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### Title

Higher Levels of Plasma interleukin-6 Are Associated with Lower BOLD Responses to Working Memory Load in Older Adults

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### Authors

Dev, Sheena I  
Moore, Raeanne  
Jones, Savannah R  
et al.

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(21.39%) compared to Toronto (11.81%) ( $p < 0.05$ ). The apnea group had significantly higher BMI (both as continuous [F(1,458)=34.41,  $p < 0.001$ ] and % obesity [Chisq(1)=28.52,  $p < 0.001$ ]), as well as higher rates of hypertension [Chisq(1)=20.47,  $p < 0.001$ ], burden of physical comorbidities (CIRS: severity [F(1,463)=19.34,  $p < 0.001$ ], number of systems [F(1,463)=22.84,  $p < 0.001$ ] and severity without respiratory items [F(1,463)=14.45,  $p < 0.001$ ]); a greater proportion of the apnea group had uncontrolled glucose levels ( $\% \geq 100$  mmol/L) [Chisq(1)=4.35,  $p = 0.04$ ], decreased Health-Related Quality of Life (MOS Physical) [F(1,456)=6.74,  $p = 0.01$ ], baseline depressive symptoms severity [F(1,462)=3.47,  $p = 0.03$ ], and current episode duration [F(1,462)=10.56,  $p = 0.002$ ]. A larger percentage of those with OSA also reported being treated adequately (Antidepressant Treatment History Form (ATHF) score  $\geq 3$ ) for their current depressive episode (71.79% vs 59.07%) ( $p = 0.02$ ). Those without an apnea diagnosis were 1.5 times more likely to respond to the venlafaxine (43.4% vs 27.9%) controlling for site, sex, depression severity, and physical comorbidity (HR: 1.69, 95% CI=1.07-2.66). The HRSD insomnia index did not predict time to response, nor was there a significant HRSD insomnia index and apnea interaction. There was no significant relationship between prescription/current use of treatment for OSA and treatment response in the Pittsburgh group.

**Conclusions:** Older adults with MDD and a baseline diagnosis of OSA are less likely to respond to 12 weeks of venlafaxine than those without an apnea diagnosis. Those with previously diagnosed OSA have more severe and longer episodes of depression despite adequate antidepressant therapy, as well as a greater number of physical comorbidities and decreased Health-Related Quality of Life. Physicians should consider screening for OSA when assessing older adults for depression, as it may indicate a more difficult to treat depression.

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### Higher Levels of Plasma interleukin-6 Are Associated with Lower BOLD Responses to Working Memory Load in Older Adults

Sheena I. Dev, MS<sup>1,2</sup>; Raeanne Moore, PhD<sup>1</sup>; Savannah R. Jones<sup>1</sup>; Benchawanna Soontornniyomkij, PhD<sup>1</sup>; Cristian L. Achim, PhD<sup>1</sup>; Dilip V. Jeste, MD<sup>1</sup>; Lisa T. Eyer, PhD<sup>1,2</sup>

<sup>1</sup>University of California, San Diego, San Diego, CA

<sup>2</sup>Veterans Administration Health Care System, San Diego, CA

**Introduction:** Working memory (WM) deficits have been shown to be a hallmark of cognitive aging. Further, recent neuroimaging studies have demonstrated that reduced frontal activation is associated with poorer performance on the N-back WM task. It has also been noted that older adults display a maladaptive, low-grade chronic inflammatory state, characterized by increasing levels of interleukin-6 (IL-6) with older age. Importantly, this inflammatory cytokine has also been previously linked to WM function; increased plasma concentration of IL-6 is associated with decreased WM performance in some studies. However, less is known about how inflammatory processes relate to neural activity in elderly individuals during WM tasks. The objective of this study was to determine whether levels of IL-6 predict frontal brain response during a working memory task in a sample of elderly adults.

**Methods:** Blood samples were drawn from 15 participants (mean age: 78.82, range: 60.6 to 95.9) and assessed for plasma concentration of IL-6 inflammatory cytokine. Functional magnetic resonance imaging (fMRI) was used to measure blood oxygenation level dependent (BOLD) response during an N-back working memory task previously shown to activate frontal regions of the brain. Within left and right frontal clusters significantly activated in the group as a whole, average levels of BOLD activation in the 2-back relative to 1-back conditions were quantified for each participant. Non-normal data were log transformed, and associations between these BOLD activation values, plasma levels of IL-6, age, and task performance were calculated with Pearson correlations.

**Results:** Lower BOLD activation tended to be associated with decreased accurate performance in the 2-back vs. 1 back condition on the N-back task in both left and right frontal lobes (L:  $r = 0.47$ ,  $p = 0.08$ ; R:  $r = -0.21$ ,  $p = 0.5$ ), although this relationship was not significant. As expected, older participants had higher levels of IL-6 ( $r = 0.48$ ;  $p = 0.02$ ), but age was not related to BOLD activation in the left ( $r = -0.33$ ;  $p = 0.23$ ) and right ( $r = -0.2$ ;  $p = 0.47$ ) frontal cortices nor to WM performance ( $r = -0.3$ ;  $p = 0.3$ ) in this sample. Notably, higher plasma concentration of IL-6 was associated with lower BOLD response to increased WM load in the posterior left frontal gyrus cluster, even after controlling for age and performing Bonferroni corrections for multiple comparisons ( $t = -2.39$ ;  $p = 0.02$ ).

**Conclusions:** Our findings are consistent with previous studies demonstrating higher IL-6 levels among older adults, and we extend upon this literature by showing that higher levels of this inflammatory cytokine may be related to dysfunction of

frontal lobe neural systems involved in WM tasks. That we observed an association with BOLD response but not task performance suggests that pro-inflammatory effects on neurocognition may manifest first in neural response and only later affect task performance, but this requires longitudinal testing to verify.

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**Perspectives on Advance Care Planning in Early Dementia - A Qualitative Study of Caregiver Interviews**

Kelly M. Makino, BS; Melanie A. Keltz, BS; Jessica S. Smith, BS; Anton P. Porsteinsson, MD

University of Rochester School of Medicine & Dentistry, Rochester, NY

**Introduction:** Little is known about the experiences that patients with early dementia have had with advance care planning (ACP) or their preferences for end-of-life care, especially in the United States. As part of an investigator-initiated pilot study designed by the first author to learn about patient experiences and preferences about ACP, family caregivers of patients with dementia were interviewed to learn about prior experiences and reflections on the ACP process. This qualitative study aims to describe findings from these interviews and highlights some of the themes that were identified across interviewee responses.

**Methods:** Current and survivor caregivers of patients with moderate-to-severe dementia were recruited as part of a larger study to investigate ACP experiences and preferences of patients with dementia. Structured interviews were conducted to collect information about the ACP that had been done for the patient, and to inquire about benefits/supports and barriers to ACP (Table 1). Responses to the open-ended interview questions were recorded by hand during the interview, and the written responses were analyzed by a team of three researchers (KMM, MAK, JSS) using Grounded Theory (Corbin & Strauss 2008) to identify concepts and themes among the responses. Concepts and themes were reviewed and approved by the senior experienced investigator (APP) following preliminary consensus of the first three authors.

**Results:** Our total target is ten caregivers. Of the caregivers interviewed to date, most had completed at least one form of ACP documentation such as a Health Care Proxy or Living Will. Caregivers were generally spouses of patients with advanced dementia, and approximately half of the patients were still living at the time of the interview. Numerous concepts were identified while reading the interviewee responses. These concepts were grouped into several broad themes that arose when considering all of the responses to each of the five open-ended questions (Table 2). Highlighted themes include resources and motivations for ACP, and factors that influenced ACP including characteristics of the individual patient, the patient’s relationship with his/her caregiver and family, and broader aspects of systems of care. Overall, most of the caregivers were generally satisfied with their experiences with ACP for the patient. Several reported that prior experiences they had with other family members encouraged them to think about and begin the ACP process sooner. Several also found help from the patient’s primary care provider or a specialist physician. Few barriers to ACP were listed, however several caregivers commented on the challenge of the patient’s cognitive decline and the importance of starting discussions and planning earlier in the course of the disease, and several

Table 1. Open-Ended Interview Questions

Factors That Influenced Advance Care Planning	
Facilitators	In your opinion, were there any other factors that you can identify that might have made it easier for the patient to complete advance care planning?
Barriers	Can you identify any barriers, or things that might have made advance care planning more difficult for the patient?
Possible Changes Made	
Changes	If you and the patient had the opportunity to go back in time and do things differently, are there any changes you would have made?
Wishes	Similarly, is there anything you can identify that you wish had been available or more accessible to you and your loved one to help prepare for advance care planning?
Other Comments	
	...do you have any other thoughts or comments related to advance care planning that we have not yet discussed? For example, are there any memorable experiences or important beliefs that you would like to share?