Risk and Resiliency Across the Aging Adult Lifespan

David Salat Organizer
Massachusetts General Hospita
Charlestown, Massachusetts
USA

Beau Ances, MD, PhD Co-Organizer
Washington University School of Medicine
St. Louis, Missouri
USA

Susan Bookheimer, PhD Co-Organizer
University of California, Los Angeles
Los Angeles, California
USA

Essa Yacoub Co-Organizer
Center for Magnetic Resonance Research, University of Minnesota
Minneapolis, Minnesota
USA

Overview

This symposium is particularly timely with the public release of the HCP-A dataset. Specifically, this symposium will provide valuable information regarding the data available in this dataset as well as the range of applications that can be explored through the utilization of these data.

Lecture 1: *The HCP-Style Approach to Brain Imaging and Imaging Data Phenotypes*

Matthew Glasser Presenter

Initiated a decade ago, the Human Connectome Project (HCP) offered an opportunity to re-evaluate and advance brain imaging data acquisition and analysis methods. We will review the high spatial, temporal, and angular resolution approach to multi-modal MRI data acquisition pioneered by the original young adult HCP and its application to longitudinal studies of aging in the Human Connectome Aging (HCA) project and its extension, the Adult Aging Brain Connectome project (AABC). Major gains in spatial localization precision have been achieved by using cortical surface-based methods for cross-subject alignment and avoiding unconstrained volumetric spatial smoothing. Similarly, major gains have been made in data driven fMRI denoising using spatial and temporal ICA-based approaches. These advances enabled the generation of a new multi-modal map of human cortical areas, including a machine learning areal classifier that can identify these cortical areas automatically in new subjects. Given these developments, the focus now turns to how the HCP-Style approach can be expanded and adapted to derive imaging data phenotypes (IDPs) for the hypothesis driven research that will be presented in the following sessions. Multi-modal imaging data phenotypes can be categorized into those defined within brain areas, functional networks, and white matter tracts and they can be measures derived from structural MRI, functional MRI, vascular MRI, or diffusion MRI. Using the brain's neuroanatomical organization to subdivide the data improves interpretability, signal to noise ratio, and statistical power

over traditional voxel-wise approaches by assigning findings directly to neurobiological entities, averaging out the random noise within these entities, and reducing non-independent multiple comparisons. Finally, the HCP's approach to sharing data and tools enables other investigators to apply these advances to their own studies.

Lecture 2: *Early Risk and Late Life Resilience*
Barnaly Rashid, PhD Presenter

Prior studies have identified several health and lifestyle factors, such as demographic and social determinants of health (e.g., socioeconomic status and education quality/skill), lifestyle and wellness factors (e.g. physical activity and sleep quality), and systemic and organ health (including conditions beginning at midlife, e.g. hypertension and obesity) that may confer vulnerability for or protection against risk for the development of AD and ADRD. The infrastructure developed through the HCP-A offers a unique, large, and well-characterized longitudinal sample (aged 60-90+ years) to investigate mechanisms of optimal or 'successful' cognitive aging in the oldest of the old. This session will discuss the impact of advanced aging on structural and functional brain connectivity, neurochemistry, and cognitive performance and risk, with a specific focus on understanding the factors that promote optimal cognitive aging in the latest decades of life through resilience/resistance mechanisms. Results will be discussed based on recent neuroimaging biomarkers, particularly brain structural and functional connectivity, cerebrovascular physiology, and AD biomarkers.

Lecture 3: *Neurochemical Profiles of Late Life Cognitive Risk*
Melissa Terpstra, PhD Presenter

As part of the AABC initiative, MRS data will be collected on 7T magnetic resonance spectra (MRS) longitudinally at multiple institutions alongside extensive connectome style imaging, health, behavioral and socioeconomic data. Noninvasively measured human brain chemical concentrations are sensitive to early events in the AD process because they reflect cellular mechanisms of pathogenic processes. Using ultra-high field, we have been able to robustly quantify a neurochemical profile comprised of 14 brain chemicals from key regions of the default mode network, i.e., the posterior cingulate cortex and the prefrontal cortex. Preliminary analyses identified age- and AD-associated differences in 8 neurochemicals, with a strong decline in phosphorylethanolamine (PE) concentration with age which is a putative marker of demyelination. Additional findings revealed AD-associated changes in Vitamin C (Ascorbate, Asc) concentration and suggested its involvement in pathological transition to symptomatic AD. Our findings indicate that neurochemical changes seen with 1H MRS may contribute to brain connectivity changes. This session will address current gaps in our knowledge on brain chemistry underlying cognitive decline and AD, and provide results from ultra-high field 1H MRS examinations of the neurochemistry of brain aging and AD/ADRD.

Lecture 4: *Vulnerability to and resilience against risk factors and biomarkers of Alzheimer's disease*
Beau Ances, MD, PhD Presenter

Although symptomatic manifestations of Alzheimer's disease typically only appear in later life, this condition represents a cumulative risk across the lifespan. Genetics, including apolipoprotein-E genotype have a major impact on an individual's risk from birth and lifestyle, life exposures, and health all contribute to this cumulative risk throughout the lifespan. Ultimately, a portion of individuals in the

later decade of life begin to exhibit the classical amyloid, tau, and neurodegenerative pathologies of Alzheimer's disease. However, there is great variability in the degree to which these pathologic changes impact cognition and functional outcomes. This session will describe how risk factors for, and biomarkers of Alzheimer's disease impact brain connectivity across adulthood. The overarching message is that although risk conditions and degenerative biomarkers increase the likelihood for impairment, neural connectivity patterns provide clues to mechanisms that may protect individuals from functional decline in the face of this risk and vulnerability. Results will highlight the associations between structural and functional brain connectivity and AD biomarkers, with an emphasis on future directions.