Notes for power/sample size and analysis plan for Project 4

* General understanding
  + Some immune response? Good. Too much immune response? Bad effects on neurological function.
  + Too much inflammation may lead to MCI and Alzheimer’s.
  + Certain biomarker pathways are involved somehow w/ inflammatory markers, brain structure, cognition
  + Want to look at these relationships over time
    - T/f it sounds like they’re measuring biomarkers and outcomes over time
    - Baseline and one-year follow-up
  + “Our goals are to rigorously examine links between **established and novel peripheral inflammatory markers** in circulating plasma, **memory consolidation**, **and grey matter over time**, to determine whether **peripheral inflammatory markers synergize (interaction???) with amyloid pathology to accelerate clinical progression**, and to determine whether immune cargoes from CNS-derived blood exosomes are better predictors of cognitive decline and cortical thinning when compared to total exosome markers.
* Aim 1
  + Aim 1: Evaluate longitudinal associations between markers of peripheral inflammation, cognition, and brain structure in aMCI
    - higher baseline cytokine and chemokine levels in circulating plasma will predict declines in memory consolidation and decreases in AD-signature cortical thickness (Hypothesis 1a)
    - Aim 1a: outcomes: decline in memory (change in 1-year) and change in cortical thickness (change over 1-year). covariates for Aim 1 – cytokines and chemokines (i.e. IL-6; TNF-alpha; MCP-1; Eotaxin- 1; Beta-2 microglobulin; and ACT). I have to adjust for age and sex and anything else you tell me needs to be adjusted for. For example how will we handle the known associations between inflammation, cardiovascular risk, immunological health history conditions, and APOE genotype, correlations between the health measures (i.e. BMI, history of hypercholesterolemia, NSAID use; immune-related health conditions) (67, 68) and inflammation variables, as well as t-tests using APOE genotype will be conducted. Are these confounders???
    - -----------------------------------
    - greater increases in cytokines and chemokines will be associated with greater declines in episodic memory and cortical thickness (Hypothesis 1b)
    - Reminder for Aim 1b: outcomes: decline in memory and primary covariates is now changed in cytokines and chemokines.
* Aim 2
  + Aim 2: Examine how markers of peripheral inflammation impact the relationship between AD pathology and clinical progression of aMCI
  + We will test our hypothesis of an **interaction between peripheral levels of inflammation and amyloid deposition**, such that the presence of both significant amyloid deposition and elevated peripheral inflammatory markers will be the strongest predictors of memory decline and decline in AD-signature cortical thickness over a one year period.
  + Hypothesis: there is an exaggerated inflammatory response that contributes to AD pathological processes and is more pronounced and pervasive than in non-AD aging.
  + 2a
    - Aim 2a: outcome is amyloid deposition and cortical thickness and covariates are inflammatory markers. As in Aim 1 we need to control for age and sex. Also confounders??
  + 2b
    - Aim 2b: outcome is clinical progression variables (change in memory—see study design for measures), covariates are amyloid deposition (and cortical thickness) and inflammatory markers. I want to know if cytokines and chemokines modify the association between amyloid deposition (or cortical thickness) and clinical progression. Confounders?
* Overall note
  + Based on existing clinic flow and on enrollment at the RMADC, a reasonable final sample size is projected to be 125 aMCI and 50 HC subjects. We will enroll 137 aMCI and 55 HC to allow for a 10% attrition by one year follow-up. This is the sample size I am thinking of.
    - Can you either justify this sample size?
  + Note these two groups will be combined for analysis. I am recruiting from both populations so that I get a diverse representation of cytokine levels and outcome levels. If you do your calculation and want me to recruit more people, just let me know. Also, I know we have a lot of cytokine/chemokines so I am expected you to adjust for multiple comparisons somehow. I just wanted you to know that I won’t be surprises to see an alpha <0.05.