**niCHART: From Neuroimaging Big Data to Individualized Imaging Signatures of Disease**

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**Introduction**

Neuroimaging has been widely adopted by studies of brain development and aging, as well as of neurologic, neuropsychiatric, and neurodegenerative diseases. This rapidly growing web of data that was acquired over decades in multiple studies, in conjunction with the advent of advanced machine learning methods, has created tremendous potential for knowledge discovery at a large scale. Machine learning (ML), in particular, has offered great promise for precision diagnostics as well as derivation of imaging signatures of diseases, disease subtypes, endophenotypes, and predictive models. We describe the niCHART (NeuroImaging Computational Harmonization and ARtificial intelligence Toolbox), an ecosystem of algorithms and software implementations for data pooling, statistical harmonization, and ML-based analyses across studies. After integration of distinct existing components, niCHART will enable large-scale analyses of multi-modal brain MRI data, and mapping of such data into a dimensional system of neuroimaging signatures implemented by our ML models.

**Methods**

The axes of niCHART dimensional system represent two types of information: 1) a panel of structural (sMRI), diffusion (dMRI) and functional (fMRI) imaging derived phenotypes (IDPs), and 2) complex ML-based imaging signatures (ML-IDPs) derived from carefully processed and curated data (fig. 1). Image processing module integrates advanced, validated pipelines that have been publicly released and applied to large scale studies, for consistent and reproducible processing [1-3], as well as automated tools for quality control [4]. A statistical harmonization method adapted to multi-site MRI data with presence of nonlinear age trends is utilized for explicit removal of site-related effects [5]. ML-IDP models [6-9] map the high dimensional image data into the niCHART reference frame [10]. Dimensions of niCHART capture and quantify multi-variate imaging patterns of brain change reflecting the heterogeneity of brain aging, neurodegeneration, as well as of neuropsychiatic disorders.

**Results**

niCHART reference data consist of pooled and harmonized imaging data of 65,693 individuals (84,211 time points) from 22 studies, with predominantly structural MRI. Derived imaging variables include data-driven and atlas based multi-scale brain parcellations, structural covariance units, connectivity measures, and brain networks. The dataset is used to establish normative ranges of brain structure and function, as well as a rich set of ML-IDPs (fig 2). In particular, we constructed two types of ML-IDPs. Supervised ML-IDPs, indices derived based on labels of interest, e.g. disease or clinical progression status, were applied to train models for brain aging throughout the lifespan, schizophrenia, depression, ASD, MCI and AD [6,7,8]. ML-IDPs using semi-supervised pattern clustering methods, which aim to uncover disease heterogeneity, identified two distinct neuroanatomical signatures of schizophrenia and their clinical correlates, and dissected the neuroanatomical heterogeneity of MCI and AD into 4 subtypes, with two distinct longitudinal pathways in MCI to AD progression [10]. The panel of reference ML-IDP values and pre-trained models allow users to place their images into the chart by computing the extent an individual expresses each of these imaging signatures.

**Conclusions**

niCHART will offer a software suite, along with associated machine learning models, for analysis of multimodal neuroimaging datasets. Extendible ML models provide users with the opportunity to augment current imaging-derived phenotypes with a panel of ML-based imaging signatures associated with healthy and diseased brain states. Via statistical harmonization and machine learning, two central pillars in our system, niCHART provides the machinery to derive biomarkers that focus on individual-centric analyses, and hence contribute to the concepts of precision medicine and dimensional phenomics.

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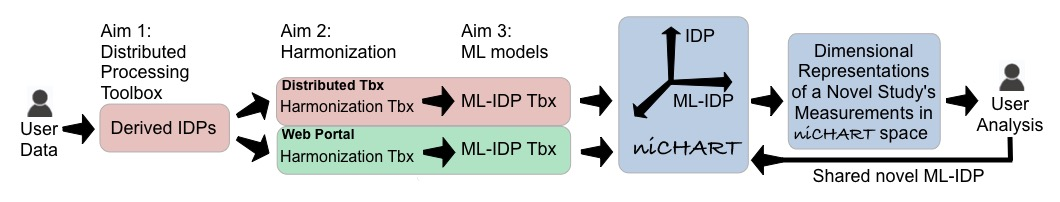
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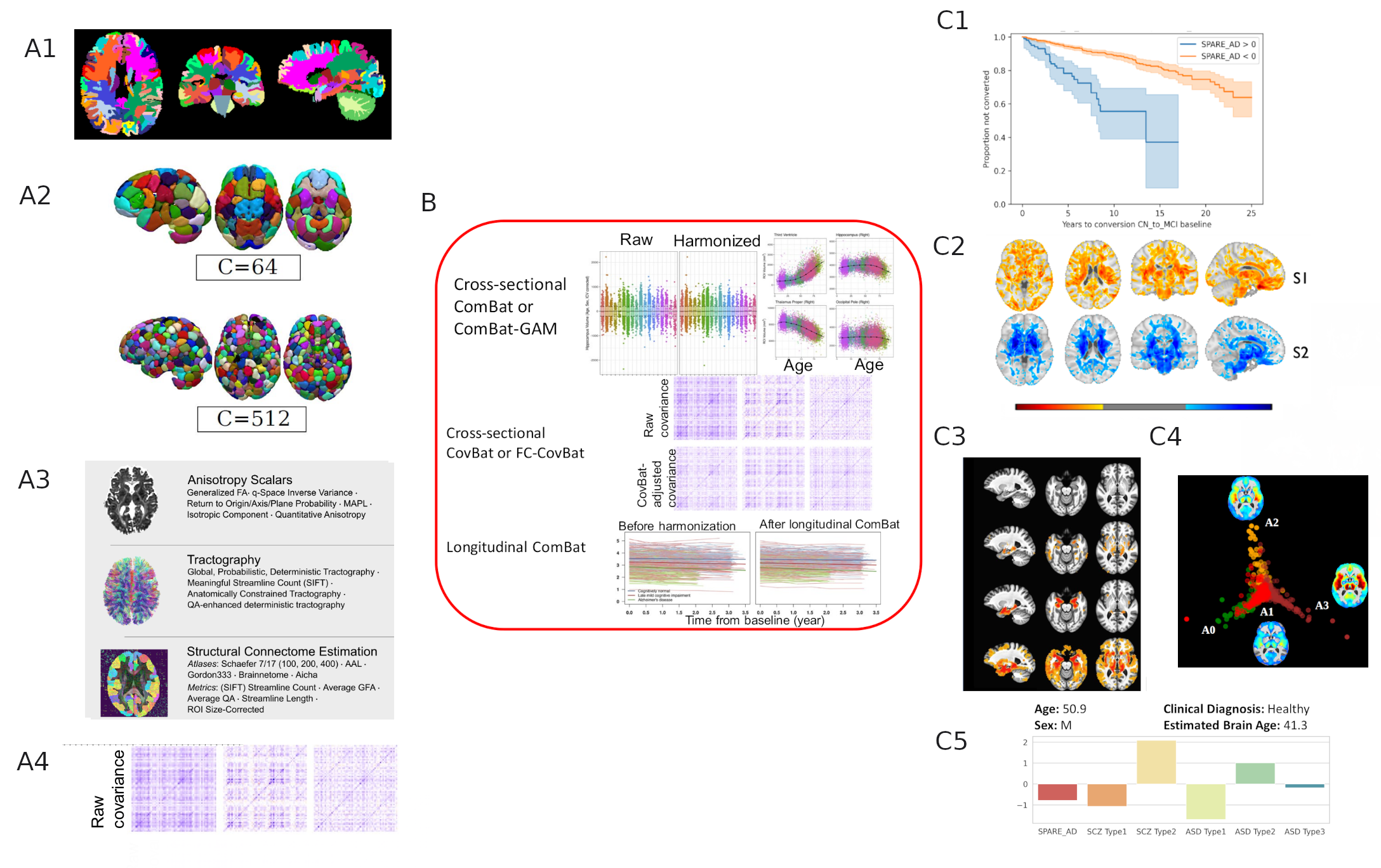
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***Figure 1:*** *Schematic of the image processing pipelines and software suite that allows researchers to use or derive, from pooled reference data and their data, a dynamically growing number of AI-based biomarkers of brain structure and function, which capture complex multi-variate patterns of typical and pathologic brain states. Dimensional niCHART serve as a canonical space within which researchers are able to harmonize their data with other studies using provided software tools, and apply a variety of ML models defined in that space.*

***Figure 2:*** *NiChart imaging phenotypes (A), statistical harmonization (B) and ML-based imaging signatures (C). A1. Structural regions of interests; A2. Data driven multi-scale non-negative matrix factorization components ; A3. DTI image variables; A4. Functional connectivity variables; B. Statistical harmonization using ComBat, CovBat and longitudinal ComBat; C1. SPARE-AD scores, survival curves for conversion from MCI to AD; C2. Schizophrenia sub-types identified using semi-supervised pattern clustering method HYDRA; C3. AD sub-types identified using semi-supervised pattern clustering method SmileGAN; C4. Heterogeneous sub-types of brain aging identified using SmileGAN; C5. Individualized ML-IDP panel for a single subject*