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Free Water Elimination Diffusion Tractography: A Comparison with Conventional and FLAIR DTI Acquisitions

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Abstract

PURPOSE—White matter tractography reconstructions using conventional diffusion tensor imaging (DTI) near cerebrospinal fluid (CSF) spaces are often adversely affected by CSF partial volume effects (PVE). This study evaluates the ability of Free Water Elimination (FWE) DTI methods to minimize the partial volume effects (PVE) of cerebral spinal fluid (CSF) for deterministic tractography applications.

MATERIALS AND METHODS—Ten healthy individuals were scanned with ‘traditional’, FLAIR (fluid-attenuated inversion recovery), and FWE DTI scans. The fornix, corpus callosum, and cingulum bundles were reconstructed using deterministic tractography. The FWE DTI scan was performed twice to separately match total acquisition time (long FWE) and number of measurements (encoding directions – the short FWE) to the FLAIR and ‘traditional’ DTI scans. PVE resolution was determined based on reconstructed tract volume. All reconstructions underwent blinded review for anatomical correctness, symmetry, and completeness.

RESULTS—Reconstructions of the fornix demonstrated that the FWE and FLAIR scans produce more complete, anatomically plausible reconstructions than ‘traditional’ DTI. Additionally, the tract reconstructions using FWE-DTI were significantly larger than when FLAIR was used with DTI ($p < 0.0005$). FLAIR and the FWE methods led to SNR reductions of 33% and 11% respectively, compared with conventional DTI. The long and short FWE acquisitions did not significantly ($p = 0.31$) differ from one another for any of the reconstructed tracts.

CONCLUSION—The FWE diffusion model overcomes CSF PVE without the time, signal to noise ratio, and volumetric coverage penalties inherent to FLAIR DTI.

Keywords

DTI; Diffusion Model; Tractography

INTRODUCTION

Diffusion Tensor Imaging (DTI) is currently the most widely used neuroimaging MRI technique for characterizing tissue microstructure (1). DTI coupled with tractography algorithms are also used to reconstruct specific white matter (WM) tracts, which may be used to define volumes of interest (VOIs) for comparison of region-specific diffusion metrics across subjects (2). The use of tractography to define VOIs reduces the user dependence, required time, and difficulty inherent to manual segmentation of successive two-dimensional image slices (3).

Diffusion weighted imaging has inherently low signal to noise ratio (SNR) due to both diffusion effects and increased echo times (TE) from the large diffusion-encoding gradient pulses required for diffusion weighting. Although the use of multi-channel array head coils may help to improve SNR, DTI is commonly acquired with spatial resolution between 2mm and 3mm in each dimension in order to maintain adequate SNR levels. Increased spatial resolution requires longer scan times that may adversely affect clinical feasibility and increase the likelihood of head motion. Large voxel sizes also lead to greater partial volume effects (PVE), especially in white matter (WM) tracts such as the fornix and the corpus callosum, which share borders with cerebrospinal fluid (CSF). Diffusion properties of both of these tracts have been extensively studied in a wide variety of applications including normal aging, mild cognitive impairment, Alzheimer's disease, traumatic brain injury, and autism (4–9).

When two tissues with differing diffusion characteristics share a voxel, the classical DTI model no longer applies. For example, the classical DTI model underestimates the fractional anisotropy (FA) and overestimates the mean diffusivity (MD) in voxels with mixtures of CSF and either WM or gray matter (GM). White matter tractography algorithms often utilize an FA threshold (e.g., $FA > 0.1$ to 0.3) to terminate the tract reconstruction. Consequently, tractography of WM proximal to CSF can prematurely terminate, which may lead to misinterpretation of that tract.

One approach to reduce PVE in DTI is the use of a fluid attenuation inversion recovery (FLAIR) preparation pulse before the acquisition of each slice. When properly timed, the FLAIR preparation reduces the signal from CSF to nearly zero, effectively eliminating PVE (3,10). However, this approach carries with it several limitations. Firstly, the WM signal, and hence, SNR is reduced approximately 25% when the inversion time (TI) is chosen to null CSF. Secondly, the relatively long inversion time for CSF suppression (2000 ms) drastically increases the repetition time (TR), and hence, overall scan time. Lastly, multislice interleaving strategies become increasingly difficult when incorporated with preparation pulses, and multi-slice acquisitions are often limited by the maximum number of slices achievable for a given inversion time.

Alternatively, a multi-component model may be used to account for PVE of CSF and brain tissue (11–15). Recently, a simple free water elimination (FWE) DTI model that requires only a minor change to acquisition protocol and does not require spatial constraints or assumptions was proposed and optimized (16). This work compares the robustness of deterministic tractography in regions with CSF contamination for traditional DTI, FLAIR DTI, and the recently proposed FWE DTI methods.

METHODS

In the FWE model, CSF is assumed to be isotropic and have a known apparent diffusion coefficient (ADC). The use of two non-zero b-values greatly simplifies the parameter space allowing accurate and stable DTI measures even without spatial constraints and assumptions. The FWE DTI signal model (17) is described by

$$S_i = S_0 \left[(1 - f) \exp(-b_i g_i^T D g_i) + f \exp(-b D_{iso}) \right] \quad [1]$$

where S_i and S_0 are the signal from the i -th diffusion and non-diffusion weighted measurements, respectively, $D_{iso} = 3 \times 10^{-3} \text{ mm}^2/\text{sec}$ is the free water diffusivity, D is the tissue diffusion tensor, b_i and g_i are the diffusion-weighting amplitude (in mm^2/s) and unit gradient encoding vector, respectively.

Ten healthy young (mean age: 25.6 yrs., range: 22–29 yrs., 8 male and 2 female) volunteers underwent four separate DTI acquisitions, constituting three distinct comparisons. All scanning was performed using informed consent and was in compliance with an approved protocol from the Institutional Review Board. Brain imaging studies were performed using a 3-Tesla MR750 Discovery scanner (General Electric Healthcare, Waukesha, WI) and a 32-channel, receive-only brain coil (Nova Medical). Diffusion tensor imaging measurements were obtained using four DTI scans: (1) standard DTI, (2) FLAIR DTI, (3) short FWE DTI and (4) long FWE DTI. Protocol parameters for each case are listed in Table 1.

In all cases, DTI was performed using a diffusion-weighted spin-echo EPI pulse sequence with a single refocusing pulse, parallel imaging with ASSET ($R=2$) and custom modifications to enable FLAIR and arbitrary encoding directions. Images were acquired using contiguous sagittal slices with 2.5 mm isotropic resolution (96×96 matrix over a 240 mm FOV). A higher order shim preceded the first DTI scan. In all cases, the TR was set to the minimum value to optimize the acquisition efficiency. All DTI cases except FLAIR had a matching slice prescription. The inversion time for the FLAIR scan was set to 2000 ms. The maximum number of slices for FLAIR DTI was limited to 34, so coverage was limited to the mid-brain region, which included all of the tracts of interest. For both standard DTI and FLAIR DTI, diffusion-weighted images were collected at a single b-value ($1,000 \text{ s/mm}^2$). The number of encoding directions was increased for standard DTI to match the scan time of FLAIR DTI. For both FWE DTI scans, diffusion-weighted data were collected at two b-values (500 and $1,500 \text{ s/mm}^2$), which is necessary for fitting the two-pool FWE model (18). For all DTI scans, the ratio of diffusion weighted images to b_0 images was maintained at the reported optimal value of 8:1 (19). The short FWE DTI protocol matched the number of diffusion encoding directions used in the FLAIR DTI studies. The long FWE

DTI protocol increased the number of diffusion encoding directions to match the overall acquisition time for standard DTI and FLAIR DTI and the number of encoding directions for standard DTI. The diffusion encoding directions were matched for the pair of standard DTI and long FWE DTI scans, and the pair of FLAIR DTI and short FWE DTI scans.

The first experiment compared standard DTI, FLAIR DTI, and long FWE DTI acquisitions with the same scan time and resolution. The second comparison was between FLAIR DTI and short FWE DTI scans with the same number of encoding directions. Lastly, the long and short FWE scans were compared to judge the effect of acquiring a different numbers of diffusion-weighted images.

The traditional and FLAIR DTI scans were single shell acquisitions that were reconstructed per our standard laboratory pipeline that included a combination of FSL, Camino and custom Matlab tools. The preprocessing steps included movement and eddy current correction, gradient direction correction, brain extraction, and a single tensor fit with Camino (20,21). Eddy current correction and brain extraction were carried out using the FSL toolkit (22). For the FWE scans, the process was the same except that the FWE DTI model in Equation 1 was fit in Matlab (16) and the resulting free water component removed prior to performing tractography with Camino. As the FWE model treats the signal from each voxel as a combination of a single tensor and a free water signal, the removal of the free water signal provides a better probe of the underlying tissue diffusion tensor. Up to this point, all processing had been performed in the individual space for each scan.

In order to define the VOIs to be used for tractography, a template image was constructed for each individual subject using DTI-TK, which performs DTI spatial normalization using the full tensor for alignment (23). For each individual subject, the number of slices from each scan was reduced to match that of the FLAIR scan and create the subject-specific template. The FA map from the template was used to define the tractography VOIs, which were inverse warped into the native space for each scan (24).

Whole-brain tractography was performed using the fiber assignment by continuous tracking (FACT) algorithm (25) as implemented in the Camino software package. Tracts were seeded at the center of every voxel with an FA greater than or equal to 0.3. Specific tracts were then reconstructed by constraining viable fibers through the use of targeted inclusion and exclusion VOIs. An FA threshold of 0.3 and a curvature threshold of 60 degrees over 5 mm were used as stopping criteria. Visualization was carried out using TrackVis (26).

The primary metric for comparison was tract volume. Within the confines of being consistent with known anatomy, a larger reconstruction volume is likely indicative of fewer prematurely terminated tracts (3,27,28). Tract volume was determined by multiplying the voxel volume (15.625 mm^3) by the number of voxels that contain any portion of a tract. The FA and MD along the tracts were also compared, however, these metrics cannot be used to determine reconstruction quality. Statistical significance was determined using a paired student's t-test with $\alpha = 0.05$ and Bonferroni correction for multiple comparisons. The effect of acquisition and reconstruction on the homogeneity of diffusion measures within a

single coherent structure was assessed by analyzing the standard deviation of a given metric along a single tract.

Native-space tractography reconstructions were performed for the corpus callosum (CC), fornix, and cingulum. The first two tracts were chosen because of their proximity to CSF filled spaces such as the ventricles and interhemispheric fissure. The cingulum bundles are not adjacent to CSF spaces and, thus, are control tracts. A single VOI defined on the midsagittal FA image was used to define the corpus callosum, Figure 1. This was further subdivided into five regions using the scheme proposed by Hofer and Frahm, based on fiber projection regions (29). These regions were prefrontal (CC-I), premotor and supplementary motor (CC-II), primary motor (CC-III), primary sensory (CC-IV), and parietal, temporal, and visual (CC-V). The fornix was delineated based on intersection with two primary VOIs in the columns and body of the fornix and one of two secondary VOIs in the left and right crux (30), Figure 2. The right and left cingulum bundles were defined by tracts that pass through a pair of VOIs – anterior above the corpus callosum genu and posterior above the corpus callosum splenium – placed on the thin green white matter tracts immediately superior to the corpus callosum (31,32), Figure 2.

All reconstructions underwent a blinded review from two separate reviewers with substantial experience in deterministic tractography, an experienced neuroradiologist and an imaging scientist with significant tractography expertise. For each subject and tract, the reviewers ranked the tract reconstructions for each acquisition from best (1) to worst (4) and gave a quality score from excellent (1) to poor (4). The score was based on anatomical correctness, symmetry, and completeness. Statistical analysis of the qualitative ranks and scores were determined based on the Wilcoxon signed rank test.

Note that for the qualitative tract ranking/ratings, incomplete tract reconstructions (false negatives) were penalized more severely than inclusions of other tracts (false positives). Erroneous false tract projections may be masked out, whereas missing tracts cannot be easily repaired.

RESULTS

The SNR of the $b = 0$ images for the standard DTI scan in white matter was 47 ± 1.2 . Both the FLAIR DTI and FWE DTI scans displayed a reduction in SNR with measured values of 32 ± 0.8 and 42 ± 2.2 , respectively, corresponding to an SNR reduction of 33% and 11%, respectively, when compared to the standard DTI. As is expected, there was no discernable difference in SNR between the long and short FWE scans.

Figure 3 shows the reconstructed volume for each of the four acquisitions and seven tracts relative to the standard DTI. The FLAIR DTI sequence yields a significantly larger reconstruction than standard DTI in CC-I, CC-III, CC-V, and the fornix. Likewise, the long FWE DTI sequence was statistically larger for all reconstructed tracts. Meanwhile, the tract reconstructions from the short FWE DTI scan was larger for all CC tracts and the fornix, but not the cingulum.

For some tracts the differences between the FLAIR DTI reconstruction and the FWE DTI reconstructions were also significantly different. The long FWE DTI scan produced a larger reconstruction for CC-III, CC-IV, CC-V, and the fornix. For the short FWE DTI scan, CC-IV, CC-V, and the fornix resulted in statistically larger tract reconstructions. The two FWE DTI scans showed no significant differences ($p = 0.31$) for any of the tracts reconstructed.

The study also investigated DTI method differences in the diffusion metrics, figure 4. FLAIR DTI and standard DTI resulted in substantially similar diffusion metrics in the entirety of the corpus callosum. However, differences were noted in the fornix and cingulum bundles. In the fornix, FLAIR DTI yielded significantly smaller mean, radial (RD), and axial (AD) diffusivities along with a higher FA. In the cingulum, FLAIR DTI yielded larger mean and axial diffusivities as compared to standard DTI. Meanwhile, the FWE DTI methods were very similar to each other, but significantly differed from both standard DTI and FLAIR DTI scans in terms of mean, radial, and axial diffusivities for every reconstructed tract. Significant differences in FA were seen between both FWE DTI scans and standard DTI for all tracts except for CC-I and CC-II. As the fornix displayed the most dramatic metric changes and the highest degree of PVE, as measured by mean f -value, figure 5 shows these reconstructions from one subject in more detail. This figure shows the reconstructed tracts from each method along with the spatial distribution of FA and MD along the tracts.

The spatial distribution of f -value can be visualized along each tract in figure 6. For both the fornix and CC, the f -value shows a pattern consistent with PVE from the ventricles. The superior portion of the fornix and the inferior portion of the CC that border the ventricles do indeed have the largest f -value. In the CC the f -value was seen to increase from anterior to posterior for the corpus callosum, figures 4 and 6. Clearly this is skewed by the relative amount of PVE for each tract with the ventricles and for CC tracts which penetrate into the cortex, which is more highly partial volumed with CSF. When removing the highly partial volumed voxels ($f > 0.5$), the resulting mean f -value is found in table 2. With the exception of CC-V to CC-IV, each tract has a significantly larger f -value than the one immediately anterior to it. The cingulum bundles show the lowest mean f -value and little spatial variation along the tracts, figures 4 and 6.

The means of the standard deviations along the fornix and cingulum are shown in table 3. Values are provided for FA, MD, RD, and AD. The standard deviations for the diffusivity metrics (MD, RD, AD) in the fornix are reduced with FLAIR DTI and the FWE DTI acquisitions compared to standard DTI. This is not seen in the cingulum, where variability in diffusivity measures for the PVE resolving techniques is comparable or greater than standard DTI. For both tracts, variability of FA increases from standard DTI to FLAIR DTI and then to the FWE DTI techniques. Though not shown, all of the corpus callosum tracts displayed the same pattern as the fornix, though to a lesser extent.

The qualitative tract ranks and scores from the blinded reviewers are listed in table 4. These metrics indicate that the FWE scans yielded better tract reconstructions for the fornix and the corpus callosum ($p = 0.015$ vs. DTI and FLAIR). For the cingulum bundles, the FLAIR reconstructions were scored and ranked as best, though ranks and scores were similar with

the FWE long reconstruction ($p = 0.3$). For all tracts, the standard DTI reconstruction was scored as worst.

DISCUSSION

This work demonstrates the utility of a simple diffusion model to alleviate deleterious effects of unwanted mixing of CSF and brain tissues, thereby improving tractography. The tracts produced with the proposed FWE DTI were more complete than those produced using traditional DTI. Compared to FLAIR DTI, which also shows tractography advantages compared to DTI, the FWE DTI scan can be performed in almost half the time and with more volumetric coverage. The benefits of FWE DTI were greatest in the fornix due to its close proximity to CSF.

For the tracts with high CSF PVE (fornix and corpus callosum), the FLAIR DTI and FWE DTI scans led to a reduction in standard deviation for the diffusivity measures along a tract with the reduction greatest for FLAIR DTI. In contrast, the cingulum, which is not adjacent to CSF, had increased variability using either FLAIR DTI or FWE DTI methods, which have decreased SNR. The SNR penalty from FLAIR DTI may increase the standard deviation along the tracts. Also, the added complexity of the FWE DTI model in the cingulum may introduce uncertainty by fitting more parameters than are necessary since the expected free water fraction f is zero.

The similarity between metrics and reconstructions from the long and short FWE scans is akin to the similarity between DTI metrics with varying numbers of diffusion weighted images (19). It is expected that the increased number of images will improve the estimate and, thus, reduce the uncertainty. However, both acquisitions ought to lead to substantially similar metrics, as indicated by our results.

When considering the diffusion metrics associated with each technique, it becomes apparent that the FWE techniques do not simply remove the effects of CSF. If this were the case, the FWE metrics would be more in line with the measures from FLAIR DTI. However, FWE DTI results in a greater FA and reduced diffusivity measures even in tissues without CSF PVE. For example, the cingulum bundles, though not being in direct contact with CSF, have a mean f -value of 0.13 ± 0.03 and 0.12 ± 0.05 for the long and short FWE DTI protocols, respectively. It has been hypothesized that this signal arises from the extracellular space (ECS) (13,15). The results here suggest that, for this theory to be true, water in the ECS must diffuse freely yet have a T1 that is distinct from CSF and, thus, not nulled by FLAIR.

In addition to removing CSF PVE, the f -value may also reflect properties of tissue microstructure and organization. Much like diffusion kurtosis imaging (DKI) (33) quantifies the deviation from monoexponential signal decay, a non-zero f -value may be an alternative means of modeling this deviation. Thus, even when analyzing tracts distal from CSF, the presence of a non-zero f -value reflects the inadequacy of the DTI model to represent the measured diffusion decay. If indeed the f -value in parenchyma reflects kurtosis effects, then the prior constraint (16) on the maximum acquisition b-value of 1500 s/mm^2 is unnecessary.

The CC shows both a quantitative) and qualitative pattern of increasing f -value from anterior to posterior. Studies with light and electron microscopy have noted that the fiber size and density of the CC is regionally dependent (34,35). These studies note that the highest fiber density and smallest mean axon diameter is in the anterior CC with decreasing density and increasing diameter moving posterior. The lowest density and largest average diameter occurs in the posterior mid-body with the fiber density increasing in the most posterior portion. While certainly not conclusive evidence, this observation qualitatively aligns with the postulation that f -value corresponds to the ECS.

The volume and quality of reconstructions using the FWE model provides evidence for resolution of PVE, however, the interpretation of diffusion metrics is potentially complicated. Tensor metrics (FA and MD) are dramatically different than in DTI, even in regions removed from CSF. Additionally, no definitive interpretation of the f -value exists when distal from CSF. Further investigation is necessary in order to meaningfully evaluate diffusion metrics with the FWE model.

The experiment presented here investigated a single deterministic tractography algorithm and three specific white matter pathways. Investigation on the effects of using various deterministic algorithms or probabilistic tractography was not performed.

In conclusion, this work confirms that the FWE DTI method is capable of alleviating the partial volume effects of CSF at the borders of white matter tracts. This is especially evident in the fornix, which has high partial volume averaging with CSF. In this tract FWE DTI produces a larger, fuller reconstruction than using FLAIR DTI. The FWE DTI method provides greater anatomical coverage, time efficiency, and SNR when compared with FLAIR. However, both FWE DTI and FLAIR DTI methods will improve the microstructural characterization of tracts with CSF PVE. It was also confirmed that the f -value reflects more than just CSF PVE and, thus, diffusion metrics with FWE DTI are distinct from those with FLAIR and DTI, even in regions distal from CSF interfaces.

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Figure 1.

Seed ROI and example segmentation of the corpus callosum overlaid on an FA map. The CC was segmented into the following five regions: CC-I (yellow), CC-II (red), CC-III (orange), CC-IV (green), and CC-V (blue). The middle image shows a streamline reconstruction of the CC with DEC encoding based on the primary eigenvector. The rightmost image shows the same reconstruction with color determined by the seed VOI from which the tract originated.

Figure 2. Example of the VOIs used to define the fornix (top row) and cingulum (bottom row). Fornix tracts were reconstructed if they passed through the columns (yellow), body (blue) and either the right crux (red) or left crux (green). Cingulum tracts were reconstructed if they passed through an anterior VOI (left: red, right: pink) and a posterior VOI (left: blue, right: green).

Figure 3.
Reconstructed volume for seven tracts and four acquisitions. The marker shape denotes acquisition type and color gives the reconstructed tract.

Figure 4.
Diffusion metrics for each of the tracts and acquisitions.

Figure 5.

Streamline reconstruction of the fornix from one subject. The color coding is based on the FA (top set) or MD (bottom set) of the tract. The reconstruction is presented in axial (top row), sagittal (middle), and coronal (bottom) views within each set of images.

Figure 6.

f -value projected onto the reconstruction of the fornix (left), cingulum (center), and corpus callosum (right). The fornix displayed the greatest degree of PVE as it is located inferior and proximal to the CSF filled ventricles. Corpus callosum reconstructions from two separate subjects are shown. The blue arrows show the area of PVE with the ventricles. Green arrows show tracts, which propagate through the cortex where PVE are common due to the folded nature of the cortex.

Table 1

Relevant scan parameters for the four acquisitions to be compared.

	FLAIR DTI	Standard DTI	FWE (long)	FWE (short)
Acquisition time	9:00	9:00	9:00	5:24
TR (ms)	10000	6000	6000	6000
TE (ms)	63.1	63.1	68.9	68.9
Number of images $\times$ b-value	6 $\times$ 0 48 $\times$ 1000	10 $\times$ 0 80 $\times$ 1000	10 $\times$ 0 40 $\times$ 500 40 $\times$ 1500	6 $\times$ 0 24 $\times$ 500 24 $\times$ 1500
Number of slices	34	64	60	60

Table 2

Mean isotropic signal component for CC regions with and without correction for highly partial volumed voxels.

Tract:	CC-I	CC-II	CC-III	CC-IV	CC-V
Without Correction	0.164 ± 0.025	0.197 ± 0.030	0.226 ± 0.034	0.266 ± 0.027	0.278 ± 0.021
With Correction	0.156 ± 0.021	0.183 ± 0.022	0.222 ± 0.036	0.260 ± 0.029	0.264 ± 0.020

Table 3

Mean of the standard deviations of the diffusion metrics along the fornix and cingulum.

	Fornix				Cingulum			
	DTI	FLAIR	FWE long	FWE short	DTI	FLAIR	FWE long	FWE short
FA	0.12	0.13	0.17	0.16	0.09	0.11	0.12	0.14
MD	0.26	0.10	0.15	0.15	0.04	0.03	0.04	0.05
RD	0.26	0.13	0.16	0.15	0.07	0.08	0.07	0.08
AD	0.33	0.26	0.29	0.31	0.11	0.15	0.15	0.18

Table 4

Mean of the standard deviations of the blinded review rank and score.

	Rank				Score			
	Standard DTI	FLAIR	FWE (Long)	FWE (Short)	Standard DTI	FLAIR	FWE (Long)	FWE (Short)
Fornix	4.00 ± 0.00	2.78 ± 0.57*	1.28 ± 0.45*†	1.95 ± 0.61*†	3.86 ± 0.36	2.55 ± 0.90*	1.13 ± 0.31*†	1.55 ± 0.63*†
Corpus Callosum	3.93 ± 0.25	2.65 ± 0.71*	1.80 ± 0.81*†	1.63 ± 0.67*†	2.38 ± 0.67	1.83 ± 0.58*	1.38 ± 0.48*†	1.38 ± 0.48*†
Cingulum Bundles	3.18 ± 1.07	2.03 ± 1.08*	2.05 ± 0.83*	2.75 ± 1.10†	2.03 ± 0.82	1.45 ± 0.50*	1.58 ± 0.68*	1.93 ± 0.76†

Rank is from best (1) to worst (4) and score is from excellent (1) to poor (4). Significant differences ($p < 0.05$) from Standard DTI (*) and FLAIR (†) reconstructions are indicated.