Core G: Imaging Specific Aims

The DIAN cohort represents an unparalleled, comprehensive repository of preclinical and clinical ADAD imaging biomarkers, including amyloid and metabolic PET and structural and functional MRI. In this unique cohort, the largely cross-sectional data obtained to date has generated critical data to outline a timeline for the appearance of imaging biomarkers prior to the symptomatic onset of AD. We now propose in the next budget period to obtain critical longitudinal data, with imaging every two years, so that the preliminary cross-sectional findings can be validated. Primary imaging data from this study has been shared with investigators worldwide and, via a consortium with the independently funded and operated DIAN Trials Unit (DIAN-TU), with major pharmaceutical companies for the purpose of designing clinical trials. We propose to continue our original imaging aims and also to extend them, to include:

Aim 1: Oversee the collection of all baseline and longitudinal imaging data in DIAN participants. These include MR scans for morphometrics and amyloid related imaging abnormalities (ARIA) and for brain function, including rs-fcMRI, ASL for relative cerebral blood flow (rCBF), and DTI for white matter connectivity. Also included are FDG PET scans for metabolism and PIB PET scans for fibrillar amyloid. All participants will have MRI and PET imaging every two years, in conjunction with their clinical visits, until they reach a Clinical Dementia Rating (CDR) of 2 or higher. The Imaging Core will supervise the functions of the ADNI QC subcontracts (headed by Clifford Jack, M.D. for MR and Robert Koeppe, Ph.D. for PET imaging).

Aim 2: Perform image processing and analysis to extract biologically relevant measures from the image data set. For MRI, these measures include whole brain volume and cortical and subcortical regional measures of gray matter volume, rCBF, and connectivity measured using rs-fcMRI and DTI. For PET, these include relative glucose metabolism and PIB-derived estimates of beta-amyloid fibrillar plaque deposition. The Imaging Core will achieve Aim 2 with a suite of interrelated image processing routines. The primary processing line will involve, (a) registration of the anatomic MR scans with the PET images, (b) segmentation and parcellation of the anatomic MRI images via FreeSurfer (c) generation of ROIs and gray matter volumes from FreeSurfer, (d) application of the FreeSurfer and hand-drawn ROIs to the coregistered PET PIB and PET FDG scans, and (e) processing of regional activity values to yield regional PIB standardized uptake value ratios (SUVRs) and relative metabolism.

Aim 3: Further evaluate critical imaging findings identified in the first budget period including (a) compare cross-sectional evaluation of the temporal ordering of imaging biomarkers in ADAD longitudinal imaging data, (b) characterize a possible hypermetabolic phase of disease identified by FDG PET in asymptomatic MCs early in the course of amyloid deposition, (c) assess similarities between the hypometabolic phase on FDG PET and regionally decreased rCBF on MRI, and (d) further characterize the finding of potentially accelerated brain injury, consisting of microhemorrhages, white matter hyperintensity, and infarction in the late stages of ADAD.

Aim 4: During the course of the current grant, we have adapted the imaging design to incorporate new imaging techniques and approaches, including MRI rs-fcMRI, ASL, DTI and, in a limited fashion, florbetapir PET. As exploratory analyses in this renewal we will: (a) continue to harmonize the DIAN imaging protocol with ADNI and to perform parallel analyses, to allow for full comparison of the DIAN and ADNI cohorts, (b) compare the PET amyloid amyloid imaging results to the CSF data (Core E) and to evaluate surrogate measures for FDG PET (such as ASL), in order to potentially reduce radiation dose to current study participants and future AD patients, (c) perform genotype-phenotype examination of regional amyloid deposition, regional atrophy, and regional brain function, based on specific genetic mutations in conjunction with the Clinical, Genetics, and Neuropathogy Cores, and (d) evaluate new PET imaging tracers, including those that identify tau , as they become available.