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Peripheral inflammation related to lower fMRI activation during a working memory task and resting functional connectivity among older adults: a preliminary study

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Objective: Peripheral inflammation has been associated with adverse effects on cognition and brain structure in late life, a process called ‘inflammaging.’ Identifying biomarkers of preclinical cognitive decline is critical in the development of preventative therapies, and peripheral inflammation may be able to serve as an indicator of cognitive decline. However, little is known regarding the relationship between peripheral inflammation and brain structure and function among older adults.

Methods: Twenty-four older adults (mean age = 78) underwent a functional magnetic resonance imaging (fMRI) resting state functional connectivity scan, and a subset (n = 14) completed the n-Back working memory task in the scanner. All participants completed a blood draw, and inflammation was measured with interleukin 6 (IL-6) and C-Reactive Protein (CRP).

Results: Surprisingly, age was unrelated to measures of inflammation (IL-6, CRP) or brain function (default mode network (DMN) connectivity; working memory performance; blood oxygenation level dependent (BOLD) activation with higher working memory load). However, lower functional connectivity between the left parietal seed and all other DMN regions was associated with higher levels of IL-6 and CRP. Additionally, greater plasma concentration of IL-6 was associated with lower BOLD activation in the left middle frontal gyrus in response to increased working memory load.

Conclusions: These preliminary findings support the importance of IL-6 and CRP in brain function among older adults. Frontal and parietal regions may be particularly sensitive to the effects of inflammation. Additionally, these findings provide preliminary evidence of inflammatory contributions to level of neural activity, even after accounting for vascular risk factors.

Key words: inflammation; aging; cognitive health; resting state connectivity; functional MRI

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Introduction

Advanced age is often accompanied by cognitive decline, even in the absence of a neurological or neurovascular disorder. Decades of research characterizing the cognitive profile of older adults indicates verbal memory and processing speed appear to be most vulnerable to age-related decline (Ownby,

2010). Using non-invasive methods such as functional magnetic resonance imaging (fMRI), research groups have begun to explore the etiology of cognitive decline in healthy aging by examining neural mechanisms of change with age. This line of research has emphasized that the pace and nature of neural aging is variable among older adults, and this variation is related to individual differences in cognitive performance (Eyler

et al., 2011). The biological and environmental factors predictive of this heterogeneity of brain functional aging are less well understood. One potential mechanism under increasing scientific study is inflammation. Several studies suggest aging is associated with a chronic, low-grade inflammation, whereby the body's normal pro-inflammatory healing process is no longer opposed adequately by anti-inflammatory action. The chronic inflammation resulting from this imbalance has been described as 'inflammaging' (Franceschi *et al.*, 2007); little is known about its role in the processes of neural aging that lead to cognitive declines in late life.

Several studies have demonstrated alterations in blood oxygenation level dependent (BOLD) activity in older age in response to episodic and working memory, language, and executive functioning tasks (Eyler *et al.*, 2011). Utilizing a working memory n-Back task in a sample of 64 adults (aged 23–78), we found older age was associated with worse working memory performance and reduced BOLD activation in prefrontal and parietal regions in response to a larger working memory load. Further, the degree of accuracy in this task was positively associated with BOLD activation in the right prefrontal cortex (Kaup *et al.*, 2014). Thus, poorer working memory performance commonly seen in advanced age is also accompanied by notable changes in neural activity in brain regions that subserve this task.

There is also a growing interest in the role of functional connectivity across brain regions in healthy brain function. Studies have demonstrated altered temporal connectivity of the BOLD signal between brain regions that form networks important for cognition among older adults. The task-negative default mode network (DMN), consisting of the bilateral angular gyrus, medial prefrontal cortex and posterior cingulate gyrus (Fox *et al.*, 2005), appears to be particularly influenced by age (Grady *et al.*, 2010). Indeed, diminished temporal connectivity between DMN regions in older adults has been consistently demonstrated (Huang *et al.*, 2015; Prakash *et al.*, 2012), even after controlling for brain atrophy (Sala-Llonch *et al.*, 2015). One cross-sectional study examined DMN connectivity in a sample of younger (mean age = 22) and older adults (mean age = 77) and reported reduced functional connectivity between posterior and anterior nodes of the DMN in the older group. (Andrews-Hanna *et al.*, 2007). Another study found intact global connectivity but reduced local connectivity within DMN regions in older adults compared with their younger counterparts (Song *et al.*, 2014). Taken together, these

studies suggest that functional connectivity, particularly within regions in the DMN, is sensitive to the effects of age.

Strength of DMN connectivity may also be an important correlate of cognitive performance in late life. Alterations in connectivity strength between DMN regions has been shown to predict worse performance in memory, executive function, and processing speed in older adults (Andrews-Hanna *et al.*, 2007; Damoiseaux *et al.*, 2008; Persson *et al.*, 2014). Thus, it is possible that notable DMN alterations observed across the lifespan may contribute to the variability in cognitive performance seen within elderly populations.

The potential role of inflammatory processes in brain and cognitive aging has only recently begun to be explored. Inflammaging, characterized by higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines, is implicated in cerebrovascular disease and may explain individual variability in the onset and progression of age-related diseases and cognitive decline (Franceschi *et al.*, 2007; Gomez *et al.*, 2005; Krabbe *et al.*, 2004). However, the literature is mixed as to whether blood serum levels of pro-inflammatory cytokines are related to cognition in older adults. For example, one study (Bettcher *et al.*, 2012) demonstrated a negative relationship between C-Reactive Protein (CRP) and verbal memory in older adults. Further, higher levels of Interleukin-6 (IL-6) and CRP have been shown to predict future global cognitive decline in otherwise healthy adults. This predictive relationship has been shown to be true even for inflammation that was present as early as mid-life, implicating both IL-6, and CRP as potential early biomarkers of cognitive decline (Adriaensen *et al.*, 2014; Laurin *et al.*, 2009). However, other studies have shown weak or no associations between inflammatory cytokines and cognitive decline in older age (Alley *et al.*, 2008; Yang *et al.*, 2015). Differences in findings between studies could be due to differences in the cognitive domains studied, the cytokines examined or the particulars of the samples investigated. The mixed results might also be due to the use of behavioral measures of cognitive performance instead of a more direct assay of neural function, because altered neural responses with age are often seen even when cognitive performance is normal (Eyler *et al.*, 2011).

Inflammation may contribute to altered brain integrity by inducing changes in myelin integrity and vascular permeability, although only a few studies have directly tested the relationship between peripheral

inflammation and brain structure and function in humans. A review of studies investigating this relationship across several clinical populations found pro-inflammatory cytokines, particularly IL-6, and CRP, were associated with decreased white matter integrity and gray matter volume in healthy aging individuals (Frodl and Amico, 2014). However, there have been no studies investigating the relationship between peripheral markers of inflammation and the functional BOLD signal in healthy aging populations.

The goal of this exploratory study was to investigate the relationship between resting state connectivity and task-related BOLD response, on the one hand, and IL-6 and CRP pro-inflammatory markers, on the other, among older adults. In doing so, these results have the potential to inform future studies investigating the benefits of anti-inflammatory agents on brain aging.

We hypothesized that (i) older age would be associated with elevated levels of IL-6 and CRP; (ii) older age would be associated with attenuated BOLD signal, evidenced by diminished temporal coherence among regions within the DMN and lower BOLD activation in response to a working memory task in prefrontal and parietal cortices; and (iii) greater concentration of these markers of inflammation would be related to blunted temporal connectivity and lower task-related BOLD response in these same regions.

Methods

Participants

Twenty-four older adults (mean age = 78; Table 1) were recruited from the Successful AGing Evaluation (SAGE) study. The SAGE study includes completion

of a comprehensive survey in areas related to successful aging, including physical and health status, positive psychological traits, and psychosocial and cognitive functioning (Jeste *et al.*, 2013). Participants interested in this study were screened to ensure eligibility based on the following criteria: right-handed, no history of neurological (e.g. stroke), psychiatric, or substance use disorders, and did not have MRI contraindications (e.g. pacemaker or other implanted metallic devices). A functional resting state scan was collected for all twenty-four participants. Because of time constraints, only a subset of 14 participated in the working memory task. The study was approved by the Internal Review Board at the University of California, San Diego (UCSD) and the UCSD Human Research Protections Program. All participants provided written, informed consent.

Blood draws

5 mL of blood was drawn by a licensed phlebotomist at UCSD's Clinical and Translational Research Institute. Plasma aliquots from all participants were tested using a sandwich immunoassay with MSD MULTI-SPOT[®] Assay kits (Meso Scale Discovery, Rockville, MD). Protein targets were captured with pre-coated antibodies immobilized on independent spots in a 96-well plate. Detection antibodies were conjugated with the electrochemiluminescence (ECL) compound MSD SULFO-TAG. A voltage was then applied to the plate electrode and the labeled antibodies emitted light. The intensity of the light emission was measured to quantify measures of all target proteins present in the sample. MSD DISCOVERY WORKBENCH[®] analysis software was used to generate standard curves by fitting the electrochemiluminescence signal from calibrators to a 4-parameter logistic model with a

Table 1 Demographic characteristics of participants

	rsConnectivity (n = 24)			n-Back Task (n = 14)			t or χ^2	p
	Mean	SD	Range	Mean	SD	Range		
Age	78	10.08	61–96	77	7.98	61–92	1.001	0.33
Education	16	2	12–20	16	2	14–20	0.151	0.88
Gender (% female)	50%			57%			0.354	0.55
IL-6 (pg/mL)	1.72	1.02	0.70–4.20	1.84	1.19	0.75–4.20	−0.480	0.64
CRP (pg/mL)	4851.53	6545.1	293–65482	5844.88	8018.76	293.04–65482	−1.017	0.32
Systolic BP	141.74	19.5	111–183	144.42	15.66	116–173	−0.774	0.45
Pulse	63.32	15.70	18–86	66.83	12.07	48–86	−1.303	0.21
Weight (kg)	73.77	17.46	41–115	74.63	13.99	50–90	−0.273	0.79

IL-6 = interleukin-6; CRP = C-reactive protein; rsConnectivity = resting state connectivity; SD = standard deviation; pg/mL = pictogram per milliliter; BP = blood pressure; kg = kilograms

$1/\gamma^2$ weighting. Three concentration ranges of quality controls were used to evaluate assay accuracy and precisions in order to ensure reliable and accurate results.

Image acquisition

Imaging data were acquired using a research dedicated 3 Tesla General Electric Excite MRI scanner with an 8-channel head coil. High resolution structural T1-weighted MRI images were acquired using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence. The resulting images were utilized to localize the functional signal. BOLD signal was acquired during the n-Back functional scan using gradient echo planar imaging (TR = 2500 msec, TE = 32 ms, 4-mm slice thickness/no gap, FOV = 25.6 cm, bandwidth = 125, 195 repetitions). The BOLD signal for the resting state connectivity scan was measured with T2*-weighted echo planar images collected with eyes open (TR = 3000 ms, FOV = 256 ms, BW = 250, 32 axial 4-mm slices, 5 min). 2dfish field maps were collected to correct for distortion of the echoplanar imaging (EPI) images due to inhomogeneities in the static magnetic field.

Image processing and analysis

Resting state functional scan. Raw fMRI data preprocessing was implemented with the National Institute of Health's Analysis of Functional

NeuroImages (AFNI) software package (Cox, 1996), using a streamlined pathway that included (i) removal of the first time point to account for signal stabilization; (ii) removal of skull and surrounding tissue; (iii) spatial smoothing to 6 full-width-to-half-maximum; (iv) grand mean scaling; (v) application of high-pass temporal filter and low-pass temporal filter; and (vi) removal of linear and quadratic trends. Each participant's anatomical scan underwent cerebral spinal fluid, white matter (WM) and grey matter (GM) segmentation using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) FMRIB Linear Image Registration Tool (FLIRT) program and were subsequently registered to functional maps. Automated motion correction was then applied to all participants to correct for excessive motion during scan time. A visual inspection was conducted and remaining data points with excessive motion were rejected.

Sources of variance were accounted for by regressing the following: (i) six motion parameters; (ii) the whole-brain global signal; and (iii) CSF and WM signal. Regression of each of these parameters was conducted in stepwise fashion and residual time courses were utilized in final correlational analysis. Time series within each DMN seed (Fox *et al.*, 2005) were extracted and maps of voxel-wise correlations to each seed region's time course were calculated. An averaged DMN group correlation map was created, and peak nodes were identified in order to locate more precise DMN seed locations in the current sample.

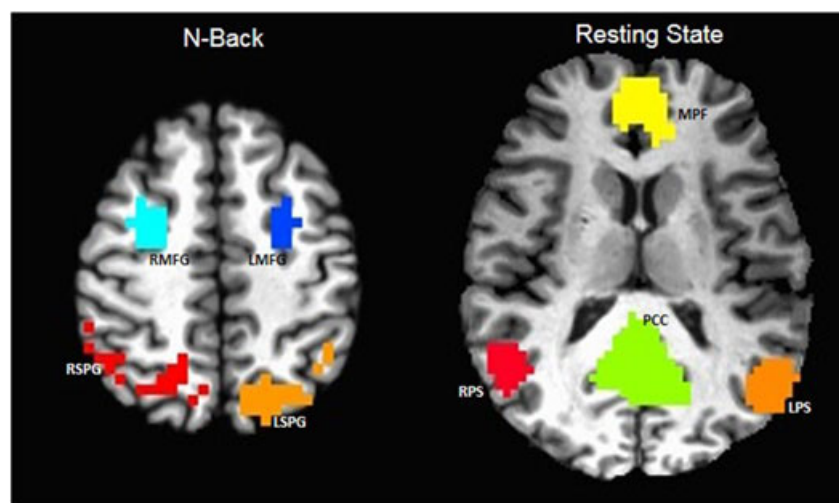


Figure 1 Axial view of regions of interest in N-back functional scan (left) and resting state connectivity scan (right). Images presented in radiological convention (R = L). RMFG = right middle frontal gyrus; LMFG = left middle frontal gyrus; RSPG = right superior parietal gyrus; LSPG = left superior parietal gyrus; MPF = medial prefrontal gyrus; PCC = posterior cingulate cortex; RPS = right parietal seed; LPS = left parietal seed.

The DMN regions that were identified in our small sample included bilateral angular gyri, medial prefrontal cortex, and posterior cingulate cortex (Figure 1). The mean time course in each peak node region identified was extracted for each participant and correlated pairwise, using Pearson's r , with all other nodes. Pairwise correlations were then converted to Fisher's Z and an average connectivity score of each node with all other nodes was calculated.

n-Back working memory task. A subset of 14 participants (mean age = 77; Table 1) completed the n-Back task during the fMRI scan. This task was designed to tax working memory, and has been previously shown to elicit response from frontal and parietal regions (Owen *et al.*, 2005). Further, studies have demonstrated reduced BOLD activity in these regions among older adults (Kaup *et al.*, 2014). Each participant completed six 0-Back, five 1-Back, and five 2-Back blocks (Braver *et al.*, 1997; Cohen *et al.*, 1997) that alternated in a pre-determined sequence (Figure 2). Mean accuracy was calculated for each condition and 2-back versus 1-back contrasts were designed to measure increased working memory load.

fMRI data processing for the n-Back task was also implemented using AFNI software. The fMRI data were analyzed and overlaid onto structural T1-weighted images. The first two images of each session were discarded to account for signal stabilization. Field map and slice timing corrections were applied to the EPI images, and individual functional-to-anatomical alignment was conducted to the center image of the functional time series. Following automated motion correction, visual inspection was used to examine uncorrected motion outliers, and time points with excessive motion were discarded. Images were spatially blurred to 6 mm full-width at half-maximum and the functional data were transformed into standardized Talairach space (Talairach and Tournoux, 1988) and resampled at 4 mm³ resolution.

The association between BOLD signal and task conditions was calculated with multiple regressions using AFNI's 3Ddeconvolve program, using the 2-back versus 1-back contrast as the dependent variable. The model accounted for linear and quadratic trends, as well as degree of motion in three angles of rotation. Regions of interest were identified as clusters of 32 contiguous voxels in which all voxels were significant at $p < 0.01$. BOLD response within clusters in the bilateral middle frontal and superior parietal gyri (Figure 1) were extracted from each participant and

entered into Statistical Package for the Social Sciences (SPSS) for further statistical analysis.

Statistical analysis

All quantitative variables were checked for normality, and mean concentrations of CRP and IL-6 were log transformed to correct for non-normal distribution. Given the link between inflammation and cardiovascular diseases (Pearson *et al.*, 2003), vascular risk factors including systolic blood pressure, pulse, and weight were correlated with CRP and IL-6. To test our *a priori* hypotheses, Pearson's correlations were used to determine the relationship between age and mean concentrations of IL-6 and CRP (hypothesis 1), age and BOLD activity at rest and during the n-Back working memory task (hypothesis 2), and mean concentrations of both inflammatory cytokines and BOLD activity at rest and during task performance (hypothesis 3). Multiple comparisons were corrected for by applying family-wise Bonferroni corrections to comparisons between inflammatory cytokines and resting state ($p < 0.01$) and working memory ($p < 0.01$) BOLD response.

Results

Demographic and health characteristics

Contrary to our hypothesis, older age was not related to IL-6 or CRP levels in the full sample. Males had significantly higher levels of IL-6 than females ($t = -2.23$, $p = 0.04$). Systolic blood pressure, pulse, weight, and education were not related to IL-6 or CRP. The subgroup of 14 participants who performed the n-Back functional task did not significantly differ from the larger sample in IL-6, CRP or any demographic variable (Table 1).

Default mode network (DMN) resting state connectivity and inflammation

There was no significant relationship between age and DMN connectivity (Table 2). Lower temporal connectivity between the left parietal seed and all other DMN regions was associated with higher levels of IL-6 ($r = -0.53$; $p < 0.01$; Figure 3) and CRP ($r = -0.44$; $p = 0.04$). This relationship remained significant even after controlling for gender. Only the association with IL-6 survived Bonferroni family-wise correction ($p < 0.01$).

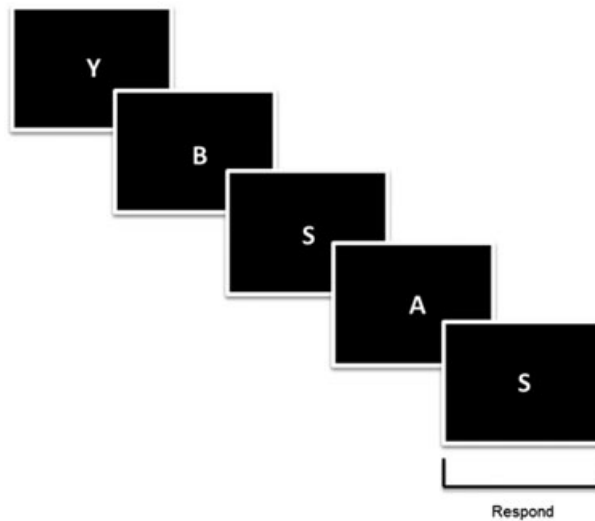


Figure 2 The n-Back task consists of 0-Back, 1-Back, and 2-Back blocks. During each block, a series of 11 letters are presented in a random order for 500 ms each. In the 0-Back condition, participants were instructed to respond every time the target letter 'X' appeared on the screen. In the 1-Back condition, participants were instructed to respond every time the letter on the screen matched the letter previously shown. In the 2-Back condition (shown in Figure), participants were instructed to respond every time the letter on the screen matched the letter shown two letters previously.

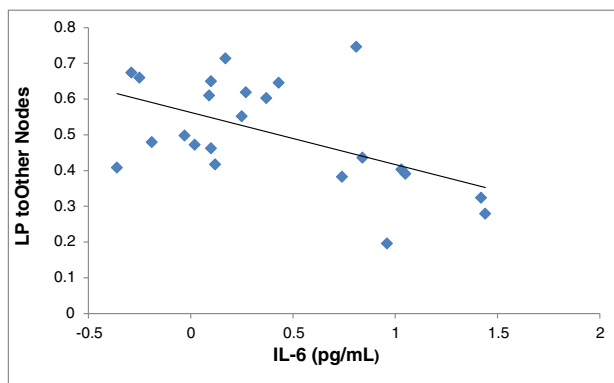


Figure 3 Scatter plot demonstrating the relationship between resting state connectivity between the left parietal region and other nodes in the default mode network and pro-inflammatory cytokine Interleukin-6 (IL-6). Pearson correlation was significant at $p = 0.01$.

n-Back functional task and inflammation

Age was not associated with working memory performance or BOLD activation response to higher working memory load in the smaller sample that was given the n-Back task. IL-6 and CRP were not related to load-related working memory performance (2-back minus 1-back accuracy). Lower BOLD activation was associated with worse load-related working memory performance at a trend level ($r = 0.47$, $p = 0.08$). While there were no gender differences in working memory performance, females in this sample exhibited greater BOLD signal in bilateral frontal gyri. Greater plasma concentration of IL-6 was significantly associated with

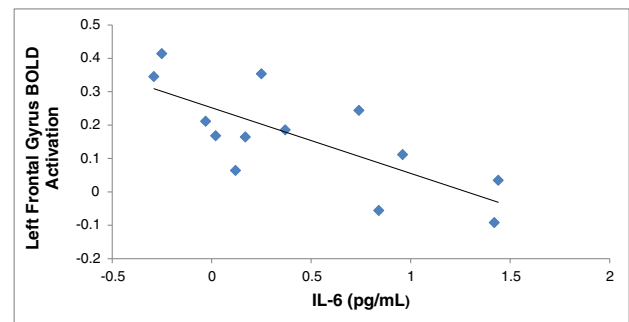


Figure 4 Scatter plot demonstrating the relationship change in blood oxygenation level dependent (BOLD) activation in response to higher working memory load in the left middle frontal gyrus and pro-inflammatory cytokine Interleukin 6 (IL-6). Pearson correlation was significant at $p = 0.003$.

lower BOLD activation in the left middle frontal gyrus (Figure 4) in response to increased working memory load ($r = -0.75$, $p = 0.003$). This relationship remained significant even after controlling for age and correcting for multiple comparisons.

Discussion

This exploratory study investigated the relationship between pro-inflammatory cytokines and BOLD activation both during rest and in response to a task. Contrary to our hypotheses, age was unrelated to IL-6 and CRP levels or to BOLD activation or connectivity in our small sample of older adults

Table 2 Pearson's correlations demonstration the relationship between age, IL-6 and CRP, and BOLD activation during a resting state scan and working memory task

	Age		IL-6		CRP	
	Pearson <i>r</i>	<i>p</i>	Pearson <i>r</i>	<i>p</i>	Pearson <i>r</i>	<i>p</i>
rsConnectivity						
PCC → Others	−0.08	0.71	−0.27	0.22	−0.40	0.07
MPF → Others	−0.06	0.78	−0.24	0.27	−0.29	0.20
LPS → Others	−0.09	0.68	−0.53	0.01**	−0.44	0.04*
RPS → Others	−0.05	0.81	−0.28	0.20	−0.30	0.18
n-Back Task						
Right middle frontal gyrus	−0.07	0.83	−0.51	0.08	−0.16	0.61
Left middle frontal gyrus	−0.15	0.61	−0.75	0.003**	−0.49	0.09
Right superior parietal gyrus	−0.52	0.07	−0.52	0.07	−0.26	0.40
Left superior parietal gyrus	−0.09	0.76	−0.34	0.25	−0.21	0.50

* $p \leq 0.05$ ** $p \leq 0.01$

rsConnectivity = resting state connectivity; IL-6 = Interleukin-6; CRP = C-reactive protein; PCC = posterior cingulate cortex; MPF = medial prefrontal cortex; LPS = left parietal seed; RPS = right parietal seed

ranging in age from 61 to 96. However, there were notable relationships between inflammatory markers and brain function. Older adults with greater blood serum levels of IL-6 exhibited significantly less coherence between the left parietal BOLD signal and that of other regions within the DMN. A similar association with CRP did not survive Bonferroni correction. Consistent with these findings, older adults with greater levels of IL-6, but not CRP, demonstrated less BOLD activation in response to increased working memory demand in the left middle frontal gyrus. The results of this preliminary study indicate neural activity in frontal and parietal regions may be particularly sensitive to changes in inflammatory status, even among a small sample of older individuals who appear to have remained resistant to the usual effects of older age on both inflammation and BOLD response.

The lack of evidence to support an age-related effect on inflammation and neural activity in our sample is inconsistent with previously published studies that have demonstrated greater inflammatory response and altered BOLD activation with older age. This inconsistency can be explained in a number of ways. First, our small sample size may have limited our ability to detect significant relationships (i.e. limited statistical variance in age). Further, our sample only included individuals who are aged 60 and older and thus may have excluded important age related changes that occur in the fifth and sixth decades of life.

Chronically elevated levels of inflammation have been linked to a greater risk for cardiovascular diseases (CVD) known to impact cognition in older adults (Pearson *et al.*, 2003). Further, some studies have also demonstrated an association between cardiovascular

disease risk factors (e.g. blood pressure) and brain structure in both middle aged (McEvoy *et al.*, 2015) and older (Gasecki *et al.*, 2013) adults. Our finding that pro-inflammatory IL-6 was associated with diminished coherency between the left parietal seed and other nodes in the DMN further supports the negative impact of cardiovascular risk on neural activity. These results also add to the existing literature by implicating IL-6 as a potential marker to detect age-related vascular burden prior to the onset of functional and cognitive decline associated with brain aging. Interestingly, the IL-6 signaling system has recently become a more popular candidate for direct therapeutic intervention, due to its higher position in the inflammatory cascade. CRP, although a more sensitive predictor of future vascular risk, is less likely to be an effective intervention target as it has yet to be causally linked to vascular dysfunction (Ridker, 2016). Thus, it is possible that IL-6 plays a more direct role in immune-related physiological alterations, including those occurring inside the central nervous system. Our findings also suggest parietal lobe connections may be particularly vulnerable to changes induced by IL-6 elevations. Future investigations should examine the inter-relationships between pro-inflammatory markers, BOLD activation, and cognitive decline among older adults.

Research suggests resting state connectivity may reflect the integrity of white matter tracts known to connect network nodes (Greicius *et al.*, 2009; Vidal-Pineiro *et al.*, 2014). To this end, our results are consistent with previous diffusion tensor imaging studies demonstrating negative relationships between pro-inflammatory cytokines and white matter integrity. For example, one study found higher levels of CRP were associated with lower global fractional

anisotropy (FA) as well as FA in regional white matter tracts in frontal regions (corona radiata and corpus callosum) in community-dwelling, stroke-free older adults (Wersching *et al.*, 2010). It is possible that the disruption of neural activity across regions of the DMN in the presence of greater pro-inflammatory cytokines seen in the current study may represent underlying structural abnormalities in tracts responsible for connecting these nodes. However, more prospective studies are needed to confirm this hypothesis.

Among the participants who completed the n-Back working memory task, those with higher blood serum levels of IL-6 exhibited less increase in BOLD activation in response to harder task demands than those with lower levels of IL-6. Older adults frequently demonstrate an attenuated BOLD response (Kaup *et al.*, 2014; Nagel *et al.*, 2011), which may reflect an inability to employ the compensatory over-activation necessary for maintaining accurate performance during higher task demand. This compensatory response is typically seen in younger adults, but has been less consistently demonstrated in the aging population (Reuter-Lorenz and Cappell, 2008). Our results raise the possibility that inflammatory processes may contribute to the variability documented in the expected compensatory BOLD activation, and future studies including younger comparison samples may help better elucidate the role of inflammation on neural compensation during task performance among older adults.

There are several limitations to this study. The small sample size and lack of comparison group limits our ability to detect relationships and impacts the generalizability of our findings. Our study was cross-sectional, which does not allow for causal conclusions about the relationship between pro-inflammatory cytokines and BOLD response. Another limitation is that the blood draws took place on a different day than the fMRI procedures (mean number of days between visits = 82.17; range = 3–232), which may diminish the strength and interpretability of the relationships found. Future larger longitudinal studies are needed in order to establish potential temporal relationships and to fully understand the complex interplay between inflammation and neural activity in normal aging. Although it is well known that compromised brain structure and function leads to long-term declines in cognitive performance, this study did not examine cognitive outcomes. Thus, we cannot make conclusions about the impact of these biomarkers on validated neuropsychological tests of

cognitive ability. Future longitudinal studies should focus on documenting whether inflammation mediates disruption in neural activity due to aging and whether this complicated inter-relationship results in cognitive impairment. Finally, this study did not incorporate structural brain measures to determine whether the observed relationships with brain function are driven by age-related differences in regional brain volume.

Despite these limitations, this study is among the first to report a relationship between pro-inflammatory cytokines and BOLD response in healthy older adults. In particular, findings support the importance of IL-6 in brain function and propose that frontal and parietal regions may be particularly sensitive to the effects of inflammation, as well as implicate inflammatory contributions to observed disruptions in neural activity. If replicated, these results might lead to a program of research investigating the use of anti-inflammatory agents as potential treatments to combat brain aging in the normal aging population.

Conflict of interest

None declared.

Key Points

- Peripheral inflammation is known to have adverse effects on cognitive and brain structure in late life ('inflammaging'), yet little is known about how peripheral inflammation is related to brain function in older adults.
- In a sample of relatively healthy community-dwelling older adults, lower resting state functional connectivity between the left parietal seed and all other default mode network regions was associated with higher levels of proinflammatory cytokine IL-6, and greater concentration of IL-6 was associated with lower BOLD activation in the middle the left middle frontal gyrus in response to increased working memory load. Age was unrelated to proinflammatory cytokines or brain function in this sample.
- Peripheral inflammation may be an important contributor to frontal and parietal brain function in late life. Larger studies are needed to replicate these findings.

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