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Harmonization of multi-center diffusion tensor imaging data: Challenges and solutions.

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Introduction

Diffusion tensor imaging (DTI) has become an essential tool for mapping white matter microstructure and investigating connectivity patterns in the human brain. Large-scale, multi-center studies are increasingly recognized as necessary for achieving sufficient statistical power, improving generalizability, and enabling the study of rare conditions or subtle neurobiological effects. However, multi-center DTI research faces a fundamental challenge: variability introduced by differences in scanner hardware, acquisition protocols, gradient directions, and reconstruction algorithms. These inconsistencies can lead to systematic biases in derived diffusion metrics such as fractional anisotropy (FA), mean diffusivity (MD), and radial and axial diffusivity. Without proper harmonization, such site-related differences can obscure genuine biological effects and compromise the reproducibility and validity of findings, ultimately limiting the potential impact of collaborative neuroimaging efforts [1].

One of the primary sources of variability in multi-center DTI datasets arises from differences in MRI scanner vendors and models. Even when acquisition parameters are nominally matched, intrinsic differences in gradient performance, hardware calibration, and signal-to-noise characteristics can produce systematic deviations in diffusion measurements. Additionally, protocol-related differences—such as variations in voxel size, number of diffusion directions, b-values, and echo times—can influence the accuracy and precision of tensor estimation. Reconstruction pipelines, including eddy current correction, motion correction, and susceptibility distortion correction, can further introduce variability depending on the software and parameter settings used. These differences make it difficult to directly compare or pool data across sites without first addressing these non-biological sources of variability through harmonization techniques [2].

Harmonization methods for multi-center DTI data can broadly be classified into prospective and retrospective approaches. Prospective harmonization involves standardizing acquisition protocols, hardware calibration procedures, and preprocessing pipelines before data collection begins. While this is the ideal scenario, it is often challenging to achieve across diverse research sites due to logistical constraints, ongoing studies with established protocols, and hardware differences that limit full standardization. Retrospective harmonization, on the other hand, focuses on adjusting datasets after acquisition to account for site-specific effects. Statistical methods such as ComBat, originally

developed for genomics data, have been adapted for neuroimaging and are widely used to remove unwanted site-related variability while preserving biological variation of interest. Other approaches employ machine learning models, including domain adaptation techniques, to map data from different sites into a common feature space [3].

Recent advances in harmonization have also leveraged the use of traveling subjects and calibration phantoms. Traveling subject designs involve scanning the same individuals across multiple sites, enabling direct estimation of site-specific bias factors that can be applied to correct the broader dataset. Calibration phantoms, which provide stable and reproducible diffusion measurements, can be scanned periodically to monitor scanner stability and help model systematic drift or variability over time. Moreover, harmonization strategies increasingly integrate multi-shell and advanced diffusion models such as neurite orientation dispersion and density imaging (NODDI), which may be more sensitive to microstructural differences while also being susceptible to site effects. Combining these approaches with standardized preprocessing pipelines—such as those implemented in FSL, MRtrix, or the UK Biobank protocols—further enhances the consistency and comparability of DTI metrics across centers [4].

Despite these methodological advances, several challenges remain in the harmonization of multi-center DTI data. Retrospective methods like ComBat require sufficiently large datasets with balanced covariates to accurately estimate and remove site effects, and they may perform less effectively when biological differences are confounded with site differences. Machine learning-based harmonization methods may introduce overfitting or inadvertently remove meaningful biological variance if not carefully validated. Furthermore, harmonization approaches must be robust to the inclusion of data from newly added sites, as ongoing multi-center studies often expand over time. Another persistent issue is the lack of universally accepted standards for evaluating harmonization success; metrics such as reduced site classification accuracy, preserved group differences, and improved cross-site reproducibility must be considered in combination to assess effectiveness. Addressing these challenges will require not only technical innovations but also collaborative agreements on best practices and validation benchmarks within the neuroimaging community [5].

Conclusion

The harmonization of multi-center diffusion tensor imaging data is essential for ensuring the validity, reproducibility, and interpretability of large-scale neuroimaging studies. By addressing scanner- and protocol-related variability through a combination of prospective standardization, retrospective statistical adjustment, and calibration-based monitoring, researchers can mitigate the confounding effects of site differences and enhance the reliability of cross-site comparisons. While methods such as ComBat, machine learning-based domain adaptation, and traveling subject designs have demonstrated considerable promise, challenges remain in achieving robust and universally applicable solutions. As multi-center collaborations continue to expand, harmonization will play a pivotal role in enabling meaningful integration of DTI datasets, ultimately supporting more accurate mapping of white matter architecture and advancing our understanding of brain connectivity in health and disease.

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