Towards Lifespan Brain Charts of Normal Brain Growth, Aging, and Neuropsychiatric Disease

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Overview

In our view, the ultimate goal for brain charts is to provide reference norms of phenotypes derived from neuroimaging data, analogous to pediatric growth charts for height and weight. In the case of anatomical MRI, brain charts enable brain morphological phenotypes derived from individual MRI scans, such as cortical thickness or gray matter volume, to be quantitatively benchmarked to population norms. The result is highly interpretable metrics that place an individual on a continuous dimension of brain deviation. The ambitious goal of widely adopted brain charts that add value to research and clinical studies has not yet been achievable because of difficulty in amassing multi-site data, image processing challenges (especially early in life), and accurately modeling normative brain development. Our application is designed to provide attendees with insight into recent studies that seek to overcome these challenges and provide a roadmap for the utility of brain charts in future neuroimaging studies of the human brain. To this end, Lana Vasung, M.D., Ph.D., will begin the symposium discussing prenatal and perinatal imaging, and the unique challenges and importance of incorporating this developmental stage into normative imaging models. Next, Francesca Biondo, Ph.D., will present her work on the application of the brain age paradigm to studies of children and adolescents, and the relationship between the brain age approach and other normative modeling approaches. Richard Bethlehem, Ph.D., will present the development of a lifespanning brain chart resource designed to be applicable to any brain structural MRI study. Finally, Maria Di Biase, Ph.D., will focus on the application of normative modeling to schizophrenia and its particular relevance in the context of inter-individual heterogeneity. Assuming a 75-minute window, each presentation will be 12 minutes long with 3 minutes of discussion in between presentations, followed by an additional 15 minutes of discussion led by Aaron Alexander-Bloch, M.D., Ph.D., Damien Fair, P.A., Ph.D., and Kate Mills, Ph.D. The discussion will focus on the importance of normative modeling in the context of the broader field of developmental human brain

mapping as well as challenges that remain for the goal of widely-adopted brain charts that add practical value for research and clinical studies (and ongoing strategies to address these challenges).

Lecture 1: *The unique challenges and importance of incorporating prenatal brain MRI into lifespan models*
Lana Vasung Presenter

The prenatal development of the human nervous system is one of the most complex processes in the realm of neuroscience. The unique species-specific features and transient neuronal/axonal scaffolds are often stage-specific and require a comprehensive week-by-week evaluation during fetal in-utero lifespan. Despite the clinical and research endeavors, in-utero MRI imaging of the fetal brain remains in its infancy. Consequently, the amount of information and knowledge fetal neuroimaging provides to the research community is currently modest and, to a large extent, fragmentary. The unique challenges of incorporating in-utero MRI into lifespan models are primarily tied to slower technological advancements in the field. [e.g., a limited number of MRI sequences that capture transient brain structures, incompatibility of fetal MRI processing pipelines, lack of harmonized multi-modal cross-site MRI acquisition protocols, and non-existence of public access web-based portals for visualizing, searching, and sophisticated mining of fetal structural and functional neuroimaging data]. In addition, we are also limited by inadequate 'ground-truth' knowledge about neurogenic events that occur in the human fetal brain [i.e., lack of comprehensive gene expression, histology, and/or ex-vivo MRI studies]. Hence, the framework for interpreting fetal MRI findings and estimating 'fetal brain age' frequently relies on our understanding of the structure-function relationship in the adult brain, despite the widely accepted concept that the fetal brain is 'not just a small adult brain'.This talk will focus on the importance of incorporating findings from in-utero fetal brain MRI into lifespan models by considering and emphasizing fetal-specific biomarkers of corticogenesis [e.g., changes in the thickness and surface of fetal cortex: the subplate and cortical plate]. Furthermore, we will also discuss periods of reorganization [e.g., overgrowth and retraction of axons associated with regional changes in brain volume] that display considerable inter-individual differences and lay the foundation for postnatal spatio-temporal brain maturation [e.g., growth of corpus callosum and corticospinal tract]. Finally, we will also address the sensitivity and specificity of certain findings (e.g., increased brain volumes, enlargement of ventricles) and a broad divergence of postnatal conditions associated with them.

Lecture 2: *Brain age models in childhood and adolescence*
Francesca Biondo Presenter

The brain-age paradigm uses neuroimaging data to provide a simple metric of brain health that is condensed into a single metric. This biomarker has previously been shown to be robust and sensitive to both current and future cognitive and health outcomes. However, so far, this paradigm has primarily focused on adult populations with negligible research focused on brain-age models in childhood and adolescence. This talk will present our attempts at developing such models, using collaborative multi-site data which we then test on a completely independent dataset. The main neuroimaging feature sets used to train the brain-age models are primarily FreeSurfer-based and include grey matter, subcortical and white matter volumes. We use a wide array of machine learning methods to train the models whilst using separate training-validation sets to minimise overfitting. We proceed to apply the best-performing brain-age model to the test data to investigate associations between brain-age pad (predicted age difference, calculated as brain-predicted age minus actual chronological age) and cognitive outcomes in children. Challenges faced in these analyses are discussed, including problems related to sparseness of

data and, discrepancies between sites, cohorts and preprocessing pipelines. What does brain-age reveal in this younger population? Although in adult populations, older-than-expected (positive) brain-ages have typically been associated with negative health outcomes, it is unclear whether neurodevelopment signatures linked to poorer cognitive outcomes in children are associated with positive or negative brain-age pads. The unique challenges of developmental neuroimaging highlight the complementary strengths and weaknesses of brain age models compared to other brain charting methods discussed in the symposium.

Lecture 3: *An interactive resource to provide benchmark models of brain structure from the prenatal period through end of life*
Richard Bethlehem Presenter

This talk focuses on the development of an interactive resource (https://www.brainchart.io) to benchmark individual differences in brain morphology, measured from any current or future magnetic resonance imaging (MRI) study, against normative age-related trends. With the goal of basing these reference charts on the largest and most inclusive dataset available, we aggregated 123,984 MRI scans from 101,457 participants in over 100 studies – from 115 days post-conception through 100 postnatal years. Cerebrum tissue volumes and other global or regional MRI metrics were quantified by centile scores, relative to non-linear trajectories, demonstrating concurrent validity with non-MRI brain growth milestones, high stability over longitudinal assessments, and robustness to differences between studies. Brain charts identified previously unreported neurodevelopmental milestones, and centile scores had increased heritability compared to non-centiled MRI phenotypes. Crucially, for future clinical purposes, centile scores provided a standardised and interpretable measure of deviation that revealed new patterns of neuroanatomical differences across neurological and psychiatric disorders. In sum, brain charts for the human lifespan are an essential first step towards robust, standardised quantification of deviation from age-related trends in multiple commonly-used neuroimaging phenotypes. Our global collaborative study provides such an anchorpoint for neuroimaging research and will facilitate implementation of quantitative standards in clinical studies.

Lecture 4: *Normative models add value to studies of brain deviation in schizophrenia*
Maria Di Biase Presenter

This talk presents recent applications of normative modelling in schizophrenia to examine i) heterogeneity in the loci of cortical abnormalities and ii) the biological basis of this heterogeneity. While gray and white matter abnormalities are indeed a core neuropathological feature of schizophrenia, our findings suggest that the anatomical loci affected by these abnormalities differ vastly across individuals to the extent that group-average maps of schizophrenia pathology do not accurately resemble individual patients. For this reason, we cannot neatly pin down schizophrenia-related brain changes to circumscribed cortical regions using conventional case-control paradigms. What underlies such vast heterogeneity? Our follow-up studies indicate that marked heterogeneity results from interindividual variation in cellular pathologies across individuals with schizophrenia, as inferred from systematically combining deviations from normative ranges of brain structure with spatially-resolved gene expression data and person-specific genomic variation. Collectively, these studies call to question the viability of ongoing endeavors to derive group-average cortical maps of schizophrenia pathology. Decomposing cortical heterogeneity through combining normative models of brain phenotypes with multi-scale omics enables prioritization of schizophrenia subsets and cell types of interest for future disease modeling efforts.