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### Title

Association Between Peripheral Immune Markers and Functional Neuroimaging Findings Among Healthy Older Adults

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**Results:** The 226 inpatients' data will be analyzed using bivariate and multivariate analyses (e.g. logistic regression) and the results will be presented at the conference.

**Conclusions:** We expect that extreme weather conditions would have a negative impact on a specific subgroup of patients (e.g. those living in long-term care facilities), and that extreme weather conditions (e.g. excessive snow and rain) will be associated with less psychiatric emergency room visits and hospitalizations. The association between climate and psychiatric health services, as well as the characteristics of these patients may help guide us to allocate specific resources and provide intervention to prevent emergency room visit and rehospitalization (e.g. home visits, etc) especially during periods of extreme weather conditions.

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### Association Between Peripheral Immune Markers and Functional Neuroimaging Findings Among Healthy Older Adults

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**Introduction:** Healthy aging is accompanied by changes in brain response, including in resting state functional connectivity, which has been linked to cognitive decline. Several studies also suggest a link between inflammatory processes and cognitive dysfunction. It has been proposed that inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) contribute to cognitive decline, particularly memory loss and the etiologic progression of dementia, but findings have been mixed. Additionally, many studies have suggested that in healthy adults free of neurological and vascular disease, elevated levels of inflammatory and vascular risk biomarkers can contribute to brain abnormalities detected by MRI, which is thought to be a more sensitive measure of cognitive functioning. Among elderly adults, increased IL-6 and CRP have been associated with structural brain changes in temporal and frontal regions, yet MRI research in this field is still in the earliest stages and more studies are needed. The objective of this study was to examine the associations between IL-6, CRP, neuropsychological functioning, and resting-state functional connectivity among healthy older adults.

**Methods:** Twenty-four older adults aged 61-96 (mean age=80; 48% female) completed an fMRI exam and a resting-state (task-independent) functional connectivity scan. Average regional BOLD signal fluctuations were correlated across several nodes within the canonical default mode network (DMN). Participants also completed a neuropsychological battery and were assessed for plasma concentrations of inflammation (IL-6) and vascular risk measures (CRP, serum amyloid A (SAA), soluble vascular cell adhesion molecule (VCAM), and soluble intercellular adhesion molecule (ICAM)). Correlational analyses were conducted to examine relationships between the blood-based biomarkers and demographics, composite measures of neurocognitive functioning domains (attention, working memory, language, memory, motor speed, information processing, and executive functioning), and connectivity-strength within parts of the default mode network. Stepwise regression analysis was used to examine the main effects and interaction of IL-6 and CRP in predicting functional connectivity strength after controlling for significant clinical correlates.

**Results:** SAA, VCAM, and ICAM were not related to resting state default mode network connection strength. Degree of connectivity within the following DMN connections was negatively related to both IL-6 and CRP: lateral parietal (LP) to all other DMN nodes (IL-6:  $r=-0.59$ ,  $p<0.01$ ; CRP:  $r=-0.51$ ,  $p=0.02$ ) and LP to just the posterior cingulate cortex (PCC) (IL-6:  $r=-0.55$ ,  $p<0.01$ ; CRP:  $r=-0.45$ ,  $p=0.03$ ). A similar relationship between IL-6 and medial prefrontal (MFP) to LP connection strength ( $r=-0.51$ ,  $p=0.01$ ) was also observed. Males had significantly higher levels of IL-6 than females ( $r=0.44$ ,  $p=0.04$ ); no relationships with other demographic characteristics (age, race/ethnicity, and education) or neurocognition were observed with IL-6 or CRP. Controlling for gender, an overall stepwise regression model predicting both the LP to all others= DMN strength (adjusted  $R^2=0.35$ ,  $p<0.01$ ) and the LP to PCC connection (adjusted  $R^2=0.21$ ,  $p=0.02$ ) were significant. In both models, IL-6 was the only significant predictor of connection strength (LP to other DMN:  $t(20)=-3.47$ ,  $p<0.01$ ; LP to PCC:  $t(20)=-2.58$ ,  $p=0.02$ ).

**Conclusions:** Research examining the relationship between inflammation and connectivity within resting state networks like the DMN is still in the early stages. This study found that older adults with higher levels of IL-6, a known risk marker for health morbidity, particularly cardiovascular disease, had less coherence between LP signal and that of other DMN nodes. An association between greater DMN connectivity and better cognition (specifically episodic memory retrieval) in the the parietal regions has previously been identified (Sestieri et al., 2011). Research on the relationships between IL-6, CRP, and neuropsychological performance is mixed, with some evidence for and some against a cross-sectional relationship. In our sample of older

adults, we did not find a relationship between IL-6, CRP, and performance on standard neuropsychological tests. Although limited in sample size and preliminary, these results point to a possible relationship between a potentially more sensitive measure of neurocognitive integrity, resting DMN functional connectivity, and neuroinflammation in the healthy aging brain that can be tested in longitudinal studies on biological indicators of cognitive decline.

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### Personality Traits and Mood - Relevance to the Early Incidence of Subjective Cognitive Complaints

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**Introduction:** Alzheimer's disease (AD) is the most common cause of dementia in the elderly population of the United States, with a gradual and progressive decline in two or more cognitive domains, most commonly involving episodic memory and executive function, sufficient to cause social or occupational impairment. Former studies support the presence of a long preclinical phase of the disease with subjective memory complaints (SCI), estimated to begin approximately 10-15 years prior to the onset of clinical symptoms (Holtzman, 2012). The goal of our study is to examine the relationship between subclinical mood symptoms, specific personality traits and subjective memory complaints. Previous research indicates that elevated neuroticism and lower levels of conscientiousness and openness may be important risk markers for cognitive decline, including AD (Duberstein, 2011). In addition, research also shows a significant relationship between neuroticism and inattention (Denburg, 2009), which can be indirectly related to memory complaints. Depression has also been identified as a risk factor for dementia (Li, 2011). However, not all studies have found a significant association between depression and dementia (Becker, 2009). Relatively few studies have been done on the population with SCI in relation to the above parameters, which could predict an etiological role, in the incidence of neurocognitive disorders later on in life.

**Methods:** Two groups of participants were included in this study, a) healthy older adults with subjective memory complaints (SCI, n = 4; Mean age - 61.25 years; Std. Dev. -  $\pm$  9.42) and b) healthy older adults without specific cognitive concerns (Controls, n = 4; Mean age - 64.5 years; Std. Dev. -  $\pm$  8.54). Both groups underwent a neuropsychological testing battery, to assess cognition (memory, learning and executive functioning), a Mini Mental Status Exam (MMSE), mood and personality questionnaires (i.e. the Geriatric Depression Scale (GDS), Beck Depression Scale (BDS), and Big Five Inventory (BFI). They also completed the Memory Functioning Questionnaire (MFQ), which assesses subjective memory function. A two-sample t-test was performed to test for group differences and a Pearson correlation was implemented to assess the associations between personality, mood and memory complaints within the entire sample.

**Results:** Currently our study is underway; however the preliminary analysis on an initial sample indicates no significant difference between the groups (CONTROL & SCI) on Mini Mental Status Exam (MMSE) and self-assessment questionnaires - GDS, BDS and BFI. As expected we did find a significant difference in subjective memory function (more specifically retrospective functioning on the MFQ) between the two groups. This indicates that the SCI individuals indeed report a greater decline in memory function as they age, compared to controls ( $p = 0.04$ ). However no significant difference was observed for the frequency of forgetting measure of the MFQ, demonstrating that the amount of memory complaints is not significant between the groups. No significant difference was observed on neuropsychological testing for memory (Wechsler Memory Scale - IV) between the two groups. This is expected, as SCI's per definition do not show any deficits on formal cognitive testing. A significant positive correlation was observed between GDS, BDS and neuroticism in the total study population (Table 1). The extraversion and agreeableness components had a significant inverse correlation with neuroticism (Table 1). A significant positive correlation was observed between frequency of forgetting and conscientiousness, which corresponds to the reporting of more memory complaints in participants with lower levels of conscientiousness.

**Conclusions:** Our initial analysis tentatively shows a strong correlation pattern between neuroticism and subclinical depressive symptoms in our participants. This indicates a close relationship between two variables that in previous research have been associated with AD (Duberstein, 2011; Li, 2011). In addition, participants with a lower degree of conscientiousness reported a larger decline in memory functioning. Lower levels of conscientiousness have previously been associated with an increased risk of cognitive decline, including AD (Duberstein, 2011). This finding supports the notion that subjective memory complaints may be a precursor to AD. We are currently expanding this dataset, to more reliably delineate the association between mood, personality, memory complaints and performance; and to comprehend their significance, in the spectrum of neurocognitive disorders.