The human brain stem is phylogenetically the oldest brain region, serving critical integrative functions and linking the spinal cord, cerebellum, basal ganglia, limbic system, and neocortex. The brain stem consists of numerous small fiber tracts and nuclei that regulate sensory, motor, and autonomic functions. Small lesions due to diverse disorders (eg, multiple sclerosis,3 neoplasms,4–6 infection,4 or neurodegeneration5) can cause devastating consequences due to the compact juxtaposition of vital structures. Furthermore, the brain stem also contains anatomic targets for functional neurosurgery.4,6,7 Conventional MR imaging does not provide adequate contrast or spatial resolution of many brain stem substructures to define their involvement in specific clinical cases or direct precise surgical targeting.

Because clinical 3T MR imaging cannot reliably discriminate many small brain stem structures, clinicians and researchers must infer brain stem anatomy relative to craniocaudal position, a few identifiable internal features, and surface topography. Susceptibility-weighted MR imaging6 demonstrates some additional in-
ternal features that can improve indirect localization, but images from this sequence are also vulnerable to distortion from the skull base. Ultra-high-field in vivo MR imaging and advanced diffusion methods also improve discrimination of more brain stem structures. Diffusion methods though are vulnerable to spatial distortions, require long acquisition times, and depend on modeling assumptions that are difficult to validate directly in human tissue. Ultra-high-field MR imaging is limited by increased geometric distortion and signal loss at the skull base and is only available at major academic centers with dedicated technical support staff.

MR imaging microscopy can help characterize dissected, isolated ex vivo human brain stem samples and can illustrate detailed anatomy for teaching and guiding image interpretation in living subjects. These acquisitions require long scan times (>12 hours) using small dedicated radiofrequency coils that cannot accommodate the whole brain and are limited to single or few specimens. Furthermore, image contrast may be altered relative to typical clinical MR imaging in living subjects by MR imaging water-relaxation changes associated with higher field strengths, the post-mortem interval, and formaldehyde fixation. We recently developed a rapid 3T postmortem anatomic MR imaging protocol to screen postmortem whole brains in sudden unexplained death of childhood (SUDC). This protocol washes the brain thoroughly, then uses optimized-but-conventional MR imaging sequences, a 3T MR imaging system, and a head coil available at most institutions. The optimized 2D TSE sequence, in particular, produces exquisite anatomic contrast for subcortical structures in all 3 planes, comparable with neuroanatomic atlases with histologic stains. Here we demonstrate how the optimized TSE sequence can precisely delineate brain stem anatomy across multiple samples.

MATERIALS AND METHODS

Sample Procurement and Preparation
Whole-brain samples were obtained from an institutional review board–approved and Health Insurance Portability and Accountability Act–compliant multisite research study, the SUDC Registry and Research Collaborative, which used ex vivo MR imaging screening before gross pathologic assessment, brain cutting, and histopathology for forensic investigation. For each subject, the postmortem brain was removed intact by the local medical examiner; then, it was immersion-fixed in a 4% formaldehyde solution for at least 21 days to reach near equilibrium with presumed fixative-induced nervous tissue T2 changes. The brain was shipped to our institution and was then washed continuously in water for 48 hours to eliminate MR imaging relaxation changes from the free aldehyde fixative solution. Individual brains with MR imaging data included for the figures and tables in this study (n = 13) met the following criteria: 1) transected at or below the pyramidal decussation; 2) no MR imaging or pathological abnormality (outside the hippocampus) identified by a board-certified neuroradiologist and neuropathologist respectively; 3) no T1-hyperintense fixation bands in the brain stem or diencephalic structures due to variable fixation penetration; and 4) a prerefrigeration postmortem interval of <24 hours.

FIG 1. Parasagittal and coronal T2-weighted MR images of the postmortem human brain stem. A. Canonical axial brain stem levels parallel to the anterior/posterior commissure plane that are found in Fig 2 are represented with the solid lines and On-line Fig 1 with the dashed line. Only selected brain stem substructures are labeled in coaligned sagittal and coronal images to orient the reader relative to the craniocaudal axial slice positions. The On-line Table provides a complete list of labeled anatomy for all figures, indicated by the numbers in parentheses in the legends. Note the trochlear nerve (asterisk) only seen in some brains.

Whole-Brain MR Imaging Protocol
Each brain was immersed under water within a custom 3D-printed container specifically designed to conform to a 64-channel head and neck coil on a 3T Magnetom Prisma MR imaging scanner (Siemens, Erlangen, Germany). Sealed water-filled disposable powderless latex medical gloves were gently wedged between the container and brain to prevent motion and to optimize the coil-filling factor. Scout sequences identified the brain position; then, 2D high-resolution TSE MR imaging sequences of the whole brain were obtained in coronal, sagittal, and axial planes relative to the anterior/posterior commissure (ACPC) plane. In selected cases, additional images were obtained in oblique planes to illustrate specific anatomic relationships within the brain stem. T2-weighted TSE sequence parameters were the following: TR = 5380 ms, TE = 53 ms, echo-train length = 7, echo spacing = 10.8 ms, bandwidth = 415 Hz/pixel, slice thickness = 0.8 mm, 116 slices (no interslice gap), in-plane resolution = 0.35 × 0.35 mm, concatenations = 2, averages = 10, total time = 2 hours (full protocol available on request). Optimization of sequence parameters for contrast resolution within the brain stem, diencephalic structures, and cerebral hemispheres using TSE sequences with 3T MR imaging is reported separately.
While brain stem anatomy is typically shown in the axial plane, the On-line Table for the complete list of labeled substructures. Brainstem videos demonstrate the reproducibility of anatomic contrast for 4 selected axial section positions on the sagittal image. On-line Fig 1 demonstrates the reproducibility of anatomic contrast for 4 selected axial section positions.

**RESULTS**

Axial images of the brain stem at 7 canonical anatomic levels are shown in Fig 2 and On-line Fig 1, with labeled substructures (see The On-line Table for the complete list of labeled substructures). While brain stem anatomy is typically shown in the axial plane, Fig 1 also demonstrates selected sagittal and coronal views with axial section positions on the sagittal image. On-line Fig 1 demonstrates the reproducibility of anatomic contrast for 4 selected brains at both the caudal midbrain and middle pons levels. Videos of the brain stem in 3 planes are provided in On-line Videos 1–3.

All numbered structures could be directly identified for each subject by both board-certified neuroradiologists. The mean postnatal age for the subjects included in this study was 32.1 ± 6.1 months.

We briefly describe the course, orientation, and shape of 5 major white matter pathways based on the 13 whole-brain specimens (all measurements are reported as mean ± SD). The numbers in parentheses refer to the numbers of the brain structures listed in the On-line Table. The corticospinal tract (28) (Fig 3) is the major motor pathway controlling the voluntary movements of the limbs and trunk. The CST at the midbrain level is 1.3 ± 0.1 cm lateral to the midsagittal plane and descends within the cerebral peduncle (24) from the posterior limb of the internal capsule at a 31° ± 7° angle from superolateral to inferomedial in the coronal plane. The center of the tract is 0.6 ± 0.05 cm deep to the ventral surface and 0.4 ± 0.09 cm lateral to the midsagittal plane at the midpons, while maintaining a rounded shape before converging fibers descend to the medullary pyramids (34) at a less steep superolateral-to-inferomedial 14° ± 2° angle. The pyramids form the ventral surface of the medulla and are 0.26 ± 0.04 cm lateral to the midsagittal plane. The CST descends at a 5° ± 2° anterosuperior-to-inferoposterior angle relative to the long axis of the brain stem in the sagittal plane. CST signal intensity remains T2-hypointense even with tract dispersion in the pontine levels (Fig 2).

After the internal arcuate fibers (37) decussate, the medial lemniscus (9) (Fig 4) is in the central paramedian medulla with an elongated ovoid shape and its long axis oriented anterior to posterior on axial images. The ML is a sensory pathway conveying fine touch, vibration, and proprioception of the skin and joints. As the ML ascends, its long axis rotates at 56° ± 11°, 80° ± 9°, 115° ± 13°, and 130° ± 4° angles relative to the midsagittal plane at the caudal pons, middle pons, cranial pons, and midbrain levels, respectively. The tract is located 0.3 ± 0.05 cm and 0.8 ± 0.06 cm lateral to the midsagittal plane at the pons and midbrain levels, respectively. In the sagittal plane, the ML ascends at a 4° ± 1° anteroinferior-to-posterosuperior angle relative to the long axis of the brain stem at the medulla but pivots posteriorly 18° ± 5° at the pontomedullary junction and pivots again posteriorly 17° ± 3° at the midbrain. The ML maintains uniform signal intensity until the fibers become less distinct just before terminating in the ventral posterolateral thalamic nucleus (50).

The medial longitudinal fasciculus (16) (Fig 5) is a small tear drop–shaped tract just deep to the rhomboid fossa, 0.05 ± 0.01 cm lateral to the midsagittal plane. The MLF coordinates connections among the oculomotor, trochlear, and abducens nuclei for control of conjugate eye movements. The tract ascends at a 5° ± 2° angle posteroinferior to anterosuperior relative to the long axis of the brain stem on sagittal images in the medullary and pontine levels. At the midbrain, the tract takes a 20° ± 6° ventral turn to terminate along the walls of the inferior third ventricle (58). At its cranial termination, the MLF signal becomes less conspicuous. On axial midbrain slices, the MLF is 0.16 ± 0.02 cm lateral to the midsagittal plane with the long axis oriented at 137° ± 7° antero-medial to posterosilateral.

Fibers descending from the red nucleus (3) to the ipsilateral inferior medullary olive (35) are within the central tegmental tract (26) (On-line Fig 2), located 0.3 ± 0.04 cm lateral to the midsagittal plane.

**FIG 2.** Axial modified T2-weighted TSE images at 6 canonical levels of the postmortem brain stem orientated parallel to the anterior/posterior commissure plane. Upper row: A, cranial midbrain; B, caudal midbrain. Middle row: C, cranial pons; D, caudal pons. Lower row: E, cranial medulla; F, caudal medulla. Improved image contrast from the modified TSE sequence directly demonstrates even small structures like the medial longitudinal fasciculus (16). Note the sensory decussation of the medial lemniscus in the caudal medulla (asterisk, F). The motor decussation is demonstrated in Fig 3.
Table provides measurements of configuration with an inner concave angle of 114°. On axial images, the superior cerebellar peduncle has a parabolic inferoposterior to the anterosuperior angle in the sagittal plane. The tract is round and maintains a less distinct hypointense signal compared with the other major tracts described here. The CTT contains ascending taste fibers from the solitary nucleus, whereas the descending fibers are part of a feedback circuit (dentatorubro-olivary) responsible for modulating motor activity.

The inferior half of the dentatorubrothalamic tract (Online Fig 3) ascends to the superior cerebellar peduncle (7) at a 27° ± 3° inferoposterior to the anterosuperior angle in the sagittal plane. The tract courses inferiorly and parallel to the long axis of the brain stem in the sagittal plane until a 10° ± 2° anterior bend to meet the inferior olive. The CTT contains ascending taste fibers from the solitary nucleus, whereas the descending fibers are part of a feedback circuit (dentatorubro-olivary) responsible for modulating motor activity.

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The midpons contains the spinal sensory (48) and motor nuclei (66) of the trigeminal nerve. The trigeminal motor nucleus was best seen at the cranial-midpons level junction just medial to the superior cerebellar peduncles (7). The trigeminal sensory spinal nucleus was not reliably seen in the pons in all brains but could be identified at the cervicomedullary junction (Fig 3). The facial nucleus was not seen, but its fascicles (67) were identified in the midpons within the respective genu and colliculus bordering the abducens nucleus (17). The superior olivary complex (31) was identified at the lower pons level, posterolateral to the medial lemniscus (9) (Fig 2). Within the medulla, the inferior olivary nucleus (35) was clearly seen, but the dorsal and medial accessory olivary nuclei and ambiguous nucleus were not. Cochlear (19) and vestibular (36) nuclear group positions were seen along the lateral and dorsal medullary surface, but their subnuclei could not be discerned. The dorsal motor nucleus of the vagus (57) and the hypoglossal nucleus (40) could be identified on axial images and further directly distinguished on a parasagittal image at the level of the medial longitudinal fasciculus (Fig 5). The cuneate (41) and gracile (42) nuclei in the caudal dorsal medulla were identified giving rise to the internal arcuate fibers (37).

### DISCUSSION

This modified TSE sequence provided detailed images of brain stem anatomy using whole postmortem brains and a widely available clinical 3T MR imaging system. Previous studies have used ultra-high-field MR imaging, dissected and isolated brain stem samples, specialized radiofrequency coils, and/or relatively long acquisition times. Anatomic image contrast was generated directly from the MR imaging sequence without mathematically complex, off-line, model-based reconstructions as required for relaxation-mapping or advanced diffusion-based contrasts. Such techniques have been difficult to validate. This postmortem MR imaging protocol directly visualizes many small brain stem structures such as the MLF (<1 mm in transverse dimension) that are beyond the spatial resolution or detection limits of current state-of-the-art diffusion-weighted imaging techniques. Furthermore, direction-encoded color images of diffusion anisotropy cannot discriminate adjacent structures with parallel craniocaudal orientations (eg, vertical columns within the midbrain; Fig 3B). Conversely, T2-weighted contrast reported here cannot discriminate all brain stem structures identified with histology such as distinguishing the dentatorubrothalamic projections from the red nucleus they envelope (On-line Fig 405). T2-weighted contrast detects but cannot resolve the individual crossing or interdigitating fiber bundles of the sensory, motor, or superior cerebellar peduncle decussations (Figs 2F, 3D, and On-line Fig 3B, respectively). Future work will evaluate potential synergies for brain stem structure resolution when this TSE contrast is combined with diffusion, susceptibility, and other MR imaging contrasts at 3T (or ultra-high-field MR imaging). This optimized TSE sequence also produces exquisite contrast resolution of subthalamic, thalamic, and basal ganglia structures that will be described in a separate companion report.

For clinicians, it is challenging to learn and retain brain stem anatomy because internal structures are only discriminated on stained histology slides, unlike imaging performed in clinical practice. We must mentally juxtapose structures discriminated by specific histology stains onto MR images on the basis of mostly the craniocaudal position and brain stem surface features. Here, knowledge and mental maps of brain stem neuroanatomy may be facilitated because this postmortem protocol provides anatomic discrimination of brain stem structures comparable with histology atlases, yet it is derived from a commonly used clinical

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**Selected measurements for 5 major brain stem white matter tracts at 3 canonical axial planes***

| Tract | Fig | CC | Cranial Medulla | Mid Pons | Caudal Midbrain |
|-------|-----|----|----------------|----------|----------------|
| CST (L) | 3 | 517 ± 48 | 2.9 ± 0.6 | 3.7 ± 0.5 | 8.8 ± 2.6 |
| CST (R) | 3 | 518 ± 48 | 2.7 ± 0.3 | 3.3 ± 0.4 | 7.3 ± 1.4 |
| ML | 4 | 46.9 ± 5.5 | 5.6 ± 0.8 | 0.6 ± 0.1 | 2.9 ± 0.6 |
| MLF | 5 | 39.6 ± 3.4 | 1.0 ± 0.3 | 0.5 ± 0.6 | 0.5 ± 0.2 |
| CTT | 6 | 67.7 ± 4.0 | 2.6 ± 0.4 | 1.6 ± 0.3 | 3.4 ± 0.8 |

Note: **CC indicates craniocaudal, AP, anteroposterior; TV, transverse; Fig, figure; L, left; R, right.**

*Units are millimeters or square millimeters, and data are mean ± SD, with 13 SUDC samples.

*All measurements of the right and left corticospinal tracts were compared separately. Cross-sectional areas trended toward small statistical differences in the medulla (p = .099) and pons (p = .063), but not the midbrain (p = .363).}

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MR imaging sequence and contrast mechanism (albeit with higher spatial resolution). MR imaging data facilitate the creation of user-controllable videos to evaluate the orientation and evolution of specific pathways throughout the brain stem (On-line Videos 1–3). Furthermore, multiplanar images or series can illustrate specific brain stem tracts or key anatomic relationships in novel ways—that is, the oblique coronal plane perpendicular to the long axis of the hippocampus, just deep to the rhomboid fossa, illustrates functional cell columns of cranial nuclei V, VI, VII, VIII, X, and XII (On-line Fig 4). It would be technically challenging and resource- and time-intensive to obtain such images from histologic sections of individual human brain stem samples; hence, previous histologic or MR imaging–based brain stem images emphasized idealized axial views.19,20,33 The postmortem MR imaging protocol can be applied quickly and inexpensively across many samples without tissue consumption. This feature should enhance the experiential component of learning by exposing trainees to more individual variations in brain stem anatomy (On-line Fig 1).

The ability to directly visualize specific brain stem structures in multiple individual brains also facilitates creation of normative coordinates for structures in specific fiducial planes and surfaces that can be used in clinical studies. For example, our data from SUDC brains predict that a lesion in the midbrain tegmentum, 0.1, 0.3, or 0.8 cm lateral to the midsagittal plane, would involve the MLF, CTT, or ML, respectively. We estimated the size and cross-sectional areas of several major brain stem tracts (Table). We observed a trend (P < .10) toward ~20% larger cross-sectional areas for the left corticospinal tract in the pons and medulla (Table). While handedness is less established in young children,39 functional asymmetries in brain stem structures may alter the numbers of axons, degree of myelination, and/or myelin compaction that could affect TSE MR imaging contrast. These asymmetries may change during childhood. The potential corticospinal tract asymmetries and brain stem pathway coordinates and sizes will require further future investigation in adult brains without neurologic disease and documented handedness. Future work could also produce a group-based brain atlas and/or a normative data base of brain stem structures across different ages and sex. These data could assess changes to brain stem structure with aging or subcortical dementias40–43 or could be used as a structural template for extracting other forms of quantitative MR imaging data in postmortem investigations.

The use of pediatric brains from an SUDC study is a limitation for the measurements reported in this study. Deformity or relaxation of the posterior fossa structures from procurement, agonal hydration status, or brain changes associated with formaldehyde fixation also may affect the external validity of these results. While repeatability measures of the cross-sectional area in this preliminary study were lower than the differences observed among tracts or between the right and left CST, manual measurements are prone to error from image noise, slice orientation, and rater biases. Measurements in the sagittal plane may also be confounded by variable posterior angulation of the lower brain stem created during specimen procurement. Assignments of brain stem structures were made by consensus between 2 board–certified neuroradiologists using standard reference texts based on histologic staining;28–31 inter- or intraobserver variability for structure identification was not assessed. TSE signal intensity correlated inversely with myelin staining in the histology of different brain samples; however, the biophysical basis for gradations of T2-weighted signal variation in the brain stem will require further investigation. Histology sampling and specific stains were restricted to the SUDC forensic investigation. MR imaging relaxation parameters of these ex vivo brains differ from those in vivo due to the postmortem interval,22 formaldehyde fixation and tissue penetration,23–25 incomplete myelination,44,45 or subtle unrecognized SUDC pathology.46 Preliminary experiments suggested that true 3D T2-weighted MR imaging acquisitions47 did not produce such exquisite contrast resolution of the brain stem, but this will be the subject of future investigation.

**CONCLUSIONS**

An optimized TSE T2 sequence applied to washed postmortem brain samples revealed exquisite and reproducible brain stem anatomic MR imaging contrast comparable with histologic atlases. The current results suggest that intrinsic nervous tissue T2 differences could potentially generate sufficient contrast to also identify brain stem structures in vivo. It will be challenging to feasibly adapt this MR imaging protocol to living subjects, yet this would greatly enhance its applicability to neuroanatomy training, clinical practice, and future research.

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