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. **adjust fo r 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???
      * Plan: add all highlighted confounders to model, then use backwards selection w/ AIC (keeping all primary predictors in model [age, sex, baseline, inflammatory markers])
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    - **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. **Status variable**
  + WHAT IS PRIMARY PREDICTOR?
* 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 and status**??
  + 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**? And **status**
* 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.