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Persistent uncrossed corticospinal connections in patients with intractable focal epilepsy

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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.

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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.