A systematic evaluation of intraoperative white matter tract shift in pediatric epilepsy surgery using high-field MRI and probabilistic high angular resolution diffusion imaging tractography

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OBJECTIVE Characterization of intraoperative white matter tract (WMT) shift has the potential to compensate for neuronavigation inaccuracies using preoperative brain imaging. This study aimed to quantify and characterize intraoperative WMT shift from the global hemispheric to the regional tract-based scale and to investigate the impact of intraoperative factors (IOFs).

METHODS High angular resolution diffusion imaging (HARDI) diffusion-weighted data were acquired over 5 consecutive perioperative time points (MR₁ to MR₅) in 16 epilepsy patients (8 male; mean age 9.8 years, range 3.8–15.8 years) using diagnostic and intraoperative 3-T MRI scanners. MR₁ was the preoperative planning scan. MR₂ was the first intraoperative scan acquired with the patient's head fixed in the surgical position. MR₃ was the second intraoperative scan acquired following craniotomy and durotomy, prior to lesion resection. MR₄ was the last intraoperative scan acquired following lesion resection, prior to wound closure. MR₅ was a postoperative scan acquired at the 3-month follow-up visit. Ten association WMT/WMT segments and 1 projection WMT were generated via a probabilistic tractography algorithm from each MRI scan. Image registration was performed through pairwise MRI alignments using the skull segmentation. The MR₁ and MR₂ pairing represented the first surgical stage. The MR₂ and MR₃ pairing represented the second surgical stage. The MR₃ and MR₄ (or MR₅) pairing represented the third surgical stage. The WMT shift was quantified by measuring displacements between a pair of WMT centerlines. Linear mixed-effects regression analyses were carried out for 6 IOFs: head rotation, craniotomy size, durotomy size, resected lesion volume, presence of brain edema, and CSF loss via ventricular penetration.

RESULTS The average WMT shift in the operative hemisphere was 2.37 mm (range 1.92–3.03 mm) during the first surgical stage, 2.19 mm (range 1.90–3.65 mm) during the second surgical stage, and 2.92 mm (range 2.19–4.32 mm) during the third surgical stage. Greater WMT shift occurred in the operative than the nonoperative hemisphere, in the WMTs adjacent to the surgical lesion rather than those remote to it, and in the superficial rather than the deep segment of the pyramidal tract. Durotomy size and resection size were significant, independent IOFs affecting WMT shift. The presence of brain edema was a marginally significant IOF. Craniotomy size, degree of head rotation, and ventricular penetration were not significant IOFs affecting WMT shift.

CONCLUSIONS WMT shift occurs noticeably in tracts adjacent to the surgical lesions, and those motor tracts superfi-

ABBREVIATIONS AB = anterior bundle; AH-CING = anterior horizontal CING; CING = cingulum; CSD = constrained spherical deconvolution; DNET = dysembryoplastic neuroepithelial tumor; DTI = diffusion tensor imaging; EPI = echo-planar imaging; ET-CO₂ = end-tidal carbon dioxide; FOD = fiber orientation distribution; Fx = fornix; HARDI = high angular resolution diffusion imaging; ICDV = intracranial volume; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; IOF = intraoperative factor; MB = middle bundle; OR = optic radiation; PB = posterior bundle; PH-CING = parahippocampal CING; PS = probability of superiority; PT = pyramidal tract; ROI = region of interest; R²_{mar} = marginal R²; SE = standard error; SLF = superior longitudinal fasciculus; UF = uncinate fasciculus; WMT = white matter tract.

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cially placed in the operative hemisphere. Intraoperative probabilistic HARDI tractography following craniotomy, durotomy, and lesion resection may compensate for intraoperative WMT shift and improve neuronavigation accuracy.

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KEY WORDS diffusion tractography; high angular resolution diffusion imaging; intraoperative high-field MRI; pediatric epilepsy surgery; probabilistic tractography algorithm; white matter tract shift

THE major shortcoming of surgical neuronavigation systems utilizing preoperatively acquired images is the inability to account for intraoperative brain shift.^{33,37,42,47,49} Brain shift occurs as a result of various interactive factors, such as gravity, brain edema, loss of CSF, and lesion resection.^{33,37,42,47} While most notable at the cortical surface, it can also occur at the white matter level. Understanding brain shift has important practical implications, including maximizing lesion resection and preserving eloquent cortical regions and white matter tracts (WMTs).^{42,49}

Diffusion tractography is an MRI postprocessing technique that provides virtual reconstructions of WMT anatomy based on brain diffusion information.^{4,36} The technique adopted in neurosurgery typically involves diffusion tensor imaging (DTI) data acquisition and a deterministic tractography algorithm,^{10,12,38} but this approach is unable to accurately model diffusion over crossing fiber regions.^{10,29,38,55} More sophisticated diffusion-weighted MRI sequences^{1,3,21,53,54,56,57} and tractography algorithms^{6,7,44,52,55} have been developed to optimize resolution and estimation of fiber orientation over these regions.

High angular resolution diffusion imaging (HARDI) data are acquired using a higher diffusion gradient (b -value ≥ 3000 sec/mm²) and with a greater number of non-collinear diffusion directions (≥ 45 directions) than DTI data.^{1,32,54,55} HARDI acquisition therefore captures more high angular frequency details of the diffusion-weighted signal than a DTI acquisition, enabling a better estimate of the fiber orientation distribution (FOD) in each MRI voxel.^{53,54} Further, the use of a probabilistic tractography algorithm addresses the limitation of characterizing regions with uncertain diffusion estimated by providing the tractography results in the form of a probability distribution rather than a single best-fit estimate.^{6,7,44,55} Combined HARDI data acquisition and a probabilistic tractography algorithm (abbreviated as “probabilistic HARDI tractography” for the rest of this paper) is widely accepted as a more suitable method for in vivo WMT modeling and estimation for anatomical connectivity across the whole brain than DTI.^{6,7,25,38,52}

The emergence of operating suites with built-in MRI scanners, or intraoperative MRI, offers a brain shift compensation strategy by providing updated brain anatomy images when necessary.^{18,30,37} Diffusion tractography complements intraoperative MRI by permitting assessments of brain shift occurring at the WMT level.^{31,42,43,49}

Existing studies concerning evaluation of intraoperative WMT shift focused on adult brain tumor cases and single-WMT reconstruction, usually the pyramidal tract (PT), using deterministic DTI tractography.^{31,42,43,49} Evaluations were usually confined to analysis of preoperative MRI and an intraoperative postresection MRI. The im-

pacts of different intraoperative factors (IOFs) upon the WMT shift were inadequately addressed due to the limited data available. Only 1 study addressed the impact of dural opening on PT shift using additional intraoperative MRI acquisition in a patient subset.⁴⁹

In this study, we evaluated intraoperative WMT shift in the context of pediatric epilepsy surgery. We used data acquired from comparable preoperative, intraoperative, and postoperative high-field (3-T) MRI systems and generated several WMTs using probabilistic HARDI tractography.

This study had 2 aims. 1) The first aim was to quantify WMT shift across 3 surgical stages. Shift was assessed with respect to the operative and nonoperative hemispheres, proximity to the resection site, and the superficial compared with deeper segment of the WMT studied. We anticipated that greater WMT shift would be evident in the later surgery stages, in the operative hemisphere, closer to the resection site, and in the superficial rather than deeper WMT segments. 2) The second aim was to investigate the effects of 6 IOFs on WMT shifts: head rotation, craniotomy size, durotomy size, resected lesion volume, CSF loss via ventricular penetration, and brain edema. We predicted that the magnitude of WMT shift would be positively associated with each IOF, but the direction of the shift would be variable.

Methods

Patient Population

We recruited 16 children undergoing surgery for drug-resistant focal epilepsy at the Royal Children’s Hospital, Melbourne, Australia (8 male; mean age 9.8 years, range 3.8–15.8 years) for this prospective study. The study was approved by the hospital’s human research and ethics committee. Prior to study commencement, signed, informed consent was obtained from the patients’ parents or guardians and from cognitively competent patients older than 12 years old.

MRI Acquisition and Data Processing

Up to 5 perioperative MRI scans were acquired for each patient (Fig. 1), as follows:

- MR₁—preoperative MRI used for diagnosis and surgical planning, acquired several months before surgery (mean 3.8 months before surgery, range 4 days–6.8 months);
- MR₂—first intraoperative MRI scan, acquired with the patient’s head fixed in the surgical position, under anesthesia, prior to craniotomy;
- MR₃—second intraoperative MRI scan, acquired following craniotomy and durotomy, prior to lesion resection;

FIG. 1. Case 4. Axial T1-weighted MR images (**upper**) and corresponding 3D rendered skull images (**lower**) across 5 consecutive perioperative time points. The surgery was performed for resection of an angular gyrus DNET. The MR images are shown in anatomical convention to match the 3D skull renderings. MR₁ is the preoperative scan (head in a supine neutral position); MR₂, the intraoperative, pre-scalp incision scan (head rotated 90°); MR₃, the intraoperative, post-cranial and dural opening scan; MR₄, the intraoperative, post-lesion resection scan; MR₅, the 3-month postoperative scan (head in a supine neutral position). The donut-shaped markers on the 3D rendered skull images are radiopaque fiducial markers used for surgical navigation registration. The frontal and occipital skull indentations are artifacts arising from pin fixation of the surgical head frame. Figure is available in color online only.

- MR₄—third intraoperative MRI scan, acquired following lesion resection, prior to dura and skull closure;
- MR₅—postoperative MRI scan, acquired at the 3-month follow-up visit (mean 3.4 months after surgery, range 2.6–4.4 months).

MR₁ and MR₅ were acquired using a diagnostic 3T MRI scanner (Siemens Magnetom Trio) with a 32-channel head coil. MR₂, MR₃, and MR₄ were acquired using a 3-T movable Siemens intraoperative MRI scanner (IMRIS, Manitoba, Canada) with an 8-channel head coil in the operating room with radiofrequency shielding.

The MRI sequences required for this study included a T1-weighted anatomical sequence and a HARDI diffusion sequence. The anatomical sequence acquired was a T1-weighted high-resolution magnetization prepared gradient echo (MPRAGE) (for MR₁ and MR₅ scans, 256 × 256 acquisition matrix, FOV 250, 0.8 mm³ isotropic voxels, TR 1900 msec, TE 2.69 msec; for MR₂, MR₃, and MR₄ scans, 256 × 256 acquisition matrix, FOV 256, 1.0 mm³ isotropic voxels, TR 1800 msec, TE 2.19 msec). The HARDI diffusion data were acquired using the pulsed gradient spin echo (PGSE) sequence with a single-shot spin-echo, echo-planar imaging (EPI) read out, 60 noncollinear DW directions ($b = 3000 \text{ sec/mm}^2$), 7 b0 reference volumes, 54 contiguous slices, 2.3 mm³ isotropic voxels, TR 7600 msec, TE 110 msec. Additional T2-weighted turbo-spin echo (TSE) sequence with multiplanar reconstructions and case-specific T2-weighted 3D volumetric sequences were acquired at MR₁ and MR₅ (as per routine epilepsy workup and follow-up). The T2 volumetric sequences were also acquired at MR₂ (to assist surgical planning and intraoperative neuronavigation by fusing with the T1 volumet-

ric data) and at MR₄ (to assist postresection evaluation). They were the fluid attenuation inverse recovery (FLAIR) sequence, the dual inverse recovery (DIR) sequence, or the sampling perfection with application optimized with contrasts using different flip angle evolution (SPACE) sequence. The total acquisition times were approximately 45 minutes for MR₁ and MR₅, 35 minutes for MR₂, 20 minutes for MR₃, and 35 minutes for MR₄. MR₃ was the only study-specific intraoperative scanning session. The HARDI acquisitions were study specific, and increased MR₂ and MR₄ by about 10 minutes each. The added risks of scans to the patients for this study were considered small and included in the hospital's ethics committee-approved Parent/Guardian Information Statement Form.

The fiber orientation distribution (FOD) was estimated at each voxel of the HARDI diffusion data using the constrained spherical deconvolution (CSD) model of the MRtrix software package, version 0.2.12 (Brain Research Institute, Melbourne, Australia; software package download available at <http://www.nitrc.org/projects/mrtrix/>; user documentation can be found at <http://jdtournier.github.io/mrtrix-0.2/index.html>).^{52–54}

MR₁ through MR₅ scans were aligned using an in-house-developed automated registration procedure based on skull segmentation. Subvoxel, submillimeter accuracy of the registration procedure has been demonstrated in our previous publication.⁵

White Matter Fiber Tracking: Probabilistic HARDI Tractography

The following WMTs were reconstructed from HARDI

TABLE 1. Summary of patients' demographic and clinical characteristics and intraoperative information

Case No.	Pt Age (yrs)	Pathology	Head Position (°)	Lesion Side (Lt/Rt)	Lesion Site	Resect Lesion Vol (cm ³)	Cx Size (cm ²)	Dx Size (cm ²)	Avg. ET-CO ₂ (mm Hg)	Total IV Steroid Used (mg)	Ventricle Entered (Y/N)	Brain Edema (Y/N)
1	13.42	Gliosis	60	Lt	F	3.9	81.0	15.4	36.5	12	N	N
2	13.42	FCD	90	Lt	T	16.5	55.3	48.0	37.3	16	N	N
3	3.75	TSC	5	Rt	F, T*	9.5*	48.8	5.0†§	38.7	10.6	N	Y
4	15.83	DNET	90	Rt	F	13.5	32.4	27.5	34.3	11	N	N
5	15.50	Chronic encephalitis	90	Lt	F	12.4	82.5	73.5	36.7	16	N	N
6	12.25	Gliosis	90	Rt	T	20.7	33.8	28.0	34.7	10	Y	N
7	4.83	FCD w/ DVA	90	Lt	F	3.9	37.5	31.5	39.7	8	N	N
8	10.17	Nonspecific	90	Rt	T	46.7	30.0	24.8	38.5	16	Y	N
9	3.92	DNET	90	Lt	TPOJ‡	7.3	29.3	22.5	41.0	6	N	N
10	4.17	TSC	90	Rt	F	7.8	36.0	5.0§	34.3	8	N	Y
11	3.83	FCD	0	Lt	F	76.4	65.0	5.0§	42.0	3	N	Y
12	4.50	FCD	90	Lt	F, T, P, I*	163.3*	74.8	5.0§	35.5	6	N	Y
13	10.92	DNET	120	Rt	O	7.0	22.0	5.0§	36.3	4	N	Y
14	13.25	DNET	90	Lt	TPOJ‡	5.2	19.6	3.1§	32.3	8	N	Y
15	15.42	TSC	120	Rt	O	4.6	20.3	5.0§	34.3	16	N	Y
16	12.17	DNET	120	Rt	TPOJ‡	24.2	35.8	27.0	41.7	8	N	N

Cx = craniotomy; DVA = developmental venous anomaly; Dx = durotomy; EC = significant extra-axial collections/air; F = frontal; FCD = focal cortical dysplasia; I = insula; ICH = intracerebral hematoma; IV = intravenous; N = no; O = occipital; P = parietal; pt = patient; resect = resected; T = temporal; TSC = tuberous sclerosis complex; TPOJ = temporoparietooccipital junction; Y = yes.

* Multiple cortical lesions were resected in these cases. Combined volumes of these lesions are represented here.

† This case involved a separate craniotomy performed in the left hemicranium, without dural opening and brain resection.

‡ Temporoparietooccipital junction location included lesions involving either the subcortical white matter or cortical regions of the supramarginal gyrus, angular gyrus, posterior portions of the middle and inferior temporal gyri, or the fusiform gyrus.

§ Slit durotomy was performed in these cases.

diffusion data of each scan: pyramidal tract (PT), superior longitudinal fasciculus (SLF), optic radiation (OR), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UF), cingulum (CING), and fornix (Fx). The OR was generated in 3 bundles: anterior, middle, and posterior (AB-, MB-, and PB-OR). The CING was generated as an anterior horizontal (AH-CING) and a parahippocampal (PH-CING) segment.

All tracts were reconstructed using a knowledge-based, multiple region-of-interest (ROI) approach. The ROIs were defined manually by an experienced tractographer (the first author, J.Y.M.Y.). All tractography streamlines originated from the seed ROI and passed through a series of inclusion ROIs. Exclusion ROIs were placed in regions through which the studied WMT was known not to pass. Supplementary Table 1 summarized the ROIs defined for each WMT and WMT segments. Tractography was performed using the probabilistic tractography algorithm implemented in the MRtrix software package with default parameters (radius curvature 1 mm; stepsize 0.2 mm; minimum and maximum lengths 10 and 200 mm, respectively; FOD amplitude threshold 0.1 defined tracking termination). The reliability of this technical approach had previously been demonstrated.^{22,23,52}

Intraoperative Factor Definitions

The 6 intraoperative factors (IOFs) studied were:

- Head rotation angle (degrees): estimated angle of head rotation from the vertical line.
- Craniotomy size: measured from the patient's bone flap intraoperatively and expressed as an estimated surface area in square centimeters (cm²).
- Durotomy size: measured from the patient's dural opening intraoperatively and expressed as an estimated surface area in square centimeters (cm²). If only slit dural opening was performed due to presence of brain edema, the length of the opening was measured and multiplied by an assumed 1-cm opening width.
- Resected lesion volume: calculated from volumetric segmentation of the target resection region on preoperative MRI (in cm³).
- CSF loss via ventricular penetration: determined by whether the ventricular system was entered during lesion resection. The CSF losses through opening the subarachnoid CSF cisterns or performing arachnoid lysis were not considered.
- Presence of brain edema: judged intraoperative by the neurosurgeon observing brain swelling at the time of dural opening, immediately prior to performing the cranial and dural opening scan (MR₃), and during lesion resection.

Other intraoperative information collected included lesion location (side and lobar sites), total dosage of ce-

FIG. 2. Illustration of the analysis performed for the intraoperative WMT shift study. The effects of the 6 different IOFs were investigated across 3 pairs of MRI scans obtained over 4 consecutive time points (MR₁ to MR₄), representing the 3 surgical stages. The 3-month postoperative scans (MR₅ scans) (not shown in this figure) are used in cases with missing MR₄ scans. Three group analyses were performed for the 4 IOFs marked with asterisks (*). The remaining 2 IOFs are accounted for in the multiple intraoperative factors regression analyses carried out across the second and the third surgical stages. Non-OP = nonoperative; OP = operative; VP = ventricular penetrations.

rebral relaxation agents (diuretics/steroid) used, averaged end-tidal carbon dioxide (ET-CO₂) levels prior to all intraoperative MRI scans, the use of a brain retractor, and intraoperative complications, such as intra- or extraaxial hematoma or pneumocephalus.

Tract Shift Evaluation

WMT position was estimated using the centerline or skeleton of the tract. Tract shift was then quantified by measuring the distance between a pair of centerlines. The distance between a pair of centerlines was defined as the median of the distances between each voxel in one centerline and the closet voxel in the other centerline.

Data and Statistical Analysis

Linear mixed-effects regression, with patient ID as the random effect, was used to investigate the relationship between regional and global WMT shift and IOFs. Mixed-effects models were used to account for multiple longitudinal measurements obtained from the same individual. Figure 2 summarizes the data analysis scheme used to address both study aims.

WMT shift between MR₁ and MR₂ was used to assess the effect of head rotation, while shift between MR₂ and MR₃ was used to assess effects of cranial and dural opening size and the presence of brain edema. WMT shift between MR₃ and MR₄ (or MR₅ if MR₄ was not available)

was used to assess the effect of resected lesion volume, CSF loss, and the presence of brain edema.

Each IOF was examined in 3 ways: 1) comparing WMT shift in the operative and the nonoperative hemispheres, 2) comparing shift of WMTs adjacent to and remote to the resected lesion in the operative hemisphere (adjacent defined as those WMTs closer than 1 gyral boundary to the lesion), and 3) comparing shift of the superficial and deep segments of the PT in the operative hemisphere, where the seed ROI at the posterior limb of internal capsule was used to split the tract. The PT was chosen because it has both superficial and deep components.

The durotomy size models were estimated separately for “slit-opened” and “fully opened” durotomies. Group analyses were not possible for the “ventricular penetration” and the “brain edema” factors due to limited dichotomized patient subsets. Thus, these 2 IOFs were only accounted for in the multiple IOFs regression analysis (see statistical analysis below).

Statistical analysis was performed using the R software environment for statistical computing and graphics (R Core Team, 2013; <http://www.r-project.org/>). Supplementary Document 1 provides details on how to interpret all regression models used in this study. In brief, linear regression analysis accounting for a single IOF was first performed across all 3 pairs of MRI time points. Linear mixed-effects regression analysis accounting for multiple IOFs was then performed across the second and the third pairs of MRI time points (i.e., between MR₂ and MR₃ and between MR₃ and MR₄). This second step was necessary to dissect the independent effect of each IOF involved across the last 2 pairings of MRI time points. All regression analyses were performed with and without the intracranial volume (ICV) as a covariate.

For each regression model, the interaction between the group (i.e., operative/nonoperative, adjacent/remote, superficial/deep segment) and the designated IOF variable was first examined. If the interaction was not statistically significant, the regression model was tested without the interaction term to examine the main effects of either the group or the IOF variable. Statistics reporting included the regression coefficients, *p* value, and standard error (SE). A *p* ≤ 0.05 was defined as statistically significant. Effect size was reported by using the marginal R² (R²_{mar}) and associated probability of superiority (PS). A large effect size was defined as R²_{mar} > 0.14 and PS > 71; a medium effect size was defined as R²_{mar} > 0.05 and PS > 64; and a small effect size was defined as R²_{mar} < 0.01 and PS < 56.¹³

Results

All 16 patients underwent resection of the epileptogenic zone based on converging preoperative and intraoperative data, mostly entailing lesionectomy. Twelve patients were seizure free at the 3-month postoperative follow-up visit. No patient developed permanent motor and language deficits as a result of surgery. One patient developed an expected homonymous superior quadrantanopia, confirmed by formal visual field perimetry. The resection involved the anterior temporal lobe and AB-OR (Meyer's loop). Two patients demonstrated clinical signs suggestive of a

homonymous hemianopia, but visual field perimetry was not possible in these 2 cases due to the patients' young age. In one of these cases, there was an expected visual field deficit due to extensive multifocal corticectomy, involving the parietal and temporal cortices. In the other, the patient had undergone resection of an angular gyrus dysembryoplastic neuroepithelial tumor (DNET), adjacent to the sagittal striatum white matter, containing the OR. The sagittal striatum was intact on the immediate postresection scan (MR₄) but showed significant atrophic changes on 3-month follow up scan (MR₅). Proximity of the resection resulting in compromised vascular supply to the sagittal striatum was the likely cause.

The pathology of the resected epileptogenic lesions was focal cortical dysplasia (*n* = 4; 1 patient also had a developmental venous anomaly), tuberous sclerosis complex (*n* = 3), DNET (*n* = 5), chronic encephalitis (*n* = 1), cerebral gliosis secondary to a previous tumor resection (*n* = 2), and nonspecific findings (*n* = 1).

The intraoperative information is summarized in Table 1. The surgeries included a wide range of craniotomy and durotomy sizes and various lesion sites and sizes involving each cerebral hemisphere. The majority of the surgeries (10 of 16 cases) were performed with the patient's head rotated 90° laterally. Ventricular penetration occurred in 2 cases. Seven patients had brain edema before and during lesion resection. While the average ET-CO₂ level at the time of MRI scanning and average intravenous steroid doses were similar in all cases, the patients' head positions and transient elevations of ET-CO₂ levels contributed to the brain edema initially observed in these cases. Combined maneuvers of brief hyperventilation, head elevation, CSF release via pialotomy and arachnoid lysis, and slit durotomy were able to partially reverse the brain edema and allow for safe intraoperative imaging. Brain retractors were not required for resection in any case. None of the patients had significant intracerebral hemorrhage or extra-axial collection/pneumocephalus.

MR₁, MR₂, and MR₃ scans were acquired in all patients. Five MR₁ scans were acquired under general anesthesia. Four of the acquired MR₁ scans were excluded because they were acquired on a collocated 1.5-T MRI scanner through error. MR₄ scans were acquired in 13 of 16 patients. Three MR₄ scans were not performed due to safety and logistic issues related to the long surgical time. Two MR₄ scans were excluded from further analysis. One had poor image quality due to significant EPI susceptibility distortion and head motion artifact. The other had incomplete acquisition relating to MRI hardware malfunction. In the 5 patients without usable MR₄ scans, MR₅ scans were used instead for relevant data analysis. Two of these 5 MR₅ scans were acquired under general anesthesia. Visual inspection of the HARDI diffusion data revealed negligible image distortions related to eddy current and motion artifacts.

MRI data from the following pairs of scans were available for analyses: 12 pairs of MR₁ and MR₂ scans; 16 pairs of MR₂ and MR₃ scans; 11 pairs of MR₃ and MR₄ scans; and 5 pairs of MR₃ and MR₅ scans.

The average combined time spent for preparing the operating room, additional general anesthesia, and intraoperative MRI scanning time per case was 142 minutes (range

FIG. 3. Box and whisker plots showing the average WMT shift in both operative (OP) and nonoperative (Non-OP) hemispheres across each pair of MRI scans, representing the 3 surgical stages. The plots demonstrate similar degrees of WMT shift in both hemispheres. Greater degrees and ranges of WMT shift are observed across the third surgical stage.

105–190 minutes; on average 53 minutes per scan session, range 44–62 minutes).

Average WMT Shift in Both Cerebral Hemispheres

The results of average WMT shift in both cerebral hemispheres across the 3 surgical stages are summarized in Fig. 3.

The median of average WMT shifts resulting from change in head position (MR₁ and MR₂, *n* = 12) was 2.37 mm (range 1.92–3.03 mm) for the operative hemisphere and 2.12 mm (range 1.92–2.48 mm) for the nonoperative hemisphere.

The median of average WMT shifts after cranial and dural opening and in the presence of brain edema (MR₂ and MR₃, *n* = 16) was 2.19 mm (range 1.90–3.65 mm) in the operative hemisphere and 2.19 mm (range 1.70–2.43 mm) in the nonoperative hemisphere.

The median of average WMT shifts after lesion resection and in the presence of brain edema and ventricular penetration (MR₃ and MR₄ [or MR₅], *n* = 16) was 2.92 mm (range 2.19–4.32 mm) for the operative hemisphere and 2.62 mm (range 1.84–3.64 mm) for the nonoperative hemisphere.

Single-IOF Regression Analysis

ICV was not statistically significant (*p* > 0.2) when included as a covariate in any regression model, and thus regression analyses were reported without including ICV.

A summary of the IOF regression analysis results is provided in tabular form in Fig. 4. Only the statistically significant results are shown in the table (please refer to Supplementary Tables 2–4 for all analysis statistics). A significant interaction between IOF and a group variable is indicated by the coefficient “(β₃–β₂)”. A significant main effect for the IOF variable (in a model without interaction) is indicated by β₂, and a significant main effect of the group variable is indicated by “(β₁–β₀)”.

Large effect sizes were observed in all reported statistics showing significant findings (*R*²_{mar} = 0.15–0.76; *PS* = 72–99).

A significant interaction was identified between the “fully opened” durotomy size and the hemisphere, with the WMT shift increasing more rapidly with the durotomy size in the operative rather than in the nonoperative hemisphere (statistics are provided in the navy blue section in Fig. 4; Fig. 5 shows the regression plot). No significant interactions or main effects were observed in the “slit-opened” durotomy model analysis (*p* > 0.2). A significant interaction was also identified between the resected lesion volume and the hemisphere, with the WMT shift increasing more rapidly with the increase in resected lesion volume in the operative rather than in the nonoperative hemisphere (statistics in the green section in Fig. 4). No other significant interaction effects were observed.

The WMT shift increased with the durotomy size but did not depend on the lesion proximity (yellow section in

IOFs	Group Variables					
	Op vs Non-Op		Adjacent vs Remote WMTs		Superficial vs Deep Segment of PT	
	With Interaction	Without Interaction	With Interaction	Without Interaction	With Interaction	Without Interaction
Head rotation (°)	NS	($\beta_1 - \beta_0 \pm SE = 0.26 \pm 0.08$ ($p = 0.007$; $R^2_{mar} = 0.20$; PS = 76))	NS	NS	NS	($\beta_1 - \beta_0 \pm SE = -0.69 \pm 0.32$ ($p = 0.05$; $R^2_{mar} = 0.14$; PS = 71))
Craniotomy size	NS	NS	NS	NS	NS	($\beta_1 - \beta_0 \pm SE = 1.09 \pm 0.23$ ($p < 0.001$; $R^2_{mar} = 0.36$; PS = 86))
Durotomy size	($\beta_3 - \beta_2 \pm SE = 0.02 \pm 0.003$ ($p < 0.001$; $R^2_{mar} = 0.76$; PS = 99))	NR	NS	($\beta_2 \pm SE = 0.03 \pm 0.006$ ($p = 0.003$; $R^2_{mar} = 0.56$; PS = 95))	NS	($\beta_2 \pm SE = 0.03 \pm 0.01$ ($p = 0.05$; $R^2_{mar} = 0.54$; PS = 93))
Resected lesion vol	($\beta_3 - \beta_2 \pm SE = 0.009 \pm 0.002$ ($p < 0.001$; $R^2_{mar} = 0.36$; PS = 86))	NR	NS	($\beta_2 \pm SE = 0.02 \pm 0.007$ ($p = 0.04$; $R^2_{mar} = 0.29$; PS = 81)) ($\beta_1 - \beta_0 \pm SE = -0.46 \pm 0.16$ ($p = 0.01$))	NS	($\beta_2 \pm SE = 0.02 \pm 0.01$ ($p = 0.009$; $R^2_{mar} = 0.27$; PS = 80))

FIG. 4. Summary of single-IOF regression analysis results. The statistically significant results are shown with colored background. The colors correspond to the descriptions in the *Results* section; β_2 , ($\beta_1 - \beta_0$), and ($\beta_3 - \beta_2$) are the regression coefficients for the analyses. The patients with “slit-opened” durotomies ($n = 7$) were excluded from the durotomy size analysis. NR = nonrelevant statistics (given significant interaction is observed); NS = nonsignificant (results); op, non-op = operative, non-operative. Figure is available in color online only.

Fig. 4; $\beta_2 \pm SE = 0.03 \pm 0.006$, $p = 0.003$, $R^2_{mar} = 0.56$, PS = 95). The PT shift increased with the durotomy size, and the increase was greater in its superficial segment than in the deeper segment (light green section in Fig. 4; $\beta_2 \pm SE = 0.03 \pm 0.01$, $p = 0.05$; [$\beta_1 - \beta_0$] $\pm SE = 1.23 \pm 0.30$, $p = 0.004$, $R^2_{mar} = 0.54$; PS = 93). The WMT shift increased with the resected lesion volume, and the increase was greater in the tracts adjacent rather than remote to the lesion (cyan section in Fig. 4; $\beta_2 \pm SE = 0.02 \pm 0.007$, $p = 0.04$; [$\beta_1 - \beta_0$] $\pm SE = -0.46 \pm 0.16$, $p = 0.01$, $R^2_{mar} = 0.29$, PS = 81). However, the WMT shift increase with the resected lesion volume was independent of the PT segment depth (pink section in Fig. 4; $\beta_2 \pm SE = 0.02 \pm 0.01$, $p = 0.009$, $R^2_{mar} = 0.27$, PS = 80).

The WMT shift increase was greater in the operative hemisphere independent of the degrees of head rotation (red section in Fig. 4; [$\beta_1 - \beta_0$] $\pm SE = 0.26 \pm 0.08$, $p = 0.007$, $R^2_{mar} = 0.20$, PS = 76). The WMT shift increase was greater in the superficial PT segment independent of the head rotation degrees (orange section in Fig. 4; [$\beta_1 - \beta_0$] $\pm SE = -0.69 \pm 0.32$, $p = 0.05$, $R^2_{mar} = 0.14$, PS = 71), and the craniotomy size (purple section in Fig. 4; [$\beta_1 - \beta_0$] $\pm SE = 1.09 \pm 0.23$, $p < 0.001$, $R^2_{mar} = 0.36$, PS = 86).

TABLE 2. Multiple intraoperative factor regression analysis across MR₂ and MR₃, the second surgical stage

Independent Variable	RA w/ Interaction ($R^2_{mar} = 0.55$, PS = 94)	
	$\beta \pm SE$	p Value
β_0 (baseline intercept)	1.86 $\pm$ 0.17	<0.001
β_1 (op side)	-0.13 $\pm$ 0.08	0.11
β_2 (durotomy size)	0.007 $\pm$ 0.005	0.19
β_4 (presence of brain edema)	0.31 $\pm$ 0.16	0.08
β_5 (craniotomy size)	0.0005 $\pm$ 0.003	0.85
($\beta_3 - \beta_2$) (durotomy size:op side) interaction	0.015 $\pm$ 0.003	<0.001

RA = regression analysis.

Boldface type indicates statistical significance ($p \leq 0.05$). β_0 – β_5 are the regression coefficients of the independent variables used for the analysis.

The regression coefficient β_0 intercepts of all group main effect analyses performed were nonzero (all $p \leq 0.005$). This implied WMT shifts occurring in the nonoperative hemisphere, in the WMTs remote to the lesion, and in the deep segment of the PT in the operative hemisphere were all significantly greater than zero.

Multiple-IOF Regression Analysis Results

The analysis was performed using the hemispheric sides as the group variable. The results are summarized in Table 2 (across MR₂ and MR₃) and Table 3 (across MR₃ and MR₄ [or MR₅]). These analyses include additional group variables for edema and ventricular penetration.

Across MR₂ and MR₃

A significant interaction was detected between the durotomy size and the operative hemisphere ($p < 0.001$) across MR₂ and MR₃—the second surgical stage. This meant that increased durotomy size had resulted in significantly greater WMT shifts in the operative hemisphere than in the nonoperative hemisphere, independent of the

TABLE 3. Multiple intraoperative factor regression analysis across MR₃ and MR₄ (or MR₅), the third surgical stage

Independent Variable	RA w/ Interaction ($R^2_{mar} = 0.36$, PS = 86)	
	$\beta \pm SE$	p Value
β_0 (baseline intercept)	2.65 $\pm$ 0.20	<0.001
β_1 (op side)	0.15 $\pm$ 0.09	0.14
β_2 (resected lesion vol)	0.003 $\pm$ 0.003	0.33
β_4 (presence of brain edema)	-0.25 $\pm$ 0.28	0.39
β_5 (CSF loss via ventricular penetration)	-0.09 $\pm$ 0.40	0.83
($\beta_3 - \beta_2$) (resected lesion vol: op side) interaction	0.009 $\pm$ 0.002	<0.001

Boldface type indicates statistical significance ($p \leq 0.05$). β_0 – β_5 are the regression coefficients of the independent variables used for the analysis.

TABLE 4. Results summary with respect to the study hypotheses

Variables or Factor	Does the result support the hypothesis?
Result summary by group variables	
Op vs non-op hemisphere	Yes (across all 3 surgical stages)
Adjacent vs remote WMTs	Yes (across 3rd surgical stage)
Superficial vs deep PT segment	Yes (across 2nd surgical stage)
Result summary by intraoperative factors	
Head rotation (degrees)	No
Craniotomy size	No
Durotomy size	Yes* (across 2nd surgical stage)
Resected lesion volume	Yes* (across 3rd surgical stage)
CSF loss via ventricular penetration	No
Presence of brain edema	Trend (across 2nd surgical stage)

* Significant independent effect by multiple intraoperative factor regression analysis.

other 2 IOFs. The presence of brain edema was only marginally significant ($p = 0.08$). The craniotomy size was not a significant independent factor affecting the average WMT shift in the operative hemisphere ($p = 0.85$). A large effect size was observed for this analysis ($R^2_{\text{mar}} = 0.55$, $PS = 94$).

Across MR₃ and MR₄ (or MR₅)

A significant interaction was detected between the resected lesion volume and the operative hemisphere ($p < 0.001$; large effect size: $R^2_{\text{mar}} = 0.36$, $PS = 86$) across MR₃ and MR₄ (or MR₅)—the third surgical stage. This meant that increased resected lesion volume resulted in significantly greater WMT shifts in the operative hemisphere than in the nonoperative hemisphere, independent of the other 2 IOFs.

The analysis also suggested that neither the presence of brain edema nor ventricular penetration was a significant independent variable affecting the average WMT shift across MR₃ and MR₄ (or MR₅).

Direction of WMT Shift

The direction of WMT shift was variable and independent of the cortical surface brain shift. It was influenced by multiple interactive IOFs, such as the head position (i.e., gravity), presence of brain edema, ventricular penetration, and following lesion resection. Figures 6 and 7 and Video 1 show selected WMT shift images from one patient (Case 2), highlighting these pertinent findings.

VIDEO 1. Video clip demonstrating a 3D rotating file of Fig. 6.

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Discussion

In this study, we characterized WMT shift during the

FIG. 5. Average WMT shift examined by interaction analysis between “fully opened” durotomy size and the hemispheric group variable, across MR₂ and MR₃ scans (the second surgical stage). The gray-shaded areas on either side of the regression lines represent the 95% confidence intervals. The plot shows that significant interaction existed between the durotomy size and the hemispheric group variables. It implies that increased durotomy size is associated with greater degree of average WMT shift in the operative hemisphere (OP) than the nonoperative (Non-OP) hemisphere.

FIG. 6. Case 2. Overlapping consecutive perioperative MR images and ILF tractography showing the differences in the progressive cortical surface and subcortical WMT shifts over the course of the surgery. This 13-year-old boy's operation involved resection of a 16.5-cm³ left anterior and mesial temporal focal cortical dysplasia (lesion indicated by yellow area in A). He underwent a left temporal craniotomy with 90° lateral head position. A 55.3-cm² craniotomy and a 48.0-cm² durotomy were performed. The operation was uneventful. The ventricular system was not entered, and there was no visible brain edema. **A:** 3D rendered brain image reconstructed using the preoperative MRI, showing ILF tractography in both hemispheres and the targeted resecting lesion. The red line represents the coronal level of MR images displayed in B–D. **B–D:** Overlapped images of temporal stem portions of ILF from consecutive MRI pairs are displayed on top of the overlapped anatomical T1-weighted MR images. The ILFs from the 4 consecutive MRI scans are labeled with different colors (white for MR₁, green for MR₂, yellow for MR₃, and orange for MR₄). The coronal MR images are displayed in radiological convention with lateral orientation, simulating the surgical position. White arrows mark the direction of cortical surface brain shift. Colored arrows mark the directions of the ILF shift across each pair of MR images. The length of the arrows represents magnitude of the tract shift. The images demonstrate the directions of ILF shift occurred are variable and independent to the shift observed at the cortical surface. Figure is available in color online only.

course of epilepsy surgery by means of pairwise comparison of MRI scans performed over 5 perioperative time points. Eleven different association and projection WMT/WMT segments were reconstructed using CSD modeling of HARDI diffusion data and probabilistic tractography. The pairwise MRI comparisons enabled both the etiology and the magnitude of WMT shift to be studied across 3 consecutive surgical stages. We then examined and dissociated the impacts of 6 different IOFs on the tract shift, from a global hemispheric to a regional tract-based scale.

The study demonstrated a median value of average WMT shift occurring in the operative hemisphere of about

FIG. 7. Case 2. 3D reconstructions of ILF tractography centerlines over 4 consecutive MRI scans displayed on partially cut-away brain images. The color schemes of the centerlines reflect the 4 MRI time points (white for MR₁, green for MR₂, yellow for MR₃, and orange for MR₄). The selected viewpoints demonstrate the 3D changes in ILF shift orientations, progressively over the surgical course. **A:** Inferior view. **B:** Anterior view. **C:** Lateral view. **D:** Posteroinferior view. Figure is available in color online only.

2.5 mm for each of the 3 surgical stages. This equates to a total maximum shift of about 7.5 mm, if shift at each stage is in the same direction. Table 4 summarizes the results against the study hypotheses by the group variables and by the IOFs.

WMT shift was greater in the operative hemisphere (across all surgical stages), in the WMTs closer to the lesion (across the third surgical stage), and in the superficial rather than deeper segment of the PT (across the second surgical stage). Greater WMT shift occurred with increased durotomy size and increased resected lesion volume, independent of the effects of other IOFs. The presence of brain edema was only a marginally significant IOF. The hypothesis of greater WMT shift with increased craniotomy size is not supported. The results do not support the hypotheses of greater WMT shift in context of increased head rotation (as measured in degrees) and with increased CSF loss via ventricular penetration.

Direct outcome comparisons with other studies are constrained by differences in study design, MRI hardware, and methodological approaches of tractography and analysis of WMT shift. Our study is the first to address WMT shift in pediatric patients undergoing epilepsy surgery, incorporate data from a high-field intraoperative MRI scanner, and address WMT shift across multiple surgical stages.

The average WMT shift demonstrated in the operative hemisphere in our study is consistent with other reports.^{31,41–43,49} Nimsy et al.⁴¹ in 2005 reported a maximum 15-mm (either inward or outward) intraoperative WMT shift following resective surgery performed in 38 mixed adult and pediatric brain tumor and temporal lobe epilep-

sy cases. Maesawa et al.³¹ reported an average PT shift of 6.65 mm in 28 mixed adult and pediatric brain tumor cases. Romano et al.⁴⁹ investigated intraoperative PT shift in 20 adult brain tumor cases, with additional intraoperative MRI performed after dural opening, and reported a maximum 7.50-mm (either inward or outward) PT shift after dural opening. This is similar to our finding of total WMT shift for the first and the second surgical stages (6.68 mm). Further, Romano et al. also reported a maximum 9.70-mm inward to 11.00-mm outward PT shift after tumor resection. This is also consistent with our finding (11.00 mm). Despite the differences in the studied pathology, similar resection lesion volumes were reported in our study (26.4 cm³, range 3.9–163.3 cm³) and the other 2 studies reporting the lesion volumes (range 4.0–149 cm³).^{42,49}

The finding of WMT shift occurring in the nonoperative hemisphere is unique to our study. Other studies assessed image registration accuracy based on the assumption that negligible brain shift took place in the nonoperative hemisphere. This may not be true, because brain shift is a dynamic biomechanical process.^{33,37} The etiology of this process is multifactorial and additive. The gravitational effect predominantly drives the tract shift during the initial surgical stage. The lesser tract shift that we observed in the nonoperative hemisphere supports this claim, given that the operative field is always positioned uppermost. With increased surgical time, progressively more tract shift occurred in the nonoperative hemisphere as result of the body's own hemodynamic and CSF volume regulation following cranial and dural opening and lesion resection. These effects are also in part due to the complex interplay between administered anesthetic and diuretic agents, intravenous fluid therapies, and the ventilation/ET-CO₂ variability occurring over the surgical time course.

Our findings showing lack of significant effects of several IOFs on the WMT shift are somewhat counterintuitive and inconsistent with other reports.^{37,39,42,49} The lack of effect for the head rotation degrees and the degree of CSF loss could be due to the sampling bias and the method used to define the IOF. Thirteen of the 16 surgeries were performed in the lateral (90° head rotation, *n* = 10) and oblique lateral (120° head rotation, *n* = 3) positions. Analysis of ventricular penetration as a single IOF was not possible due to the small sample size (*n* = 2). We analyzed CSF loss by ventricular penetration, and ignored the potentially significant loss through opening the subarachnoid CSF cisterns. There is no good mechanism to accurately quantify the loss of CSF that is not related to ventricular puncture. The effect of CSF loss may be masked by the effect of lesion resection across the last surgical stage. The lack of effect for craniotomy size is related to the discordance between the cranial and dural opening size in our study cohort. In 7 of 16 patients, only slit durotomy was performed prior to the second intraoperative (MR₃) scan, due to associated brain edema. The dura mater was purposely not opened in full to prevent dangerous brain herniation. Other studies do not make such a distinction.⁴⁹ The marginal effect of the presence of brain edema in this study is attributable to the stabilization of edema prior to scanning and the small number of patients with edema.

The findings of this study have several obvious clinical

implications. Intraoperative WMT shift is a dynamic process that is more difficult to observe than cortical surface shift. Visualization of cortical surface shift can be guided by the surface gyral and vascular anatomy.^{39,49} Confirmation of the intraoperative WMT position is necessary through shift-compensated tractography reconstruction.

Notable WMT shift can occur following cranial and dural openings, prior to lesion resection (average shift 2.19 mm, range 1.90–3.65 mm), and durotomy size and the presence of brain edema are the predominant IOFs influencing the WMT shift at this stage. This highlights the necessity of updating image-guided neuronavigation following dural opening through intraoperative MRI scan acquisition.

The surgical stage-wise breakdown of WMT shift helps with refining the proposed safety resection margin. Conventional evidence comes from direct subcortical electrical stimulation studies validating WMT position proposed by the preoperative diffusion tractography.^{8,26,34} The difference of the functional and structural position is typically around 10.00 mm, representing combined electrical stimulation errors, tracking errors and errors encountered with image registration, and errors from intraoperative brain shift. Our results show that about one-half to two-thirds of this previously reported safety margin can be attributed to the intraoperative WMT shift prior to lesion resection, suggesting a more refined safety resection margin of 5.00 mm. Incidentally, this is similar to the “worst case scenario” proposed by Nimsy et al.⁴⁰ when intraoperative WMT shift is not considered.

It is important to bear in mind that the purpose of this study was to evaluate the potential clinical value of advanced tractography measures. Tractography images were retrospectively reconstructed from the HARDI diffusion data and were not used to guide intraoperative neuronavigation. Current navigation systems do not allow for image recalibration incorporating real-time HARDI tractography images. Knowledge acquired from this study could assist with the development of computer simulation models in predicting and correcting registration errors caused by intraoperative brain shift when using preoperative brain images for neuronavigation guidance.^{24,45,48,51} It remains unclear how much and what frequency of intraoperative MRI data are sufficient for these simulation models, given the complexity of brain and WMT shifts occurring in different surgical scenarios and in different procedures.¹⁹

Interpretation of the findings from this study is limited by the small sample size and heterogeneous epilepsy characteristics and pathologies. We note that large effect sizes were reported from the majority of regression analyses. Recent seizures^{9,58,59} and developmental pathologies with disorganized WMTs^{2,15,16,20,27,50} could contribute to the individual differences in brain diffusion data, thus inadvertently affecting the accuracy of tractography reconstructions. Brain edema was subjectively defined in this study without quantification, and its impact on WMT shifts was partially compensated for, prior to acquisition of the intraoperative images. We used the term “brain edema” as a descriptor of brain swelling that occurred at the time of dural opening. This was multifactorial, being potentially

due to combinations of perilesional edema, hemodynamic and ventilation factors, and possible seizure activity. The findings with regard to impact of degrees of head rotation and CSF loss on WMT shift require further clarification. Our quantitative analysis of the WMT shifts did not fully address the differences in shift direction between surgical stages. Figure 6 shows that the trajectories of the tract shift during surgery can be complex. Internal inconsistency associated with MRI hardware and scanning noises inherently limits the image registration and tractography accuracy that can be achieved in this study. Although negligible on visual inspection, motion artifacts occur with head movement, and with cardiac/CSF pulsation. Subtle image distortions occur with magnetic field and gradient field inhomogeneity. Radiofrequency noise and signal attenuation occur relating to the surface coil distance. Interscanner variability exists between processing of a conventional diagnostic and an intraoperative MRI scanner. Manual segmentation of the diffusion tractography introduces operator-dependent bias. Aligning a preoperatively acquired scan (MR₁) and an intraoperatively acquired scan (MR₂) negates the influence of developmental brain growth. Using MR₅ to replace the missing MR₄ data negates the WMT shift relating to anatomical restoration and development that may occur postoperatively.

Future directions arising from this study include addressing the effect on WMT shift of the location and pathology-related tissue characteristics in a larger clinical sample. Investigations of WMT shift relating to pharmacological and anesthetic interventions would be of interest but would require controlled manipulation of parameters affecting intracerebral pressure, more appropriately performed in brain phantom or animal models. Practical challenges remain for integration of neuronavigation software capable of processing HARDI diffusion data and performing probabilistic tractography in real-time during surgery. This would involve computational upgrades to improve efficiency of diffusion data acquisition using the intraoperative MRI scan^{11,35,46} and tractography processing using either an automated^{17,28} or a semi-automated, manual interactive method.¹⁴

Conclusions

Intraoperative WMT shift is a progressive, dynamic process affecting the whole brain and is influenced by multiple IOFs. This study demonstrates greater WMT shift in the operative hemisphere, in the WMTs adjacent to the surgical lesion, and in the superficial segment of the PT. Noticeable WMT shifts can occur following dural opening, prior to lesion resection. The durotomy size and the resection size are significant independent IOFs affecting the WMT shift. The presence of brain edema is a marginally significant IOF. Application of the tractography techniques and the knowledge acquired from this study may help compensate for intraoperative WMT shift and improve neuronavigation accuracy using either preoperative or intraoperative MRI data.

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Conception and design: Yang, Beare. Acquisition of data: Yang, Maixner. Analysis and interpretation of data: all authors. Drafting

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Supplemental Information

Videos

Video 1. <https://vimeo.com/195798997>.

Online-Only Content

Supplemental material is available with the online version of the article.

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