. Results

Of 137 patients (10 months–23 years) who had nTMS for presurgical planning, 21 patients (11.8 ± 4.6 years, age range: 1–18 years) met the predefined criteria for the analysis (Fig. 1). Seventy-six patients had the tibialis anterior mapped in both hemispheres, and 63 of those 76 had a unilateral seizure focus. Preserved ipsilateral tibialis anterior motor cortex representation, in only one hemisphere, was found in 25 of the 63 patients with a unilateral seizure focus. Of the 25 who had preserved ipsilateral tibialis anterior representation in only one hemisphere, 4 were excluded due to radiographic lesions of the corticospinal tract and/or motor cortex (lesion including the precentral gyrus n = 3, bilateral periventricular leukomalacia n = 1). In total, 21 patients met criteria for tibialis anterior motor representation in one hemisphere (Fig. 2). Among these patients, 20 out of 21 (95%) had the preserved ipsilateral corticospinal signal in the epileptic hemisphere (chi square > 11.7; $P < 0.001$).

Comparisons between patients with ipsilateral CST connections persisting in the epileptic hemisphere (Fig. 1, red outline; Table 1) and patients with strictly crossed CST connectivity (Fig. 1, green outline; Table 2) revealed no difference ($P > 0.05$, n.s.) in a range of measured parameters. There was no difference in the mean age at time of exam, age a time of seizure onset, seizure frequency, seizure focus location (if organized by lobe), or seizure etiology Additionally, there was no difference in verbal and nonverbal IQ scores between the two groups.

4. Discussion

In patients with epilepsy who have a unilateral seizure focus, we find that preserved uncrossed corticospinal connectivity for the foot is significantly more likely in the epileptic hemisphere than in the nonepileptic hemisphere. These results suggest that a pathologically preserved immature corticospinal connectivity may accompany epilepsy. We thus hypothesize as to why the normal development of crossed motor laterality was not seen in these patients, specifically from the affected hemisphere.

One explanation for our findings is that CST lateralization is disrupted by persistent seizures, interictal discharges, or aberrant cortical excitability adjacent to the seizure focus. Thus, immature connections may be

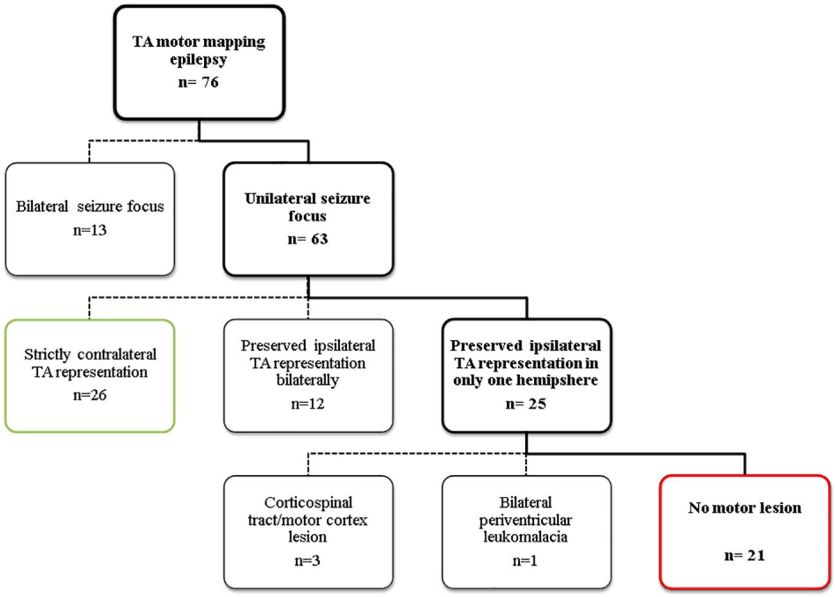

Fig. 1. Inclusion criteria and analysis. Twenty-one patients met the predefined criteria for TA motor representation in only one hemisphere (outlined in red). Among these patients, 20 out of 21 (95%, chi square > 11.7; $P < 0.001$) had the preserved ipsilateral corticospinal signal in the epileptic hemisphere. Patients with strictly contralateral corticospinal tract TA representation in both the healthy and the epileptic hemisphere are outlined in green.

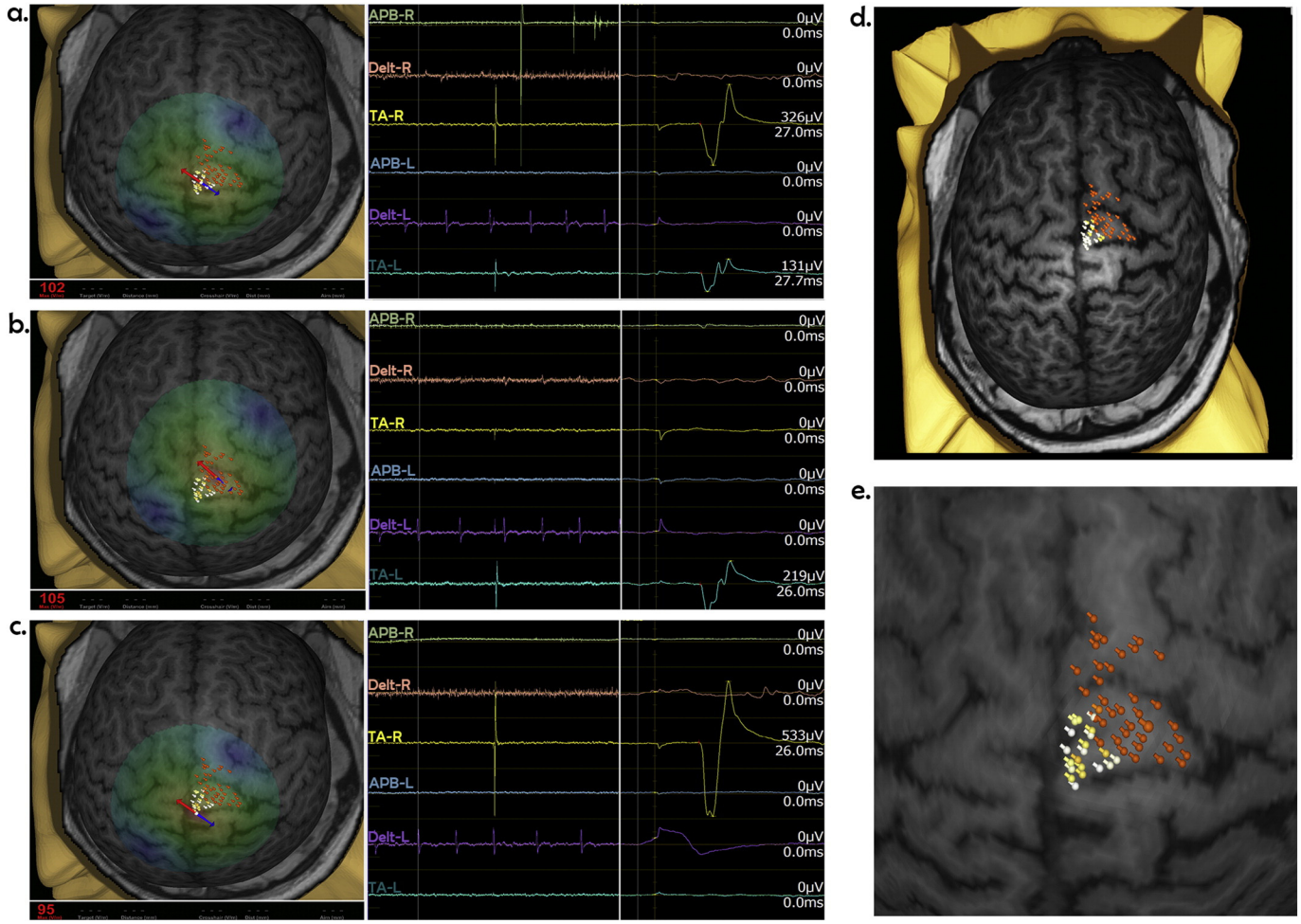

Fig. 2. Preserved bilateral foot motor cortex representation in the right hemisphere in a patient with a right hemisphere seizure focus. *Left panel:* An approximation of stimulating electric field induced by nTMS is displayed on a 3D reconstruction the patient's cortex. Field center is indicated by the junction between the red and blue arrows indicating the direction of induced current. The color coding in the composite map indicates left TA (TA-L) activation in orange, right TA (TA-R) activation in white, and bilateral TA activation in yellow. (a) Sample TA-L MEP (teal deflection) and TA-R MEP (yellow deflection) showing bilateral TA motor cortex representation resultant from right hemisphere stimulation. (b) Sample TA-L MEP (teal deflection) resultant from right hemisphere stimulation. (c) Sample TA-R MEP (yellow deflection) resultant from right hemisphere stimulation showing ipsilateral corticospinal foot connectivity. *Right panel:* (d) Color-coded right hemisphere composite map of the TA-L in orange, TA-R in white, and bilateral TA in yellow. (e) Enlarged view of the stimulation sites eliciting left and right TA MEPs in the right hemisphere.

maintained by mechanisms of use-dependent synaptic plasticity [15,16] or by use-dependent myelination of the corticospinal tract [15,17–19]. An extension of these hypotheses is that the likelihood of preserved ipsilateral connectivity is proportional to some patient characteristics, such as seizure frequency, age of epilepsy onset, or proximity of the seizure focus to the motor strip. Yet, for now, these will have to remain hypotheses without support of data as we found no difference between the patient-specific characteristics summarized in Tables 1 and 2. This may be a sample size issue that can be resolved with prospective surveillance of the focal epilepsy population by nTMS, which will certainly increase sample size (although this is beyond the scope of the present report). Alternatively, preserved ipsilateral CST connectivity may be an all-or-none phenomenon to which undescribed patient characteristics predispose an individual with focal epilepsy. We anticipate the identification of a neurologic signal that governs pruning of ipsilateral CST connections and that is aberrant in patients with childhood focal epilepsy to be the work of near-future experiments.

An alternative explanation for preserved uncrossed motor connectivity in the epileptic hemisphere is that residual uncrossed corticospinal projections are normally present but effectively inhibited over the course of development and become pathologically disinhibited in association with epilepsy. Such physiology may be governed by cortical inhibitory tone, akin to the visual cortex critical period that is determined by the maturation of specific GABA circuits [20]. We thus hypothesize that similar maturation of GABA-mediated cortical inhibition is aberrant in some epilepsies and particularly in the hemisphere that contains the seizure focus where the critical period may be extended by ongoing seizures. Plausibly, regional insufficient GABA-mediated inhibition in this setting also accounts for the seizures arising in the epileptic hemisphere.

Importantly, the abnormal development of laterality associated with pediatric epilepsy likely extends beyond the motor system. This is in line with fMRI studies showing less hemispheric specialization in association with pediatric epilepsy [21–23].

Limitations of our study include (1) absent intraoperative confirmation of the laterality of the tibialis anterior motor cortex representation, although previous studies have shown excellent correspondence between nTMS and direct current stimulation mapping results [24]; (2) a focus on the pediatric population such that we cannot address whether the development of crossed laterality in the motor system is delayed beyond adolescence or never develops; and (3) restriction of analysis to the tibialis anterior muscle. We recognize as well that bilateral corticospinal connections may in fact exist in both hemispheres, although the threshold for activating the ipsilateral corticospinal connections may be greater in one hemisphere.

We anticipate scientific extensions of this study to include a similar analysis in patients with adult-onset epilepsy to address the

Table 2
Summary of patients with strictly crossed corticospinal tract connectivity (Fig. 1, green outline) who met all other predefined criteria (Fig. 1, green outline; n = 26): (1) age at time of visit; (2); sex (3) age of first reported seizure; (4) seizure onset zone; (5) underlying etiology; (6) seizure semiology as defined by the International League Against Epilepsy 2017 criteria; (7) seizure frequency classified by more than one seizure per day, less than one seizure per day but multiple seizures a week/per month, and one to two seizures per year; (8) presence or absence of a fine motor deficit in the dominant hand; (9) metrics of patient verbal IQ; and (10) nonverbal IQ.

Age (yrs)	Sex (F/M)	Handedness (R/L/A)	Age of seizure onset (yrs)	Seizure onset zone	Etiology	Semiology at onset	Frequency	Fine motor deficit? (Y/N)	Verbal IQ	Nonverbal IQ
8	M	R	4	Right centroparietal	FCD	Focal motor	>Daily	Y	108	112
10	M	R	7	Right anterior temporal	FCD	Focal motor	Weekly to monthly	N	63	85
11	M	R	6	Right frontal	Porencephalic cyst	Dyscognitive	Weekly to monthly	N	79	95
12	F	R	2	Left temporal	Sturge–Weber syndrome	(1) Focal sensory; (2) dyscognitive	Weekly to monthly	Y	102	117
12	F	R	9	Right frontal	FCD	Dyscognitive	Weekly to monthly	N	100	97
12	F	R	2.2	Left frontoparietal	Unknown	GTC	>Daily	N	114	104
12	F	R	3	Left frontal parietal	Unknown	Focal motor	>Daily	N	130	128
12	F	R	4	Left temporal	Unknown	Focal motor	Weekly to monthly	Y	89	98
12	M	R	11	Left frontoparietal	Stroke	Focal motor	>Daily	Y	78	74
12	M	L	0	Right temporal	Unknown	(1) Dyscognitive; (2) focal motor	Weekly to monthly	N	121	112
13	M	R	7	Left temporal	FCD	Dyscognitive	>Daily	N	95	84
14	M	R	6	Left temporal occipital	Unknown	(1) Dyscognitive; (2) GTC	>Daily	Y	95	91
15	F	L	6	Left parietal	Unknown	Focal motor	Weekly to monthly	N	76	92
15	F	R	1	Left temporal	Unknown	(1) Focal motor; (2) GTC	Weekly to monthly	Y	78	82
15	F	R	3	Left frontal	Unknown	Focal motor	>Daily	Y	84	79
17	M	R	6	Left frontal	MCD	Focal sensory	Weekly to monthly	Y	105	104
17	M	L	12	Right parietal	FCD	Focal motor	Yearly	N	103	94
17	F	R	1	Right frontal	FCD	Focal motor	Weekly to monthly	N	134	82
17	M	R	10	Left frontal	Cerebitis; meningitis	(1) Dyscognitive; (2) GTC	>Daily	Y	87	75
17	F	R	4	Right frontal medial	Stroke	(1) Focal motor; (2) GTC	Weekly to monthly	Y	126	117
17	M	L	7	Left temporal	Stroke	Dyscognitive	Weekly to monthly	N	95	105
18	M	R	9	Left parietal	Unknown	Focal motor	>Daily	Y	105	105
18	M	R	0	Left parietal	FCD	Focal sensory	>Daily	Y	110	75
22	F	R	14	Right frontal	TBI	Dyscognitive	Weekly to monthly	Y	72	79
22	F	A	1	Left frontal	FCD	focal motor	>Daily	Y	82	71
23	F	L	10	Left central parietal	Stroke	(1) Focal sensory; (2) focal motor	>Daily	N	93	104

Abbreviations: years (yrs), female (F), male (M), right handed (R), left handed (L), ambidextrous (A), presence of fine motor deficit (Y), absence of fine motor deficit (N), focal cortical dysplasia (FCD), multiple focal cortical dysplasia (MCD), traumatic brain injury (TBI), generalized tonic–clonic (GTC).

developmental aspect of motor laterality associated with epilepsy. Future work may focus on whether the persistent uncrossed corticospinal projections are lost with surgical resection of the epileptic focus or with other successful epilepsy treatment, and whether the age of either seizure onset or epilepsy surgery impacts this functional outcome.

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Conflicts of interest

AR is a cofounder and consults for Neuro'motion Inc., consults for NeuroRex Inc., and is a coinventor of a patent for real-time integration of TMS and EEG. AR receives or has received research support in the form of material and/or funding from Sage Pharmaceuticals, Eisai Pharmaceuticals, Neuropace, Soterix, Yaruide Medical, Roche, Novartis, and Brainsway. APL has consulted for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Magstim, Neosync, and Axilum Robotics, and is a coinventor of a patent for real-time integration of TMS, EEG, and MRI.

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