Project 4:

RACHEL WEBER

Aims and Hypotheses

1. Aim 1
   1. Hypothesis a. Higher baseline levels of cytokines and chemokines is associated with greater declines in episodic memory and decreased cortical thickness
   2. Hypothesis b. Greater increases in cytokines and chemokines is associated with greater declines in episodic memory and decreased cortical thickness
2. Aim 2
   1. Hypothesis: Presence of Amyloid Deposition and elevated peripheral inflammatory markers is the strongest predictor of memory decline and decline in AD-signature cortical thickness
3. Aim 3
   1. Hypothesis a. Levels of cytokines and chemokines from CNS-derived exosomes will be higher in aMCI relative to HC subjects.
   2. Hypothesis b. High levels of inflammatory markers from CNS-derived exosomes and increases in these levels better predicts memory decline and decreases in AD-signature on neuroimaging relative to total exosomes.

Aim 1—Analysis Plan

Hypothesis A:

1. $memory\ decline = baseline\ cytokines + sex + age + BMI + NSAIDS$
2. $memory\ decline = baseline\ chemokines + sex + age + BMI + NSAIDS$
3. $\Delta\ cortical\ thickness = baseline\ cytokines + sex + age + BMI + NSAIDS$
4. $\Delta\ cortical\ thickness = baseline\ chemokines + sex + age + BMI + NSAIDS$

5. Overall F-tests will determine model significance
6. Variables will be significant if p-value is below .05
7. Partial F-tests will determine individual variable significance

Hypothesis B:

1. Model will be repeated but will use $\Delta\ cytokines$ and $\Delta\ chemokines$ in place of baseline.

Aim 2—Analysis Plan

1. $\Delta\ amyloid\ deposition = baseline\ inflammatory\ markers + sex + age + BMI + APOE + NSAIDs$
2. $\Delta\ cortical\ thickness = baseline\ inflammatory\ markers + sex + age + BMI + APOE + NSAIDs$
3. $memory\ decline = \Delta\ amyloid\ dep. + sex + age + BMI + APOE + NSAIDs$

vs.

$memory\ decline = \Delta\ amyloid\ dep. + base\ inflam. + sex + age + BMI + APOE + NSAIDs$

4. $memory\ decline = \Delta\ cortical\ thickness + sex + age + BMI + APOE + NSAIDs$

vs.

$memory\ decline = \Delta\ cortical\ thickness + base\ inflam. + sex + age + BMI + APOE + NSAIDs$

3 and 4 to check if chemokines/cytokines are effect modifiers

Aim 3—Sample Size Calculation

1. Power Calculation
   - Desired Power: 0.8
   - Enrollement: 137 aMCI and 55 control—192 total
     - Ratio of control to aMIC = 55:137
     - $N = \frac{N(1+k)^2}{4k}$ for total sample size given unequal group sizes where k is the group ratio and N is the sample given from the power calculation
   - SD of ΔMCI: 0.5
   - True Difference in Means: 4.6
   - Significance Level: 0.05
   - Test correlations: .25, .5, .75

Whitley E, Ball J. Statistics review 4: sample size calculations. *Crit Care*. 2002;6(4):335-41.

Aim 3—Analysis Plan

1. $\Delta\, Memory = baseline\ markers + sex + age + BMI + NSAIDs + APOE + aMCI_{Yes}$
   - aMCI status included as precision variable. Will elucidate is there is a difference between healthy controls and aMCI when all other variables remain constant. Significance at p = 0.05
2. $\Delta\, ADsignature = baseline\ markers + sex + age + BMI + NSAIDs + APOE + aMCI_{Yes}$
3. $\Delta\, Memory = \Delta\, markers + sex + age + BMI + NSAIDs + APOE + aMCI_{Yes}$
4. $\Delta\, ADsignature = \Delta\, markers + sex + age + BMI + NSAIDs + APOE + aMCI_{Yes}$