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Longitudinal Inflammation, Cognitive Decline, and Alzheimer's Disease: A Mini-Review

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Introduction

The role of inflammation in cognitive decline has generated considerable interest, although few longitudinal evaluations have been conducted. A review of the literature yields mixed findings, but suggests that inflammatory dysregulation is evident and may be related to clinical outcomes. The directionality, magnitude, and progression of these associations remain unclear. Future studies employing *multiple* time points of inflammatory data along with Alzheimer's disease biomarkers are critical for explication of longitudinal inflammation in cognitive decline.

Inflammation as a potential catalyst for cognitive decline and neurodegenerative disease has generated considerable interest over the past decade, and spawned numerous debates regarding the role of pro-inflammatory regulation in aging adults. Current research suggests that pro-inflammatory markers increase with age [1], display altered profiles in neurodegenerative diseases [2], and correlate with deleterious cognitive outcomes in late life [3, 4]. In terms of underlying mechanisms, older adults with higher systemic levels of inflammatory markers have been shown to evidence smaller hippocampi [5] and medial temporal lobes [4] relative to those with low levels of inflammation. Over and above traditional vascular risk factors, recent evidence also suggests that inflammation induces changes in vascular permeability, endothelial function, and microvascular structure, all of which may contribute to the pathogenesis of cerebrovascular disease and affect white matter integrity [6, 7].

Although the breadth of evidence suggests that inflammatory processes differentially change with age and disease states, it remains unclear if inflammation plays a fundamental role in defining clinical course. The repeated failure of anti-inflammatory therapy clinical trials brings the influential nature of inflammation into further question, as many trials have shown no effect of non-steroidal anti-inflammatory drug use on incident risk [8] or later development of Alzheimer's disease [9]. In line with this concern, prior reviews have aptly questioned whether pro-inflammatory processes are simply spectators of an already evolving pathophysiology or represent a critical lynchpin in the disease trajectory [10, 11]. The vast majority of clinical research, however, has focused on cross-sectional examinations of inflammatory markers, rendering it difficult to determine the chronicity of inflammatory levels, much less to identify dynamic relationships with cognition and clinical function over

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time. In order to garner a preliminary understanding of how inflammatory markers change and possibly exert negative effects in neurodegenerative disease, longitudinal cohort analyses with multiple inflammatory markers are imperative.

This review aims to synthesize recent research on the longitudinal association between inflammation and clinical presentation in older adults at risk for Alzheimer's disease, and critically outline methodological considerations and unanswered questions for future research. Brief attention will be directed towards studies evaluating the predictive role of baseline inflammation in longitudinal cognitive decline, followed by a focused review of studies that a) incorporate two or more time points of inflammatory markers *and* b) evaluate cognitive decline or conversion to Alzheimer's disease. Search terms used to identify studies included combinations of the following three categories: longitudinal [*longitudinal* or *change*]; aging [*aging*, *older adult,* or *Alzheimer's*]; and inflammation [inflammation, inflammatory, cytokine, IL-1, IL-6, CRP, or *TNF-alpha*]. Of note, 'cognitive decline' was typically defined in studies as a decline in *global* cognitive functioning, but in some studies it was also referred to as declines on specific neuropsychological tests, namely episodic memory consolidation (e.g. delayed recall) and/or executive function measures.

Baseline Inflammation as a Predictor for Longitudinal Cognitive Decline in Older Adults

Early studies in this research area focused on the relationship between baseline inflammatory markers and longitudinal cognitive decline in older adults [12-16], and suggested that higher levels of pro-inflammatory markers may predict future decline. Results gleaned from the seminal Honolulu Asia Aging Study revealed particularly striking results, indicating that in a large prospective sample of Japanese American men, higher mid-life levels of CRP were associated with a 3-fold increased risk of dementia 25 years later [17]. This finding gained traction and was followed by a series of generally supportive results from large cohort studies on cognitive decline [12, 14, 18], and extended to other pro-inflammatory cytokines, including IL-6, IL-1beta, and TNF-alpha. Broadening research to individuals with baseline cognitive impairment, smaller clinical studies furthered suggested that baseline plasma and CSF markers of soluble TNF receptors [19] and serum levels of TNF-alpha [20] were related to not only cognitive decline, but also the likelihood of converting to Alzheimer's disease and the rapidity of Alzheimer's disease progression. In addition to a baseline role of inflammation in future clinical trajectories, the presence of acute inflammatory events, such as respiratory infections or delirium [20, 21] have also been associated with exacerbations of clinical presentation and precipitous cognitive declines in AD.

Although considerable evidence points to an early role for inflammatory processes in disease onset and progression, accumulating research also highlights a more complicated picture, in which pro-inflammatory markers inconsistently and at times inversely relate to cognitive decline. Several large, comprehensive studies have found no association between baseline inflammation and future risk of AD or non-AD dementia, or have noted no independent effects over and above traditional vascular risk factors [22-25]. These findings are particularly notable in the oldest-old, where either no associations or opposing findings have

been observed. More recently, Lima and colleagues reported that increased baseline levels of serum CRP were associated with *decreased* risk of cognitive decline in the oldest old [26]. Similar paradoxical findings have also been reported for cardiovascular risk factors. Several conditions (e.g. high body mass, elevated cholesterol) that confer risk in middle age do not seem to confer risk in the oldest old, and in fact display reversed associations with cognitive impairment [27, 28]. It may be that marked differences in age and demographics between studies explains the contradictory findings. Alternatively, conceptualizing inflammation as fundamental precipitator of cognitive decline, *independent* of other vascular modifiers, may be dubious. Vascular disease (e.g. atherosclerosis) invokes an inflammatory process by nature, and thus disentangling the two has proven to be difficult. Although several studies show that the presence of inflammation strengthens the association between vascular risk and cognitive decline [29, 30], the interrelationships and independent contributions of the two remain unclear. As such, differences in baseline vascular risk factors between studies may also explain different or opposing findings.

Further obscuring our understanding of inflammation-associated clinical outcomes is the single-time point evaluation of cytokines, which provides only a snapshot of a likely evolving inflammatory process. In order to clarify the current research landscape on inflammation and cognitive decline, the following sections will focus exclusively on studies incorporating two or more assays of inflammation and cognitive outcomes measures.

Longitudinal Measures of Inflammation as Predictors for Cognitive Decline in Older Adults

Longitudinal Measures of Inflammation and Healthy Older Adults

An examination of studies utilizing more than one biological specimen in the context of a healthy older adult baseline sample yielded four investigations [31-34]. Two of the four studies reported no associations between longitudinal inflammation and cognitive decline [32, 33], one reported an association between increases in inflammation and subsequent decline [31], and one described associations between increases in inflammation and lower risk of a dementia diagnosis [34].

The two studies reporting null findings evaluated longitudinal inflammation as a secondary or exploratory component of their investigations, and diverged markedly in population demographics. Specifically, Teunissen and colleagues (2003) examined two time points of a range of serum inflammatory factors (see Table 1) in a subsample of 65 middle aged men and women, as part of the Maastricht Aging Study (MAAS). Baseline mean age for their sample was 54 years, and participants were followed for 6 years. In contrast, a study by Sundelof and colleagues (2009) evaluated two time points of serum CRP and IL-6 in a sample of 704 older men, as part of the Uppsala Longitudinal Study of Adult Men (ULSAM). Baseline mean age was approximately 70, and participants were followed for 7+ years. Although the studies varied in terms of age and gender, the outcome variables of interest also differed, with the ULSAM study evaluating risk of conversion to dementia, and MAAS evaluating correlations with cognitive decline (an appropriate outcome given the age demographic). Both studies ultimately yielded negative findings; however, it remains

unclear how change in inflammatory markers related to absolute levels of inflammation, whether proximal (nearest to outcome variable) assays were more predictive of outcomes, and if controlling for baseline inflammatory levels impacted the effect of change on outcomes.

Addressing several of the aforementioned concerns, a recent study employing the Cardiovascular Health Study-All Stars (CHS All Stars) dataset reported a significant association between increases in pro-inflammatory markers (IL-6, CRP) and cognitive decline [31]. The sample included both men and women with median age of 84.9 years, thus placing this study on the spectrum of oldest-old adults, and outcome measures included cognitive measures (digit symbol substitution test, DSST; general mental status test, 3MS) and an index of cerebrovascular disease (CVD). Increases in IL-6 and CRP predicted both incident cognitive impairment and CVD at the final assessment. Furthermore, over a period of 9 years (2 time points), older adults who evidenced a doubling of CRP or IL-6 showed a *decline* on measures of general cognitive functions (3MS; CRP only) and visuospatial scanning and processing speed (DSST; CRP and IL-6). In order to address the role of change versus single time points of inflammation, the authors also evaluated the interaction between change and absolute levels. Notably, individuals who had higher levels of CRP and IL-6 at the first time point showed little additional risk of incident cognitive impairment if their levels increased over time; thus, whereas change in inflammation was a significant predictor of outcome, the effect was dampened when taking into consideration initial levels. Similarly, when evaluating the association between increase in inflammatory levels and decrease in general cognitive functions (i.e. 3MS), the effects were reduced for individuals who began with elevated CRP levels. This study thus offers support for evaluating both distal, baseline markers of inflammation as well as change in inflammation over time, while also noting that information gained from change indices are more fruitful when evaluating individuals with lower baseline inflammatory levels.

Providing a significant, but counter view on the relationship between longitudinal inflammation and cognitive decline in the oldest old (mean age=88.3 years), a recently published cohort study reported that increases in soluble IL-6 receptor levels were associated with lower risk for dementia in women [34]. Data for this study was collected from the Study of Osteoporotic Fractures (women only), and included inflammatory markers (IL-6, soluble TNF-1 receptor, soluble IL-6 receptor) measured at Years 10 and 16, with cognitive status and conversion to dementia arbitrated at Year 20. Although no significant associations were noted between IL-6, soluble TNF-1 receptor and Year 20 cognitive status, individuals with high soluble IL-6 receptor levels at Year 16, as well as those who increased from low to high levels over time showed *lower* risk of dementia. These findings differ from many epidemiological studies that typically show a positive association between levels of inflammation and later conversion to dementia, thus again raising question whether a) the oldest-old display clinically relevant differences in immunological functioning relative to young-old individuals and b) potential survival bias in the oldest-old alters interpretation. Despite focusing on a participant sample of the oldest-old, these findings stand in contrast to the prior study[31] in many ways. Only one inflammatory analyte overlapped between the two (IL-6), methodological handling of the data diverged (i.e. assessing continuous versus

dichotomous measures of inflammation), and different outcome measures were used (i.e. cognitive functions versus adjudicated diagnoses).

In summary, the small number of longitudinal healthy older adult studies highlights several questions of interest and suggests important areas for further research. The noted heterogeneity in participant samples, analytes, and outcome measures limits strong generalizations or conclusions, particularly in the two studies in which longitudinal analyses were secondary and only briefly discussed (or data not shown); however, findings gleaned from the two studies on the oldest-old document important changes in the inflammatory response that bears significance for future cognitive outcomes. The directionality of these associations is mixed, but nonetheless intimates a salient, underlying alteration in pro-inflammatory processes.

Longitudinal Measures of Inflammation and MCI/Alzheimer's Disease

Review of studies that incorporated two or more time points of specimens in a clinical sample (i.e. mild cognitive impairment, MCI; Alzheimer's disease, AD) yielded three additional investigations [35-37]. Of these, one study reported no association between longitudinal inflammation and cognitive decline [35], one described an association between increases in inflammatory markers and subsequent cognitive decline [36], and one reported significant decreases in inflammation associated with MCI conversion to AD [37].

The one reported null finding originated from a small, descriptive study of non-AD controls (n=9; mean age=71 years) and Alzheimer's disease patients (n=8; mean age=70 years), in which CSF and serum inflammatory markers were measured yearly over a period of 2-5 years [35]. Data were collected as part of the Oxford Project to Investigate Memory and Ageing (OPTIMA), and included pathologically confirmed cases. Change in inflammatory markers did not differentiate AD from non-AD controls in this study, nor did change in inflammatory levels map on to declines in cognitive functioning (in either group). A relative strength of this study is its use of pathologically confirmed AD cases, and it remains the only study to use multiple (>2) time points of inflammatory levels in relation to a cognitive outcome variable. Given the low sample size of individuals with AD, the heterogeneous sample of non-AD controls (i.e. Huntington's disease, CVD, Pick's, and Parkinson's pathologies, and normal controls), and the cognitive severity of several patients, however, it is difficult to distill the findings and draw substantial conclusions. This is particularly notable in light of cross-sectional data, which suggests that inflammatory processes may differ depending on disease severity, with higher levels of inflammation observed in *earlier* stages of the disease process [37].

Relevant to the role of longitudinal inflammation in disease severity, a similarly small evaluation of 6 MCI patients (subsample of larger study) revealed a decline in serum levels of MCP-1 (monocyte chemotactic protein-1) over 1 year in individuals who converted to AD, relatively stable levels in individuals who maintained an MCI diagnosis, and an increase in levels in individuals who were subsequently diagnosed with vascular dementia. Note that cross-sectionally, MCI and early AD patients evidenced higher levels of MCP-1 relative to both controls and severe AD patients (cross-sectional sample n=166), reiterating that early stages of pathogenesis may result in higher or peak levels of circulating

inflammatory markers relative to later stages of disease. It's important to highlight that commentary on longitudinal change is merely descriptive and somewhat speculative, as the sample size is too small and statistical analyses were thus not conducted.

A larger, recent evaluation of an AD subsample from the AddNeuroMed study addressed concerns regarding the role of disease progression by controlling for this factor in their longitudinal model [36]. Specifically, the authors divided 104 AD patients into slow, intermediate, and fast decliners, based on their change in ADAS-Cog scores (calculated as annual decline) and compared 1-year change in inflammatory markers between groups (see Table 1). AD patients who displayed a fast relative to slow cognitive decline showed an increase in levels of IL-4, IL-10, and G-CSF, whereas AD patients who evidenced an intermediate relative to slow decline showed higher levels of IL-2, IL-4, interferon- γ, and PDGF over 1 year. It is unclear why different cytokines showed elevated profiles based on disease progression, but suggests that the orchestration of the pro-inflammatory and anti-inflammatory cascade may evolve over time and may track with pathological changes.

In summary, very few longitudinal studies on inflammation have been conducted with Alzheimer's disease patients, with only one study including a sample of greater than 10 AD participants. The relatively large study of AD patients detailed increases in inflammatory markers stratified by disease progression, although no control group was included and thus relative rates of change and associations with cognitive functioning over time remain unexplored.

Longitudinal Inflammation and Cognitive Decline: Critical Gaps in the Literature

Based on the limited research available, there is clearly breadth and depth of knowledge needed to fully understand the role of longitudinal inflammation in subsequent cognitive decline. In order to ascertain rates of progression and determine whether inflammatory processes change in tandem with disease progression, studies with multiple time points of inflammatory markers are gravely needed. Statistical models of two time points provide some indication of change and for pragmatic reasons are often all researchers may have access to in retrospective studies; however, due to concerns of regression to the mean, these analyses cannot yield robust slopes nor are they amenable to modeling trajectories.

In addition to multiple time points of data, studies are needed that provide extensive evaluation of a range of cytokines, chemokines, and complement factors to help elucidate their relationships with cognitive decline while also delineating dynamic changes in individual levels over times. Several studies have reported promising results with IL-6, CRP, and TNF-alpha, thus additional evaluation of upstream versus downstream effects of these markers, as well as greater attention to additional factors in inflammatory superfamilies (e.g. TNF superfamily) is warranted.

One of the more pressing questions that remain is whether inflammatory markers play an integral versus ancillary role in disease progression. Although the aforementioned data is mixed, it suggests the possibility of an early inflammatory role in AD; what this role looks

like, and whether its function is initially beneficial or deleterious remains open for debate. An important step in the literature is to comprehensively assess the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on study findings, as the relationship between NSAIDs, peripheral inflammation, brain structure, and cognitive decline remains unclear. An additional means by which the field may inch closer to an answer is by integrating longitudinal AD biomarkers, in addition to inflammatory markers. By closely following individuals' trajectories as they move from asymptomatic, AD biomarker + (e.g. PET amyloid scan; CSF amyloid/tau) to mild stages of cognitive impairment, we may be able to elucidate important changes in the regulation of inflammatory responses. Although this will still not provide definitive evidence of a primary role, it will offer multiple streams of evidence for early vs. late immune activation.

Longitudinal Inflammation and Cognitive Decline: Methodological Considerations

In addition to the landscape of research questions, there are also several methodological considerations that are important to address. One of the many limiting factors to generalizing findings as well as comparing results between centers is the assay methodology itself. Results from aforementioned studies are understandably processed via numerous platforms and companies. Platform and assay differences have been shown to significantly impact study results, over and above simple discrepancies in magnitude [38], which may limit replication of findings. Of particular importance to longitudinal designs, difference in plate manufacturing *lots* may also have an impact on findings, rendering it necessary to calibrate new findings (2nd time point) with old (1st time point), or optimally run all time points simultaneously. Specific inflammatory analytes are also sensitive to acute, underlying illness (e.g. respiratory infection) and may have diurnal or fluctuating patterns within a single person. Finally, issues regarding specimen type (e.g. serum versus plasma) and protein subunit measurement are also both concerning for synthesizing findings in the literature [39], as subtle differences in the sections of proteins measured as well as the blood specimen used may have substantive effects on overall quantification. Although systemizing these methodological issues is cumbersome and may not be immediately feasible, maintaining consistency *within* centers, controlling for plate lots, and garnering more specific information regarding protein measurement will help minimize error and increase generalizability of longitudinal studies.

Conclusion

Isolating the role of longitudinal inflammation in cognitive decline and Alzheimer's disease remains in an incipient, albeit promising stage of inquiry. The succession of failed anti-inflammatory drug trials combined with mixed clinical research findings have been perplexing, but have also identified numerous understudied research questions. Collectively, the dearth of studies on longitudinal inflammation and cognitive decline in older adults have yielded conflicting results, but also suggest that in well-powered, primary evaluations of longitudinal inflammation, inflammatory dysregulation is evident and related to clinical outcomes. The directionality, magnitude and progression of these associations remain

unclear, as it the relative role of inflammatory processes in the earliest stages of disease. Future studies employing *multiple* time points of inflammatory data along with AD biomarkers are critical for further explication of the role of longitudinal inflammation in cognitive decline.

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Table 1

Description of studies reporting longitudinal inflammatory markers in the context of a cognitive outcome variable

Study	N	Subjects	Specimen	Inflammatory Markers	Time Points* (Years)	Outcome Measures	Findings
Galimberti et al, 2007	6	MCI	Serum	MCP-1	2 (1 yr)	*Conversion:* MCI to AD	↓ Decline in MCP-1 observed in the subgroup of MCI subjects who converted to AD
Jenny et al, 2012	1040	HC	Not Reported	CRP IL-6	2 (9 yrs)	*Cognitive:* Symbol Digit 3MS	↑ Doubling of CRP or IL-6 over time associated with decline in DSST (both) and 3MS (CRP only)
Lanzrein et al, 1998	17	AD (path confirmed) HC Other CNS	Serum CSF	IL-1β; IL-1ra; IL-6 TNF- Alpha sTNFR l, ll x1-ACT	2-5 (2-5 yrs)	*Cognitive:* CAMCOG	↔ Longitudinal inflammation did not differentiate Alzheimer's disease patients from controls
Leung et al, 2013	104	AD	Plasma	IL-1β; IL-lra; IL-2, 4-10, 12, 13, 15, 17 G-CSF	2 (1 yr)	*Cognitive:* ADAS-Cog	↑Significant increase in AD patients with a fast decline compared to slow decline over 1 year.
Metti et al, 2014	393	HC	Serum	IL-6, IL-6sR sTNF-R1	2 (6 yrs)	*Conversion:* Adjudicated diagnosis	↓ Women with high IL-6-sR at both time points or who transitioned to a high level had lower risk of dementia
Sundelof et al, 2009	704	HC	Serum	CRP IL-6	2 (7 yrs)	*Conversion:* HC to AD or Dementia	↔ Change in inflammation doesn't increase risk of AD or dementia
Teunissen et al, 2003	65	HC	Serum	Haptoglobin Albumin α_1-Fraction α_2-Fraction γ-Fraction IL-6 receptor CC16 CRP	2 (6 yrs)	*Cognitive:* Letter-Digit Coding Stroop Word Recall	↔ No association longitudinally

*Reflects time points at which inflammatory markers were drawn, followed by parenthetical indication of the number of years spanned.
Abbreviations: HC=healthy control; CNS= central nervous system; AD= Alzheimer's disease; MCI= mild cognitive impairment.