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The Impact of Stress and Inflammatory Processes on Cognitive Change in Late Adulthood

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Dedication:

To my grandfather, Dr. C.A. Perumal, who is my role model and a source of inspiration

ABSTRACT OF THE DISSERTATION

The Impact of Stress and Inflammatory Processes on
Cognitive Change in Late Adulthood

by

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Stress and inflammation are two very common, but also very complex processes that may affect cognitive decline in late adulthood. This study examined how the self-report of psychological stress and inflammatory biomarkers levels may be related to differences in trajectories of cognitive performance in late adulthood. We found weak, non-significant association between psychological stress and inflammatory biomarkers levels. Analyses also suggested that the inflammatory pathway may be important to cognition in late adulthood, since dual change growth curve model results suggested that higher levels of inflammatory biomarkers (CRP and IL-6) were associated with decrements in some aspects of cognitive performance in late adulthood. Moreover, greater psychological stress was associated with decreases in some aspects of cognitive performance in late adulthood. Greater psychological stress and/or its timing was associated with significant differences in cognitive performance levels or change on a measure of spatial abilities

(Block Design), perceptual speed abilities (Symbol Digit), verbal abilities (Synonyms), and episodic recognition memory (Thurstone Picture Memory). Although these findings suggested that both stress and inflammation affect cognitive decline in late adulthood, final analyses that incorporated both psychological stress and inflammatory biomarkers as predictors of cognitive decline in late adulthood suggested limited findings of mediation for a measure of episodic recognition memory (Thurstone Picture Memory).

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The present study aimed to better understand how stress related processes and inflammatory processes might affect cognitive performance in late adulthood. This study examined how quantitative measures of psychological stress, and inflammatory biomarkers may ultimately influence the trajectories of normal cognitive decline across different longitudinal studies of aging.

The body's physiological response to stress evolved to deal with immediate, short term threats to survival and reproduction (Butcher and Lord, 2004). However, in modern society, the body's physiological response to stress is triggered and up-regulated far more often than it was intended to in response to various types of psychological stress (Butcher and Lord, 2004). We hoped to better understand how psychological stress may affect inflammation and ultimately how these two processes may affect the role the inflammatory pathway plays in normative cognitive change.

Literature Review

Cognitive Decline in Late Adulthood

Over the last few decades, many studies of aging have focused on understanding cognition in late adulthood. Some major findings from recent studies concerning normative cognitive decline in late adulthood are discussed. These studies have given us reason to further investigate processes (i.e. stress and inflammation) that may underlie the observed patterns of cognitive change reported in late adulthood.

The Seattle Longitudinal Study has examined both cross-sectional and longitudinal changes in cognitive performance at over 5 time points over the span of more than 45 years in cognitive measures of verbal, spatial, and numeric abilities, verbal memory, and inductive reasoning (Schaie, 1994). Schaie has reported stable performance on most of these measures until age 60, except for verbal memory. Modest, non-linear declines in these cognitive abilities have been observed in participants up to eighty years of age (Schaie, 1994).

Schaie's findings from the Seattle Longitudinal Study have been observed in other studies of aging (Christensen, 2001; Finkel, Pedersen, Plomin and McClearn, 1998; Singer et al, 2003). In the Berlin Aging Study, Singer and colleagues (2003) showed rapid decline for most cognitive abilities in participants from 70 to 90 years of age; thus, extending Schaie's findings to individuals of old-old age. Similarly, the Canberra Longitudinal Study has found (Christensen, 2001) that individuals demonstrated accelerated rates of decline for most cognitive abilities, except for crystallized intelligence, which remains stable up to 85 years of age (Christensen, 2001). Lastly, in the Swedish Adoption/Twin Study of Aging it has been demonstrated that mean performance for most cognitive abilities remains stable until late adulthood where accelerating declines are observed especially for tasks that tap fluid abilities (Finkel et al, 1998, 2003; Reynolds et al, 2005). However, an examination of changes in total variance over time suggested increased variability in some fluid intelligence and memory measures over time (Finkel, Pedersen, Plomin and McClearn, 1998) which may increase nonlinearly until about age 80 years (Reynolds et al, 2005). The increases in variability

suggested that some individuals better maintained their cognitive abilities over age than others. Indeed, in large measure the increased variation across cognitive measures is due to increases in environmental variance (Reynolds et al, 2005), which suggests that environmentally mediated processes, e.g., vis-à-vis psychological stress and inflammation, may be associated with the individual differences in cognitive trajectories.

Inflammation

The factors or processes that contribute to the inflammatory pathway may ultimately affect cognitive performance in late adulthood. Studies suggest that persistent or chronic exposure to inflammation can instigate oxidative stress, cell apoptosis and possibly the destruction of neurons in the Central Nervous System (CNS) (Federico et al, 2007; Medzhitov, 2008; McGeer and McGeer, 2004; Warnberg, 2009). Oxidative stress occurs, when free radicals or unstable oxygen molecules are released during cell metabolism. This process may eventually lead to neuronal death (McGeer and McGeer 2004). As a result, chronic activation of the inflammatory pathway may lead to the formation and dispersion of free radicals and nitric oxide (NO) leading to neuronal degeneration in the brain (Federico et al, 2007; Stuchbury and Munch, 2005). Lastly, aggressive or abnormal inflammatory responses may also lead to the damage of brain tissue (Medzhitov, 2008). In addition, persistent or chronic exposure to inflammation can result in dysregulation of the immune response which may trigger changes in cognition according to the neuro-inflammatory hypothesis of Alzheimer's Disease (Rosenberg, 2005). Alzheimer's Disease (AD) is characterized by a decline in functional abilities such as memory performance (Rosenberg, 2005). The neuro-inflammatory hypothesis states

that these impairments and changes in the CNS result from inflammation. Inflammation may result from the overactivation of microglia in the brain that in turn leads to the over-expression of the major proinflammatory cytokines and related inflammatory proteins – that include Interleukin-6 (IL-6) and C-Reactive Protein (CRP) (Rosenberg, 2005). In addition, AD is associated with the formation and presence of amyloid plaques and neurofibrillary tangles (Sivaprakasam, 2009; Zaheer et al, 2008). The presence of amyloid plaques and neurofibrillary tangles are observed in brain regions that likewise show higher levels of inflammatory pathway activity such as higher levels of the inflammatory biomarkers IL-6 and CRP (Klegeris, 2007; Sivaprakasam, 2009).

Inflammatory Biomarkers

The process of inflammation is complex, and the C-Reactive Protein (CRP) and Interleukin-6 (IL-6) biomarker levels are thought to be indicative of the processes occurring within the inflammatory pathway. CRP has been associated with immune functioning, activation of the complement cascade system, and higher levels of CRP can serve as a marker of inflammation (Biro et al, 2007; Marnell et al, 2005; McGeer et al, 2005; Oksjoki et al, 2007; Sjoberg et al, 2009). In regards to immune functioning, CRP has been associated with the initiation of cell repair as well as the clearance of apoptotic cells and tissues (Biro et al, 2007).

Not only does CRP play a role in immune response functions such as cell repair and cleanup of dead cells, but also in triggering the activation of the complement cascade system. The complement cascade system belongs to the body's innate immune system and includes over 30 proteins and related fragments (Fourgeaud and Boulanger, 2007;

Sjowall et al, 2006). These complement proteins are responsible for fighting off organisms that invade the body (Marnell et al, 2005). Also, the higher plasma levels of CRP during the acute phase response of immune response (Black et al, 2004; Carlson et al, 2005; Sjowall et al, 2007; Suk et al, 2005) serve as an indication of systemic increases in inflammation during immune response. Higher levels of baseline CRP blood concentrations at the first time point of data collection have been associated with a wide range of health conditions with an underlying etiology of chronic low grade inflammation (Black et al, 2004; de Maat et al, 2004; Hurme et al, 2007).

With respect to immune response, Interleukin-6 (IL6) plays a role in the induction of fever and the release of the adrenocorticotropic hormone after exposure to infection (Snick, 1990). During acute phase response, IL-6 triggers the release of acute phase proteins such as CRP (Hirano et al, 1990).

Inflammation and Cognitive Decline in Late Adulthood

Studies have suggested that chronic inflammation is associated with the production of amyloid beta and precursor proteins. A broad variety of inflammatory proteins including acute phase proteins like C-Reactive Protein (CRP) and proinflammatory cytokines like Interleukin-6 (IL-6), that can be found in senile plaques and tangles, which are neuropathologies that have been observed in the brains of individuals with Alzheimer's disease and are also a clinical symptom of this disease (Eikelenboom, 2010; Tuppo and Arias, 2005). An increase in the levels of pro-inflammatory cytokines (i.e. IL-6) and related inflammatory proteins (i.e. CRP) have been observed in association with these pathological features of Alzheimer's Disease

(Dik et al, 2005; Eikelenboom, 2010; Finch and Morgan, 2007; Solfrizzi et al, 2006; Teunissen et al, 2003;Yaffe et al, 2003).

However, higher levels of pro-inflammatory cytokines and inflammatory serum proteins have not consistently been predictive of changes in cognitive performance during late adulthood across studies. In the Longitudinal Aging Study (LSA), higher levels of IL-6 and CRP were not associated with lower levels or rates of change in general cognition as assessed by the Mini Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975), and related tasks that assessed memory, fluid intelligence, and processing speed (Dik et al, 2005). In the Women's Health Study, higher levels of CRP were not associated with poorer cognitive performance on 5 tasks belonging to the Telephone Interview for Cognitive Status, only poorer general health (Weuve et al, 2006). In the Maastricht Aging Study (MAAS), no associations were found between higher levels of IL-6 and cognitive performance; however, higher levels of CRP were related to deficits in verbal learning abilities as assessed by completion of a word learning task (WLT) (Teunissen et al, 2003). In the Edinburgh Artery Study, higher IL-6 levels were associated with worse processing speed ability based on performance on the Weschler Digit Symbol Test (Rafnsson et al, 2007). According to the MacArthur Study of Successful Aging, higher levels of IL-6 were related to poorer general cognitive performance at baseline testing and increased risks of cognitive decline at future testing as measured by a summation of performance on five cognitive tests – Boston Naming Test, Recall of Naming items from the Boston Naming Test, the Delayed Recognition Span Test, Weschler Similarities Subtest, and a Geometric Figures test which assessed

naming, verbal memory, spatial recognition, abstraction, and spatial ability respectfully (Weaver et al, 2002). In the Health, Aging, and Body Composition (Health ABC) Study, participants with a greater risk of decline in cognitive functioning as measured by performance on the modified MMSE at follow-up had higher levels of IL-6 and CRP at testing in a prospective study (Yaffe et al, 2003). In the Einstein Aging Study (EAS), among old-old age participants with normal general cognition, higher serum levels of IL-6 and CRP were associated with decrements in executive functioning ($p<0.05$) as assessed by a digit symbol substitution, a Trail-Making Test and Phonemic fluency test but no associations were found with episodic or semantic memory (Derby et al, 2008). Cross-sectionally, Krabe and colleagues (2009) found that at age 85 in healthy Danish Octogenarians higher circulating levels of IL-6 were associated with decreases in full IQ, verbal IQ, and performance IQ. However, this same study found no relationship between higher CRP levels at age 85 and decrements in cognitive performance (Krabe et al, 2009). Lastly, at two years follow-up, elderly Chinese patients with higher CRP levels (7.0 mg/l or higher) had significantly worse MMSE scores (Xu et al, 2009). Also, those with higher plasma CRP levels had a greater risk of having a diagnosis of dementia at follow-up (Xu et al, 2009). In the Aspirin for Asymptomatic Atherosclerosis Trial, Marioni and colleagues (2009) found that higher CRP levels at baseline were associated with poorer cognitive functioning on tests of processing speed (the Digit Symbol Test and Trail Making Test, Part B) five years later. In a subset of these participants, higher CRP levels were predictive of poorer non-verbal reasoning assessed with Raven's Standard Progressive Matrices. Gimeno and colleagues (2009) found mixed associations for CRP

and IL-6 levels with cognitive decline. For men, higher CRP levels in midlife were associated with lower semantic fluency and vocabulary performance, while higher IL-6 levels were related to trend significant declines in vocabulary performance 6-12 years after blood collection. For women, higher CRP levels in midlife were associated with significant declines in vocabulary performance and no associations were found with IL-6 levels 6-12 years later. In the Honolulu Asia Aging Study (HAAS), higher CRP levels at midlife were related to significant declines in cognitive performance as assessed with the Cognitive Abilities Screening Instrument (CASI) up to 25 years later (Laurin et al, 2009). Once individuals with incident dementia were excluded from analyses, higher CRP levels were not associated with significant declines in cognitive functioning. Komulainen and colleagues (2007) found that higher baseline levels of CRP were related to poorer memory performance twelve years later on a word recall test in women. In an African-Caribbean community population (Jordanova et al, 2007), associations between IL-6 and CRP levels with a battery of psychometric tests were examined. Higher IL-6 levels at baseline were associated with declines in spatial orientation and immediate verbal recall tasks. Weak associations were found between higher IL-6 levels and cognitive performance on delayed recall and psychomotor speed tasks in, and no relationships were found between higher CRP levels and cognitive performance at a later time. Marsland and colleagues (2006), reported that elevated IL-6 levels at midlife in healthy adults was associated with poorer cognitive performance on a series of tests on executive function, working memory, attention, and auditory recognition memory in individuals belonging to the Adult Health and Behavior (AHAB) project. Hoth and colleagues (2008) found that

higher CRP levels at one time point were associated with declines on an attention-executive psychomotor composite score in individuals with cardiovascular disease. The composite score included cognitive performance on the tests of attention, executive control, and memory performance on a range of neuropsychological tests. Lastly, in the Rotterdam Study, for APOE-e4 carriers, higher IL-6 levels were associated with annual declines in global cognitive functioning (Schram et al, 2007). In the Leiden 85-plus Study, higher levels of CRP and IL-6 were related to declines in global cognitive functioning and memory annually. However, this relationship was stronger in those individuals who were *APOE*-e4 carriers (Schram et al, 2007).

Given the variation in findings across prior studies, the current project accounted for factors that may have contributed to the variability in findings across studies. For example, none of the studies mentioned have included both psychological stress measures and serum biomarkers as predictors of cognitive performance. Secondly, in the current project cognitive performance was measured longitudinally across a span of 16 years with up to 5 time points. Many studies do not look at cognitive performance at multiple time points. The greater number of time points enabled us to capture changes in cognitive decline that may be gradual and less profound. Lastly, the current study had psychological stress information at multiple time points. Most studies do not look at stress at multiple time points. This allowed us to look at the chronic nature of stress across time.

Stress

The experience of stress may have an effect on normal cognitive decline during late adulthood and may be an important explanatory factor in the mixed findings on C-Reactive Protein (CRP) and Interleukin-6 (IL-6) levels and cognitive change. Stress is an environmental factor that may moderate levels and rates of cognitive performance and or cognitive decline in late adulthood. Stress can be defined comprehensively as a person's emotional, behavioral, cognitive, and physiological cognitive response to a stressor (Clark, Bond, & Hecker, 2007). A stressor is an event or circumstance that elicits this response. Stress can be defined as circumstances that individuals would appraise to be threatening or unmanageable (Miller and Blackwell, 2006; Segerstrom, 2004). Psychological stress is a specific type of stress that occurs with recognition that an individual's adaptive capacity is taxed or exceeded by the environmental demands he or she encounters (Cohen, Janicki-Deverts, & Miller, 2007). Based on the duration of the stressor, it can be acute or chronic in nature. Acute stress is usually a time limited stressor associated with a sense of fight or flight (McEwen, 1998; Segerstrom, 2004). A chronic stressor is usually pervasive in an individual's life and can also be associated with the accumulation of many minor, daily stressors (McEwen, 1998; Segerstrom, 2004).

The physiological response to stress is mediated by two main endocrine systems – the Hypothalamic-Pituitary-Adrenocortical (HPA) Axis and the Sympathetic-Adrenal-Medullary (SAM) system (Butcher and Lord, 2004; Cohen et al, 2007) ultimately resulting in increased production of the glucocorticoid stress hormone cortisol. Sympathetic activation of the Sympathetic-Adrenal-Medullary system leads to the release

of catecholamines, which increase production of proinflammatory cytokines such as IL-6 and acute phase proteins such as CRP (McEwen, 2006). Parasympathetic activation of the Hypothalamic-Pituitary-Adrenocortical axis leads to the production of cortisol, a glucocorticoid which functions as an anti-inflammatory agent by inhibiting or decreasing the production of pro-inflammatory cytokines (McEwen, 2006; Butcher and Lord, 2004; Kemeny, 2007; Robles et al, 2005). Since cortisol initiates a negative feedback system that turns off Hypothalamic-Pituitary-Adrenocortical activation, the experience of stress over time can lead to the chronic elevation of cortisol levels. This can lead to a higher set point for circulating cortisol levels and hamper the negative feedback mechanism to function normally; thus, leading to disruptions in immune response (Cacioppo and Berntson, 2007; Miller and Blackwell, 2006; Robles et al, 2005). It is possible that this disruption can lead to an increase in cortisol levels. An elevation in cortisol levels could lead to a decrease in sensitivity to the effects of cortisol and eventually lead to an increase in the production of proinflammatory cytokines and related proteins (Davis et al, 2008).

Pro-inflammatory cytokines are integral to the first line of defense in immune response during injury or infection (Kemeny, 2007). Interleukin 6 (IL-6) and C Reactive Protein (CRP) are few of such integral pro-inflammatory agents (Kemeny, 2007) that are involved in the processes of wound healing, fever, and inflammation (Segerstrom and Miller, 2004). Elevated levels of pro-inflammatory agents and enhancement of some immune response have been observed in those individuals who report chronic stress (Miller and Blackwell, 2006). Research by Maes and colleagues (1998) suggests that psychological stress is associated with higher levels of pro-inflammatory cytokines, and

the production of these molecules may be sensitive to variations in individuals' perceptions of the severity of the experienced stressor. Also, a meta-analysis conducted by Segerstrom (2004) suggests that most chronic stressors are associated with global immunosuppression -- indicating greater decrements in immune function with the experience of long term, enduring stressors.

The physiological response to stress within the body can be induced by the experience of psychological stress. Psychological stress can be measured through an examination of the types of major life events (i.e. death of a spouse, marriage, and financial difficulties) that an individual may have experienced (Sterling and Eyer, 1988). Some studies have shown that the occurrence of major life events and or the experience of more negative life events have been associated with a higher likelihood of more adverse side effects on mental health and the onset of physical health disorders (Rabkin and Struening, 1976; Vinokur and Selzer, 1975).

Stress and Inflammation

Most studies that examine the relationship between stress and inflammation suggest that higher levels of stress are associated with higher CRP levels (e.g. Bitton et al, 2008; Blum et al, 2009; Davis et al, 2008; Janicki-Deverts et al, 2008; Kiecolt-Glaser J.K et al, 2003; McDade et al, 2006; Veldhuijizen van Zanten et al, 2005) and higher IL-6 levels (e.g. Hamer et al, 2007; Kop et al, 2008; Maes et al, 1998; Von Kanel et al, 2006; Von Kanel et al, 2008; Yasui et al, 2007). However, there are also studies that suggest weak or no associations between levels of stress and CRP or IL-6 biomarker levels (e.g. Davis et al, 2008; Goldman et al, 2005; Von Kanel et al, 2006; Kop et al, 2008; McDade

et al, 2006; Steptoe et al, 2001). The variation in these findings can be attributed to the duration of stressor being measured (e.g. acute, chronic), the type of stressor (e.g. caregiver, mental), as well as the manner in which response to the stressor was assessed (i.e. Perceived Stress Scale, General Health Questionnaire) (Segerstrom and Miller, 2004; Steptoe et al, 2007).

The studies discussed below examine the relationship between various psychological stressors and inflammatory biomarkers in a wide range of ages. Recently, a meta analysis by Steptoe and colleagues (2007) examined the relationship between the experience of acute psychological stress and changes in inflammatory biomarker levels across 30 major studies. Across most studies, acute stressors were associated with significant increases in IL-6 levels and trend significant increases in CRP levels. For instance, Veldhuijizen van Zantenz and colleagues (2005) examined the relationship between an acute lab stressor – a paced auditory serial addition test and biomarker levels in elderly patients with rheumatoid arthritis or osteoarthritis. The experience of this acute lab stressor was associated with higher CRP levels in patients with rheumatoid arthritis and higher disease activity (Veldhuijizen van Zanten et al, 2005). Similarly, Kop and colleagues (2008) studied the association between mental stress and physical stress on biomarker levels in patients with and without Coronary Artery Disease (CAD). CAD is a heart condition usually resulting from Atherosclerosis. Higher CRP levels were observed for CAD patients after being faced with the acute stressors of anger recall and mental arithmetic. In patients without CAD, the acute stressors of anger recall and physical exercise were associated with higher CRP levels (Kop et al, 2008). In regards to chronic

stress, those individuals with Crohn's Disease that reported higher levels of stress on the Perceived Stress Scale (PSS) or the Hassles Scale had higher CRP levels and were more likely to have a relapse over the course of one year (Bitton et al, 2008). Similarly, individuals with CAD, who reported difficulties in their personal life (i.e. the death of a family member) had higher CRP levels even when taking statins for cholesterol level management (Blum et al, 2009). In males belonging to the Coronary Artery Risk Development in Young Adults (CARDIA) Study, the stress associated with unemployment was related to higher CRP levels 5-8 years after the occurrence of this life event (Janicki-Deverts et al, 2008). In participants belonging to the Chicago Health, Aging, and Social Relations Study, higher perceived stress scores on the Perceived Stress Scale (PSS) were related to higher CRP levels when controlling for perceived stress scores from the previous year (McDade et al, 2006).

As to stress and IL-6 levels, Maes and colleagues (1998) stated that medical students reported higher levels of stress on the Perceived Stress Scale (PSS) and higher levels of anxiety on the State Trait Anxiety Inventory (STAI) before and after an exam had significantly higher levels of IL-6. For participants belonging to the Whitehall II Epidemiological Cohort, the experience of an acute stressor (e.g. the 5 minute Stroop Test and 5 minute Mirror Tracing) was associated with increases in IL-6 levels 45 minutes post stress (Hamer et al, 2007). Von Kanel and colleagues (2008) assessed the relationship between acute psychosocial stressors on the 13 Minute Trier Social Stress Test and inflammatory biomarker levels. This test included a preparation phase, a job interview, and a mental arithmetic task. Higher IL-6 levels were observed in healthy

participants 105 minutes post-test for those who did not take aspirin. Von Kanel and colleagues (2006) measured the stress associated with caregiving for a family member with Alzheimer's Disease (AD) with multiple measures of stress: the Brief Symptom Inventory (BSI) Global Severity Index of Psychological Stress, Perlin's Role Overload Scale, and Perlin's Expressive Support Scale. The self report of higher levels of perceived stress (BSI) and perceived social support (Perlin's Expressive Support Scale) were associated with higher IL-6 levels; however, this association disappeared when analyses were controlled for health and age. Kiecolt-Glaser and colleagues (2003) examined the influence of chronic stress through the use of the Perceived Stress Scale in caregivers for spouses with dementia and controls. Across six years, IL-6 levels were four times higher in individuals who were caregivers for a person with dementia. In a sample of adults with rheumatoid arthritis, Davis and colleagues (2008) examined the relationship between negative life events, as assessed by the Inventory of Small Life Events, with inflammatory biomarker levels. The researchers found that those individuals who reported higher levels of daily personal stress had significantly higher IL-6 production. Lastly, in a study that included pre and post menopausal women, the endorsement of higher psychological symptoms associated with menopause (i.e. via Greene's climacteric scale) predicted significant increases in IL-6 levels (Yasui et al, 2007).

Within many studies, including the ones discussed above, findings were often not consistent in the prediction of CRP and IL-6 levels. In a study that examined the stress associated with AD caregiving across three stress inventories, significant associations for

IL-6 but not CRP were reported (Von Kanel et al, 2006). An acute stressor (e.g. a color word interference test and a mirror tracing test) was associated with higher IL-6 levels, but not with CRP levels (Steptoe et al, 2001). In a study that examined the relationship between an acute stressor (e.g. anger recall, mental arithmetic) was associated with significantly higher CRP levels for controls and individuals with Coronary Artery Disease (CAD). Also, in adults with rheumatoid arthritis, higher levels of chronic stress were related to higher IL-6 production, but not higher CRP levels. Lastly, Goldman and colleagues (2005) found that moderate and high levels of stress scores, based on detailed interview data over the span of four years, was related to lower IL-6 levels.

Life Events and Cognitive Decline

The experience of life events can serve as an indicator of stress in late adulthood. Research studies have begun to examine the role of life events as a predictor of cognitive decline (Peavey et al, 2009; Peters et al, 2010; Rosnik et al, 2007; Rosnik et al, 2009; Tsolaki et al, 2010; VonDras et al, 2005). Limited findings have been found across these studies between the stress associated with life events and cognitive performance. Rosnik and colleagues (2007) reported no association between aggregate life events scores and cognitive performance for older adults over the span of 1 year in a cross-sectional study. However, various individual negative life events were associated with decrements in cognitive performance. In this study, individuals who reported financial difficulties or whom were the victim of crime had worse cognitive performance on a psychomotor speed task. In another study, Rosnick and colleagues (2009) examined the relationship between bereavement and cognitive performance six months later in a sample of older

adults whom belonged to the Changing Lives of Older Couples (CLOC) dataset. Episodic memory, verbal, reasoning, and visuospatial abilities were examined in these individuals. In this study, bereavement status was not solely predictive of poorer cognitive performance in adults ranging from fifty-eighty years of age. More specifically, participants who were younger, closer to 50 years of age, and were men had worse memory performance six months later. In another cross-sectional research study, VonDras and colleagues (2005) examined the association between stressful life events, measured by the Elders Life Stress Inventory (ELSI) (Aldwin, 1990). The investigators found that individuals who reported more stressful life events had lower levels of delayed recall performance as assessed by completion of a Weschler memory test of logical memory. This study showed that adults ranging in age from 20-40 years with higher life stress scores had delayed recall memory performance similar to adults 50 years of age and older with lower life stress scores – suggesting that the stress associated with life events could accelerate cognitive impairment. In a Greek sample, Tsolaki and colleagues (2010) looked at the association between stressful events and dementia status through the administration of the Mini-Mental Status Exam (MMSE), the Functional Cognitive Assessment Scale, and the Cambridge Cognitive Examination across seven years. Most participants who were diagnosed with dementia reported experiencing at least one stressful situation or event preceding their diagnosis. Similarly, Peavey and colleagues (2009) used the Life Events and Difficulties Schedule to measure the presence of stressful life events that occurred over the span of 3 years in relationship with cognitive performance as measured by episodic memory tests and dementia status through the

usage of the Mattis Dementia Rating Scale (MDR). In addition, salivary samples were collected to assess cortisol levels. In those individuals with mild cognitive impairment, the self report of life events stress was associated with worse cognitive performance. Significantly rapid rates of cognitive decline could only be found in those who reported the presence of stressful life events and already had mild cognitive impairment. Lastly, no positive associations were found between the self-report of life events and cortisol levels. In men belonging to the Normative Aging Study (NAS), Peters and colleagues (2010) reported that in a cross-sectional study, the self-report of a severe stressor (on the Health and Social Behavior Questionnaire) was associated with significantly lower MMSE scores, but higher scores on the Perceived Stress Scale (PSS) were not significantly related to lower MMSE scores. These findings suggested that more objective measures of stress (i.e. the Health and Social Behavior Questionnaire) compared to subjective measures of stress (i.e. Perceived Stress Scale) were predictive of cognitive dysfunction.

Stress and Cognitive Decline

There are a vast number of studies that have examined the impact stress may have on cognitive performance in late adulthood; however, most of these studies have focused on investigating the association between stress and cognitive processes that are mediated by the hippocampus (Lupien et al, 2007; Miller and O'Callaghan, 2005; McEwen and Sapolsky, 1995; McEwen et al, 1999). The hippocampus is integral to spatial learning and declarative memory, but has also been implicated in regulation of the Hypothalamic-Pituitary-Adrenocortical axis (de Kloet, 2008; McEwen, 2000a; McEwen et al, 1999). In

general, higher levels of the stress hormone cortisol have been related to changes in the structure and functionality of the hippocampus and limbic areas of the brain (Alberini, 2009). This includes hippocampal atrophy and possibly the accumulation of amyloid proteins, minimally leading to mild cognitive impairment including memory performance (Alberini, 2009; de Kloet, 2008; McEwen, 1999). These findings can best be explained by the glucocorticoid cascade hypothesis (Sapolsky, 1999). This hypothesis proposes that the increase in cortisol levels can lead to the disregulation of the Hypothalamic-Pituitary-Adrenocortical axis. This dysregulation can lead to dysfunction among the adrenal receptors that occupy the hippocampal region. Not only does this underlie damage in the hippocampus, but ultimately leads to decrements in the cognitive processes mediated by the hippocampus to compensate for the stress response gone awry (McEwen et al, 1999; Sapolsky, 1999). Such impairment has been observed in some aging rats and has included decrements in declarative, spatial, and episodic memory (McEwen, 1998). For instance, rats that endure greater levels of chronic psychological stress have significantly worse memory when it comes to completing the radial arm water maze task (Alberini, 2009). Psychological stress was induced in these rats once a social hierarchy among these rats was established. After rats were accustomed to being housed in specific cages, they were randomly housed in a new cage daily. In addition, some research suggests that chronic and repeated stressors can lead to atrophy of the hippocampus via shrinkage of dendrites in certain regions of the hippocampus. More recently, Lee and colleagues (2007) examined the association between cortisol levels and performance on cognitive tasks in adults belonging to a cross-sectional study. Those with higher cortisol

levels at pre-test, mean level, and area under the curve (AUC) had deficits in cognitive performance on tasks assessing language, processing speed, verbal and visual memory, learning and executive functioning (Lee et al, 2007). In addition, another study examined the association between salivary cortisol levels and cognitive performance over the length of 3 years (Li et al, 2006). Higher levels of cortisol were predictive of decrements in verbal recall aspects of memory as assessed by performance on proactive interference and paragraph recall tests (immediate and delayed). Also, areas other than the hippocampus may be affected by Hypothalamic-Pituitary-Adrenocortical dysregulation, since those with higher levels of cortisol also had worse performance on the Trail Marking Part B and Stroop tests which assess attention skills (Li et al, 2006). Individuals with higher levels of cortisol had steeper declines in rates of performance on a paragraph recall task. More recently, Lee and colleagues (2008), found that in adults with higher levels of cortisol in their salivary samples, who also had any Apolipoprotein Epsilon 4 allele had worse cognitive performance on a range of memory tasks. We may gain some understanding of how physiological stress response may lead to changes in inflammatory response and cognitive decline during late adulthood indirectly through the experience of psychological stress and the measurement of related biomarkers, CRP and IL-6.

Conceptual Framework

The current study extended prior work to examine a mediation model of stressful life events and inflammatory biomarkers IL-6 and CRP on a broad array of cognitive processes including those not directly mediated by the hippocampus (i.e. attention and verbal ability).

From the evolutionary perspective, the stress response system was adapted to combat acute, not chronic, stressors over the lifetime. As a result, chronic stressors in late adulthood are more likely to be associated with chronic up-regulation of the stress response systems, higher levels of inflammation, and more age-related health problems during late adulthood for adults in our current society (Butcher and Lord, 2004). Moreover, other research suggests that the presence of chronic stress is associated with the accumulation of allostatic load, "wear and tear" of the immune system, and increased levels of glucocorticoids across the lifetime which may lead to dysregulations in immune functioning (Alberini, 2009; Franceschi et al, 2007; McEwen, 1998; McEwen, 2006; Sapolosky, 1999; Stewart, 2006).

Since chronic stress has been theorized to be associated with an upregulation in immune response, including increased activation of pro-inflammatory cytokines and related inflammatory proteins, these imbalances in immune related response have been proposed to possibly contribute to the changes in cognition according to the neuro-inflammatory hypothesis (Rosenberg, 2005). As mentioned previously, this hypothesis suggests changes in the CNS and overall declines in functional abilities in AD result from inflammation in the CNS when microglia in the brain are over-activated (Rosenberg, 2005). This overactivation of microglia in the brain may lead to the over-expression of the major proinflammatory cytokines – including IL-6 (Rosenberg, 2005). These processes can eventually lead to the death of major regions of the brain (i.e. the hippocampus, frontal cortex) as evidenced by the presence of plaques and tangles (Rosenberg, 2005) and may contribute to the underlying etiology of neurodegenerative

diseases like AD (Floyd, 1999) through the production of faulty genes that produce toxins and oxidative byproducts when more proinflammatory cytokines are formed and dispersed in the brain (Floyd, 1999). These same processes that are proposed to mediate AD and prodromal phases of this disease may also underlie the age-related changes in normal cognition during late adulthood.

While the neuro-inflammatory pathway may help us better understand the link between inflammation and changes in cognitive performance during late adulthood, the glucocorticoid cascade hypothesis may help explain how stress affects cognitive decline in late adulthood. As mentioned above, this hypothesis suggests that an increase in cortisol levels in response to stress can lead to dysregulated Hypothalamic-Pituitary-Adrenocortical activity and ultimately damage regions of the brain that are associated with cortisol activity (Sapolsky, 1999). Moreover, IL-6 and CRP are unregulated in regions of the brain that evidence plaques and tangles (Klegeris, 2007; Sivaprakasam, 2009). This study aimed to bridge these theoretical tenets in an attempt to understand how psychological stress and inflammatory processes as indexed by inflammatory biomarkers IL-6 and CRP which may underlie changes in cognitive performance in late adulthood.

In this study, we were not able to measure the physiological response to stress directly. Since psychological stress is associated with physiological changes in the stress response system, we examined the experience of psychological stress and its associations with inflammatory biomarkers, CRP and IL-6, as a proxy for what is occurring within the body.

Research Questions

The following research questions address cognitive decline vis-à-vis a meditational model whereby psychological stress predicts cognitive change directly as well as indirectly through inflammatory biomarkers levels (see Figure 1).

Research Question:

(1) Does chronic psychological stress, as measured by negative life events, affect inflammation biomarkers in late adulthood?

Hypotheses:

Individuals, who experience chronic psychological stress, as measured by the self-report of negative life events, are more likely to evidence higher levels of inflammation; thus, resulting in higher levels of inflammatory biomarkers IL-6 and CRP.

Research Question:

(2) Does the process of inflammation lead to changes in cognitive performance during late adulthood?

Hypotheses:

Higher levels of inflammatory biomarkers IL-6 and CRP will be associated with greater decrements in cognitive performance in late adulthood.

Research Question:

(3) Is the experience of chronic psychological stress, as measured by negative life events associated with changes in cognitive performance in late adulthood?

Hypotheses:

Individuals, who report greater chronic psychological stress, are more likely to be at a higher risk for worse cognitive performance in late adulthood.

Research Question:

(4) How will psychological stress and the process of inflammation influence cognitive decline in late adulthood?

Hypotheses:

We predict that the relationship between chronic psychological stress and cognitive performance will be mediated by IL-6 and CRP inflammatory biomarker levels. Individuals with predominantly lower levels of psychological stress across time will tend to experience less inflammation (lower levels of inflammatory biomarkers IL-6 and CRP) and this will be associated with less decline and decrement in cognitive performance. Individuals with predominantly higher levels of psychological stress across time will tend to experience more inflammation (higher levels of inflammatory biomarkers), and this will be associated with more decline and decrements in cognitive performance.

Significance

While previous studies have attempted to understand how the process of inflammation or the processes of stress response may influence cognitive performance, no study has looked at the impact of both these processes on cognitive performance in late adulthood. The design of the current study allowed a more comprehensive understanding of the intricate relationship between psychological stress, inflammatory processes and cognitive performance across time.

We intended to: (1) confirm whether there are negative long term consequences associated with chronic stress on inflammatory levels in late adulthood, (2) evaluate whether increased inflammation levels may predict decreased cognitive performance in late adulthood, (3) evaluate whether the extent to which negative stressful life events predict decrements in cognitive performance, and (4) evaluate whether the relationship between inflammatory biomarker levels and cognitive performance in late adulthood may vary based on the level of psychological stress an individual experiences across time.

METHOD

Participants

The Swedish Adoption/Twin Study of Aging (SATSA): Our analyses included a subset of 859 twins age 50 and over that belong to the Swedish Adoption/Twin Study of Aging study. In 1984, the twins who met the criteria of being separated from each other before 11 years of age and reared apart were recruited from the Swedish Twin Registry for this longitudinal study (Finkel and Pedersen, 2004). These twins were then matched for gender, age, and county of birth with twins that were reared together. If twin pairs responded to the first questionnaire in 1984 (Q1), they were then asked to participate in the SATSA study at in person testing 1 (IPT1) subsequently. Next, in three year intervals, twins participated in IPT2 and IPT3 (Finkel and Pedersen, 2004). Next, IPT5 and IPT6 were carried out seven and ten years after IPT3 (Finkel and Pedersen, 2004). Due to limited funds, cognitive testing was not administered at IPT4, and only brief telephone questionnaires were completed.

The Origins of Variance in the Oldest-Old (*OCTO-Twin)*: The Origins of Variance in the Oldest-Old included 702 old-old monozygotic and dizygotic twins eighty years of age and older, belonging to the Swedish Twin Registry. Unlike the SATSA sample, these twins were reared together and all participants from this sample were tested in intervals of 2 years across 5 time points beginning in 1991 (Johansson et al, 2004).

The Sex Differences in Health and Aging Study (*GENDER)*: Similar to the SATSA and OCTO-Twin samples, participants in the GENDER study were recruited from the Swedish Twin Registry (Gold et al, 2002; Pedersen, Lichenstein, and Svedberg, 2002). This sample is comprised of dizygotic twins born between the years of 1906 and 1925, who are not of the same sex (Gold et al, 2002). In totality, 1699 twin pairs were identified as possible participants via a questionnaire survey, with 498 twins participating in up to 3 waves of in person testing across a 3-year interval of time beginning in 1995 (Gold et al, 2002; Pedersen et al, 2002). Across these three studies, all individuals with cognitive data were included. Individuals who were diagnosed with dementia (approximately 6%) were also included in analyses. The sample sizes at each wave and the ages of the individuals across the three studies are reported in Table 1.

Measures

Stress (Life Events): Participants belonging to the Swedish Adoption/Twin Study of Aging (SATSA) were asked questions about specific life events experienced at each wave of testing. The questions were a modified version of the Social Readjustment Rating Scale created by Holmes and Rahe (see Holmes and Rahe, 1967; Persson, 1980) concerning significant changes older individuals may face in late adulthood. The

questions assessed both positive and negative life events in relation to marriage, relationships, work, finances, and health (see Appendix). During the first wave of questionnaire completion (Q1) and 4 waves of in person testing (IPT2, IPT3, IPT5, and IPT6), participants were asked to report whether or not they experienced a list of life events. At Q1 respondents were asked to indicate which events they had ever experienced (i.e., life time incidence). Moreover, participants were asked to rate the importance or significance each life event on their life using a 3-point scale (i.e., Little importance - Some importance - Great Importance). At later assessments, respondents were asked to report whether each event had occurred, but they were not asked to rate the importance of the event with the described scale. Coding of these later waves took into account what had been reported at prior waves to reflect new events since the last occasion. The mean importance ratings at the first wave of in person testing (Q1) were used to weight life events at subsequent waves of in person testing. For example, the mean level of importance for life event 2 (Major deterioration in financial status) was 2.13. At subsequent waves, each individual's score for life event 2 was multiplied by a value of 2.13.

Life event item scores were used to construct three different negative life events summary scores at each time point: 1) a total negative life events score, 2) a controllable negative life events score, and 3) an uncontrollable negative life events score based on individuals' responses and the classification coding proposed by Holmes and Rahe (see Holmes and Rahe, 1967; Persson, 1980). The total negative life events score involved 18 self-reported life events, including major deterioration in financial status, serious illness

in a child, death of a child, serious conflicts with a child, somatic illness (self), forced change in residence because one can't manage to look after oneself, divorce, home care of spouse by proband, deterioration in married life, somatic illness (spouse), death of a spouse, nursing home care (spouse), mental illness (spouse), improvement in married life, home care (self), forced change in residence with reduced contacts, death of siblings or friends, loss of sexual ability or interest, and paying fines for minor violations of the law. The controllable negative life events score was based on five of the aforementioned events: a major deterioration in financial status, serious conflicts with a child, divorce, deterioration in married life, and paying fines for minor violations of the law. The uncontrollable negative life events score was based on the self-report of the following nine negative life events: serious illness in a child, the death of a child, home care of spouse by proband, somatic illness (spouse), death of a spouse, nursing home care (spouse), mental illness (spouse), forced change in residence with reduced contacts, and the death of siblings or friends. Given the small number of controllable life events items, we chose to compare total with uncontrollable negative life events scores before proceeding with the primary analyses.

We examined the direction and strength of the correlations between cognitive performance at each time point with total and uncontrollable negative life events scores. For the total negative life events scores and the uncontrollable negative life events scores the strength and direction for these correlations with the cognitive measures were similar and in some cases identical (see Tables 2 and 3). As a result, we decided to focus on the total negative life events scores in our analyses, rather than the uncontrollable subscale.

The mean total negative life events scores were: 6.01 (Q1), 4.41 (IPT2), 3.19 (IPT3), 4.68 (IPT5), and 2.88 (IPT6). As one can see, the average negative life events score decreased with age in this sample. See the Appendix for more detail on the construction of the negative life events scores.

Based upon the total negative life events scores constructed for each time point, psychological stress was conceptualized in two different ways. First, stress was conceptualized as an *average negative life events score* (AveStress). Since the stress measures were skewed, AveStress measure was log transformed. The effect of psychological stress was treated as a fixed effect time varying predictor (see Singer & Willet, 2003). Mixed model analyses treated the longitudinal total stress scores as having a uniform effect on the outcome (i.e., biomarker levels or cognitive traits, respectively). Second, psychological stress was conceptualized in terms of the *maximum total negative life events score* (MaxStress) reported across all the time points to capture the impact of a the time period comprised of the most negative life events during the time period assessed here. MaxStress refers to the wave at which a person received their greatest negative life events score. In addition, the age at which the participant received their maximum total negative life event score (MaxAge variable) was recorded. The MaxAge variable was determined based on the wave at which the MaxStress score occurred. The MaxStress variable was skewed, so natural log transformed values of MaxStress scores plus 1 were used in subsequent analyses.

The average maximum total negative life events score in natural log units was 1.96, or 6.10 in the original scale units ($e^{1.96}$= 7.10 – 1 =6.10), and the average age at

which the maximum total negative life events score occurred was 65.90 years of age. The frequency of individuals who reported their maximum negative life events score were 216 (Q1), 200 (IPT2), 97 (IPT3), 174 (IPT5), and 73 (IPT6) at each wave of participation. In addition, the difference between the age at which the participant reported their maximum total negative life event score (max age variable) and the age at which the biomarker levels were assayed (blood age variable; age-at-sampling) was created to measure the passage of time between the experience of the greatest negative life event score and serum analyses. (See Table 4 for detailed descriptives for maximum total negative life events score and age at which maximum total negative life events score occurred). Where indicated in the descriptions of analyses below, natural log-transformed negative life events scores were used due to non-normality.

Cognitive Measures: Cognitive measures that assess facets of memory, perceptual speed, crystallized intelligence, and fluid intelligence were examined across all three twin samples. The four main cognitive tasks studied were Synonyms, Block Design, Symbol Digit, and Thurstone's Picture Memory. The Synonyms test is a measure of an individual's verbal ability by requiring one to use their knowledge of word definitions to name and identify words with similar meanings (Dureman, Kebbon, & Osterberg, 1971). The Block Design is a visuo-spatial test that requires a person to use and evaluate novel stimuli with their spatial abilities (Dureman, Kebbon, & Osterberg, 1971). The Symbol Digit test assesses perceptual processing speed abilities by asking participants to verbally report the matching digit for the symbols that are presented (Pedersen et al, 1992). Lastly, the Thurstone Picture Memory task measures episodic memory by giving participants a

forced recognition test after the showing of line drawings comprised of 28 ordinary items (Thurstone, 1948). (See Tables 5-7 for detailed descriptives for these four cognitive measures across the SATSA, GENDER, and OCTO-twin studies).

Inflammatory Biomarkers: The inflammatory biomarkers of interest included: high sensitivity C- Reactive Protein (CRP) and Interleukin-6 (IL-6). These inflammatory biomarkers were assayed at one time point for a select subset of participants belonging to SATSA, the OCTO-Twin, and GENDER samples. Details of the assay procedures are described in Eriksson et al (2010). In brief, the assay procedures for high-sensitivity serum CRP levels, were performed at KemLab Karolinska Hospital in Stockholm, using a near infrared immunoassay rate method (NIPA rate) using Beckman reagents on Synchron LX20 automated equipment (Beckman Coulter, Fullerton, CA USA). Serum IL-6 levels were measured using the quantitative sandwich enzyme immunoassay method where the Quantikine high-sensitivity ELISA commercial kit by R&D systems were applied (Minneapolis, MN USA). IL-6 measurements were performed by KemLab Karolinska Hospital in Stockholm.

The average correlation between CRP levels at one time point and cognitive performance across multiple time points was small ranging from -0.14 to -0.02 in SATSA participants, -0.04 to 0.05 in the GENDER participants, and -0.15 to -0.10 in the OCTO-Twin participants for Block Design, Synonyms, Thurstone Picture Memory, and Symbol Digit measures. The average correlation between IL-6 levels at one time point and cognitive performance across multiple time points were small and ranged from -0.10 to -0.02 in SATSA participants, -0.16 to 0.02 in GENDER participants, and -0.11 to -0.05 in

the OCTO-Twin participants for Block Design, Synonyms, Thurstone Picture Memory, and Symbol Digit. Due to non-normality log transformed CRP and IL-6 scores were used where indicated in multi-level models described further below. (The descriptive statistics for these inflammatory biomarkers can be found in Table 8. The correlations between CRP and cognitive performance by study can be found in Table 9 for IL-6 and cognitive performance by study can be found in Table 10. The correlations between CRP and IL-6 with Negative Life Events Scores in SATSA can be found in Table 11).

Statistical Methods

We used a multilevel spline or 'dual-change' model as the primary basis to address research questions 2-4 (cf. Finkel et al, 2003). We accounted for differential rates of cognitive change before and after a defined age to estimate patterns of nonlinear cognitive change in participants who belonged to young-old through old-old age groups at the start of the studies.

A dual change model takes into account different rates of cognitive change before and after a defined turning point. Previous studies in the realm of cognitive aging have suggested that noticeable change occurs after age 65 (e.g. Schaie, 1996). In this study, rates of cognitive change were examined before and after age 75. Age 75 was chosen as the point of change since the average participant age was 75 years across the three twin samples.

Dual change growth curve models are ideal since they incorporate data analysis at two levels: individual effects (level 1) and between-individual effects (level 2) (McArdle and Nesselroade, 2003). Level 1 fixed effects incorporate the average growth curve

parameters across the three samples, while the level 2 random effects serve as an indicator of individual variation among the growth curve parameters. From the fixed effects, parameters based upon the average growth curve model among the entire sample have been determined (Finkel et al 2003). From the random effects, parameters have been calculated based upon estimated individual variation across the growth curve models (Finkel et al 2003).

The SAS PROC MIXED procedure (SAS 9.1) was used to fit the dual change growth models proposed to address research questions 2-4. Unless otherwise indicated, the TYPE=UNR (SAS 9.1) function was used. With this procedure we fitted models to determine the average linear rate of change before age 75 (slope 1; S1), the average linear rate of change after age 75 (slope 2; S2), plus estimation of the intercept. The intercept (I) represents the level of cognitive performance for each cognitive measure at the defined set point/age: 75 years. Cumulative and nested models were used to examine the association between stress traits and/or inflammatory biomarkers (CRP or IL-6) and cognitive performance (see Figure 2). Full maximum likelihood (ML) was used to estimate the parameters for the fixed and random effects (Finkel et al, 2003). When estimating the variance and covariance components, the association between the two estimated slopes, S1 and S2, was fixed to zero, since relatively few individuals had sufficient data before and after 75 years to contribute to the estimation of both slopes for each participant. To account for pair dependency, we controlled for twin pair status in the dual change models to estimate appropriate standard errors. Thus, we examined the variance between and within pairs for each model while controlling for twin pair status.

For research Question 4, the statistical modeling software MPLUS (Muthen & Muthen, 2009) was used to address the classification of individuals into meaningful subgroups via their patterns of stressful life event reports across time. We also attempted to model growth curves in MPLUS to answer this research question 4; however, these models would not converge. We were unable to find a full solution in MPLUS; hence, for the models including both stress traits and biomarkers (CRP and IL-6), SAS PROC MIXED was used. The sample size for these analyses were thus restricted to SATSA participants who had both inflammatory biomarkers (for CRP: n=165 and for IL-6: n=160) and stress scores as well as the cognitive outcomes, possibly contributing to the difficulty in finding a fully converged solution in MPLUS.

Research Question 1

Multilevel regression models were fitted to better understand the relationship between psychological stress (average total negative life events score or maximum negative life events score) and inflammatory biomarker levels. While only one time-point for the CRP and IL-6 biomarkers were available for each participant, the regression model fitted was multilevel as nesting within twin pairs was accounted for in the models.

Average total negative life events scores

In the baseline model, model 1, age at sampling (age when blood was drawn) centered at age 78 was examined as a predictor of inflammatory biomarker levels (CRP and IL-6, respectively). In model 2, age at sampling, and the average negative life event score over time (AveStress) were examined as predictors of inflammatory biomarker

levels. In the final model, a two-way interaction term between the average total negative life events score with age at sampling was included (Age*AveStress). This model allowed us to consider whether the effect of stress on biomarkers levels varied by age, e.g., whether the effect was more prominent at younger or older ages.

The three models described were nested within one another. Chi square difference tests were used to make comparisons between the nested models to test whether the average stress level across time was a significant predictor of biomarker levels and whether its effect was moderated by age at sampling.

Maximum total negative life events scores

The baseline model, model 1, entered age-at-sampling (age when blood was drawn) centered at age 78 as a predictor of inflammatory biomarker levels (CRP and IL-6, respectively) as described above. In model 2, age-at-sampling, and the maximum negative life event score (MaxStress) across time were examined as predictors of inflammatory biomarker levels. For model 3, the difference in age-at-sampling and the age at which the maximum negative life event score occurred was entered as a predictor. The inclusion of this variable was integral in understanding the importance of the timing of the peak negative life event score and its impact on biomarker levels. Positive values on the age differences variable would suggest that the blood sample assayed was collected after the maximum stress score age, whereas negative values would indicate that the blood sample assayed was collected before the maximum stress score age. In the final model, the age-at-sampling and the difference in age variable, the maximum total negative life events score, and two-way interactions terms between the maximum total

negative life events score with the age-at-sampling and the difference in ages, respectively, were included. This model allowed us to understand the influence of the psychological stress variable on the biomarker levels, rate of change resulting from the blood age or difference in ages.

The four models described were nested within one another. Chi square difference tests were used to make comparisons between the nested models to see which predictors were significant.

Research Question 2

The association between inflammatory biomarker levels (C-Reactive Protein, CRP; and Interleukin-6, IL-6) and changes in cognitive performance were examined with dual change growth models. These models allowed us to understand the influence of the inflammatory biomarker on the intercept, rate of change prior to 75 years (S1), and rate of change after 75 years (S2). In model 1, an unconditional growth model was fitted using the dual change approach as described above where age variables (Age1, Age2) were examined as predictors of cognitive performance to identify the growth trajectory. Specifically, the Age1 predictor was meant to predict linear rate of change before age 75 (S1) and was defined as the observed age minus age 75, where any values greater than age 75 were coded to zero. Similarly, the Age2 predictor was meant to predict linear rate of change after age 75 (S2) and was defined as the observed age minus age 75, where any values less than age 75 were coded to zero. Next, an inflammatory biomarker (CRP or IL-6) was included as a predictor for each of the four different cognitive measures. Since the predictor(s) were added to each preceding model, the subsequent models were nested

within one another. In model 2, the two age variables (Age1, Age2), and each inflammatory biomarker predictor (CRP or IL-6) were examined as predictors of cognitive performance. This model allowed us to see the impact of these inflammatory biomarkers on the intercept (I), i.e. cognitive level at age 75. For model 3, an interaction between age prior to 75 (Age1) with the inflammatory biomarker was added (e.g., Age1*CRP). The inclusion of the interaction between age prior to 75 years (Age1) and the inflammatory biomarker (CRP or IL-6) allowed us to determine how the inflammatory biomarker affected the intercept (I) and rate of change prior to 75 years (S1). In the final model, ages before and after 75 years (Age1, Age2), each inflammatory biomarker variable, and two-way interactions terms between the inflammatory biomarker, and ages before and after 75 years were included (e.g., CRP*Age1, CRP*Age2). The four models described are nested within one another. Chi square difference tests were used to make comparisons between the nested models to test for overall omnibus significance. Individual parameters were then examined for significance via *t*-tests and associated *p*-values.

Research Question 3

For this research question, dual change growth curve models described in detail above again were used to look at the relationship between the psychological stress variables (average negative life event score and maximum negative life events score) and changes in cognitive performance on the four cognitive measures of interest.

Average Total Negative Life Events Score

Three models were examined for the average total negative life events score across four different cognitive measures. These models allowed us to understand the influence of average stress across time on the intercept, rate of change prior to 75 years (S1), and rate of change after 75 years (S2). In model 1, the age variables were examined as predictors of cognitive performance to estimate the growth trajectory parameters (I, S1, S2). In model 2, the average negative life events score (AveStress) was added as a predictor of cognitive performance at age 75 (I). For model 3, the average negative life events score was added to the model to predict rate of change prior to 75 (S1). In the final model, the average negative life events score was added to the model to predict rate of change after age 75 (S1). The four models described are nested within one another. Chi square difference tests were used to make comparisons between the nested models to test for overall omnibus significance. Individual parameters were then examined for significance via *t*-tests and associated *p*-values.

Maximum Total Negative Life Events Score

Five models were examined for the psychological stress predictor across four different cognitive measures. These models allowed us to understand the influence of interactions among the psychological stress variable, age before and after age 75 (Age1, Age2), and age at which maximum negative life events score was experienced (MaxAge) on the intercept (I), rate of change prior to 75 years (S1), and rate of change after 75 years (S2). In model 1, the age variables (Age1, Age2) were examined as predictors of cognitive performance to estimate the growth trajectory (I, S1, S2). In addition, sex was

included as a covariate of the intercept. In model 2, the maximum total negative life events score (MaxStress) was added as a predictor of cognitive performance at age 75 (I). For model 3, an interaction between the maximum total negative life events score (MaxStress) and rate of change before age 75 (S1) were added. In model 4, an interaction between the maximum total negative life event score (MaxStress) and rate of change after age 75 (S2) was added. In the final model, interactions between the maximum negative life event score (MaxStress) and the age at which the maximum negative life events score occurred (MaxAge) were added to predict the rate of change before age 75 (S1) and the rate of change after age 75 (S2). Chi square difference tests were used to make comparisons between the nested models to test for overall omnibus significance. Individual parameters were then examined for significance via *t*-tests and associated *p*-values.

Research Question 4

Only for a subset of participants, those belonging to SATSA, was a more complex association modeled through the application of latent class analyses and dual change growth models in Mplus and SAS. First, latent class analysis was used to help classify individuals into groups based on their negative life events scores at multiple time points longitudinally by classifying different groups of individuals within a larger population (Jung and Wickrama, 2008). With latent class analysis, different classes are formed based on individuals' responses to items; thus, more meaningful subpopulations can be characterized within the total sample. Also, latent class analysis leads to the identification

of items that can distinguish individuals belonging in one class from membership in other classes (Nylund, 2007). In most instances, the number of classes needed to classify patterns of response in individuals is usually not known before completion of the latent class analysis (Geiser and Lehman, 2008).

Based on individuals' total negative life events scores across time, participants were classified into multiple groups or classes based upon the commonalities and differences in negative life events scores. Each model included the same 5 traits – log transformed negative life events scores at 5 different time points. First, a baseline model with one single class was specified. Subsequent models increased the number of classes. Three more models with an increasing number of classes (2 class, 3 class, and 4 class) were computed and compared to one another. Next, the best fitting model was determined based on a range of factors. Based on model fit comparisons, the model with the smallest Bayesian Information Criteria (BIC) and the most significant Lo, Mendell, and Rubin likelihood ratio test (LMR-LRT) was most likely the best fitting model (Jung and Wickrama, 2008). In addition, a model with a high entropy value – closer to 1 is better and no class should have less than 1% of the total sample. Lastly, the classes should also be theoretically meaningful (Jung and Wickrama, 2008).

Once class membership was determined, it was used to see whether group classification based on the experience of negative life events in late adulthood contributed to differences in cognitive decline in late adulthood. We further examined the complex association between psychological stress, inflammatory biomarker levels and cognitive performance with spline dual change growth curve models using prior conceptualizations

of stress, i.e., the maximum negative life events score, including the age at which maximum negative life events score was experienced.

RESULTS

Research Question 1

Research question 1 investigated the relationship between psychological stress and changes in inflammatory biomarker levels through the usage of dual change spline growth curve models. The average correlation between an individual's negative life events score and C-Reactive Protein (CRP) levels was 0.061, and the average correlation between an individual's negative life events score and Interleukin-6 (IL-6) levels was 0.063 (See Table 11). As previously described in the statistical methods section, four nested models were examined next to determine the influence of psychological stress on inflammatory biomarker levels.

Average Total Negative Life Events Score:

Initially, we examined the influence of the average total negative life events score across 5 time points (AveStress) on inflammatory biomarker levels (CRP and IL-6) at one time point. The predictor, AveStress, and the outcomes, CRP and IL-6, were log transformed prior to the analysis. Based on model fit comparisons, no significant associations were found between the average total negative life events scores (AveStress) and either CRP biomarker levels ($p \geq 0.157$), or IL-6 biomarker levels ($p \geq 0.480$). See Table 12 for model fits and Table 13 for fixed and random effects.

Maximum Total Negative Life Events Score:

Next, we examined the influence of psychological stress on inflammatory biomarkers based upon the greatest or maximum total negative life event score reported across time (MaxStress). We also looked at the age at which the maximum total negative life event score occurred (MaxAge) and the age at sampling of blood serum to examine whether the timing of the maximum total negative life event score might affect inflammatory biomarker levels. The predictor, MaxStress, and the outcomes, CRP and IL-6, were log transformed in the analysis. Similarly, four nested models were calculated and model fit comparisons were computed among the four nested models.

For the association between the maximum total negative life events score and CRP biomarker levels, no significant associations were found between the average total negative life events scores (MaxStress) and CRP biomarker levels ($p \geq 0.371$). In regards to IL-6 biomarker levels, trend significance was observed for Model 2 ($p = 0.083$). Within this model, every unit increase in maximum negative life events scores (MaxStress) was marginally associated with an increase of +0.14 log units of IL-6 or about 1.15 ng/L ($p = 0.081$). In addition, IL-6 levels increased with age-at-sampling, by +0.02 log units of IL-6 or about 1.02 ng/L ($p = 0.0008$). (See Tables 12 and 13 for fits and parameters). It is worth noting that the effect of MaxStress was statistically significant ($p = 0.030$) when untransformed IL-6 values were considered. Overall, the model results suggested that higher levels of stress were associated with higher IL-6 levels. Moreover, IL-6 values increased as age-at-sampling increased (see Table 13, Figure 3).

To summarize, the uniform effect of chronic stress (AveStress) across multiple time points was not associated with CRP levels or IL-6 levels. We also examined the relationship between the maximum negative life events score (MaxStress) and biomarker levels. Higher MaxStress scores were marginally associated with higher IL-6 levels but were not associated with CRP levels.

Research Question 2

Research question 2 examined the association between inflammatory biomarker levels and cognitive performance via dual change spline growth curve models. As previously described in the statistical methods section, based on model fit comparisons, four nested models were examined to determine the relationship between each inflammatory biomarker -- C-Reactive Protein (CRP) and Interleukin-6 (IL-6) -- and cognitive decline in late adulthood.

C-Reactive Protein (CRP): Based on model fit comparisons for the four nested models, no significant relationships were found between CRP levels and performance on the Symbol Digit Task or the Thurstone Picture Memory Test.

For the Block Design Test, the best fitting model was model 2 ($p = 0.004$). Model 2 included the two age variables (Age1, Age2) predicting rate of change before and after age 75 (S1, S2 respectively), and CRP levels as a predictor of cognitive performance on the Block Design Test at age 75. Higher biomarker levels of CRP were associated with significantly lower levels of cognitive performance, but not differential change on the Block Design Test. At age 75, every unit increase in logged CRP levels resulted in Block

Design Test scores that were -0.51 points lower as estimated in the model 2 results (see Figure 5).

For the Synonyms Test, the best fitting model was model 3 ($p = 0.058$). Model 3 included the two age variables, CRP levels, and an interaction between age prior to 75 with CRP levels as predictors of cognitive performance. The new predictor added to model 3 was the interaction between age prior to 75 years and CRP levels, which allowed us to determine how the CRP levels affected the rate of change prior to 75 years (S1). Individuals with higher biomarker levels of CRP had lower levels of cognitive performance, with slightly lower rates of decline before age 75 on the Synonyms Test ($p = 0.014$). Every unit increase in logged CRP levels predicted a small positive increase of +.06 points in the rate of change before age 75; however, this slight benefit waned by age 75 as individuals with higher CRP levels had trend significantly lower levels of expected cognitive performance (see Tables 14-15 and Figure 6).

Interleukin-6 (IL-6): Based on model fit comparisons for the four nested models, different associations were found between IL-6 levels and cognitive performance. The best fitting model for the Block Design Test, the Symbol Digit Test, and the Synonyms Test was model 2 (see Tables 14-15). Model 2 included the two age variables (Age1, Age2), and IL-6 levels as predictors of cognitive performance on these three cognitive tests, and allowed us to see the impact of these predictors on the intercept -- cognitive level of performance on each cognitive test at age 75.

Model 2 was the best fitting model for Block Design performance, with higher IL-6 levels being significantly related to lower levels of cognitive performance, but not differential change ($p = 0.00000246$). At age 75, every unit increase in logged IL-6 levels resulted in a drop in performance on the Block Design test by -1.51 points (see Table 15, Figure 7).

Model 2 was also the best fitting model for Symbol Digit test, with higher IL-6 levels being significantly related to lower levels of cognitive performance at age 75, but not differential change ($p = 0.0001$). At age 75, every unit increase in logged IL-6 levels led to lower levels of performance on the Symbol Digit test by -2.03 points (see Table 15).

Finally, model 2 was the best fitting model for the Synonyms test ($p = 0.002$). Higher logged IL-6 levels were associated with lower levels of cognitive performance at age 75 years on the Synonyms test by -0.945 points (see Table 15).

Lastly, model 4 was the best fitting model for IL-6 levels and Thurstone Picture Memory performance. Model 4 was the final and fullest model, which included ages before and after 75 years (Age1, Age2), IL-6 levels, and two-way interactions terms between IL-6 levels and ages before and after 75 years. Model 4 enabled us to understand the influence of IL-6 levels on the intercept, rate of change prior to 75 years (S1), and rate of change after 75 years (S2) as well as interactions with ages and the IL-6 levels. Only the effect on S2, change after age 75 was significant individually. Higher levels of IL-6 were associated with significantly faster rates of decline after age 75 years (S2) ($p = 0.010$) on the Thurstone Memory Test, by an additional -0.118 points per logged unit of

IL-6. (See Appendix, Figure 8 for the association between IL-6 and Thurstone Picture Memory Performance). See Table 14 for model fit statistics and Table 15 for fixed and random effects for the CRP levels and Cognitive Performance.

To summarize, higher CRP levels were associated with lower levels of spatial ability performance. Individuals with higher CRP levels had lower levels of verbal ability, while those with lower CRP levels had higher performance, though this benefit waned prior to age 75. Also, higher IL-6 levels were associated with lower levels of verbal ability, spatial ability, and perceptual speed performance. Participants with higher IL-6 levels had steeper memory declines after age 75.

Research Question 3

Dual change growth curve models were used to examine the relationship between psychological stress and cognitive performance for Research Question 3. As previously described in the statistical methods section, based on model fit comparisons, nested models were examined to determine the extent of this association between psychological stress (average negative life events score, AveStress, and the maximum negative life events score, MaxStress) and cognitive decline across the four cognitive measures in late adulthood.

Average Total Negative Life Events Score

Based on model fit comparisons of the four models that included the average total negative life events score, there were no significant associations found between the average negative life events score, AveStress, with performance on the Block Design test

or the Synonyms test. Model 2 best explained the relationship between AveStress and Symbol Digit test performance ($p = 0.021$). In model 2, the two age variables (Age1, Age2) and the average total negative life events score were examined as predictors of cognitive performance. This model allowed us to see the impact of these predictors on the intercept, i.e. cognitive level at age 75. Higher AveStress scores were associated with lower levels of cognitive performance on the Symbol Digit test. At age 75, every unit increase in average negative life events scores predicted lower scores on the Symbol Digit test, where every logged unit of stress resulted in a reduction of -0.38 points.

Also, model 2 best explained the association between the average negative life events score and Thurstone Picture Memory performance ($p = 0.011$). In model 2, the two age variables (Age1, Age2) and the AveStress score were examined as predictors of cognitive performance. This model allowed us to see the impact of these predictors on the intercept, i.e. cognitive level at age 75. Higher AveStress scores were associated with lower levels of cognitive performance on the Thurstone Picture Memory test. At age 75, every logged unit increase in average negative life events scores, resulted in lower scores on the Thurstone Memory Test by -0.16 points (p=0.036). See Table 16 for model fit statistics and Table 17 for fixed and random effects.

Maximum Total Negative Life Events Score

Based on model fit comparisons, the participant's age at the time of her/his maximum total negative life events score, MaxAge, significantly predicted Block Design, Symbol Digit, Synonyms, and Thurstone Picture Memory performance when controlling for the maximum stress level experienced (MaxStress).

Specifically, Model 5 was the best fitting model for the association between MaxStress and MaxAge across all cognitive tests ($p < .02$). In model 5, the two age variables, (Age1, Age2), MaxStress, MaxAge, and the interaction between MaxStress and MaxAge were examined as predictors of growth trajectories. This model allowed us to see the impact of these predictors on the intercept and rates of change before and after age 75. (See Table 16 for model fit statistics and Table 17 for fixed and random effects for Negative Life Events and Cognitive Performance.)

As indicated, model 5 was the best fitting model for the relationship between MaxStress and Maxage on Block Design performance ($p = 0.0001845$). Within this model, only MaxAge significantly predicted Block Design performance. Controlling for MaxStress levels, for every year after age 65 years that the MaxStress occurred (MaxAge), a loss of -0.12 points on the Block Design test resulted at age 75 ($p = 0.0001$). Thus, the closer the peak stress was to age 75 the worse the expected performance at age 75 years (see Figure 10, Tables 16-17).

For Symbol Digit, model 5 was again the best fitting model to explain the influence of MaxStress and MaxAge on cognitive performance ($p = 0.00003$). Upon closer examination of the individual predictors within this model, for every year increase in MaxAge after age 65, Symbol Digit performance dropped by -0.15 points at age 75 years ($p = 0.002$). The interaction between MaxStress and MaxAge was also associated with significantly lower levels of cognitive performance, indexed by a drop of -0.15 points on the Symbol Digit Test ($p = 0.021$). Controlling for MaxStress levels, for every year after age 65 years that the MaxStress occurred (MaxAge) coupled with every log

unit increase in MaxStress above the mean, the expected cognitive performance at age 75 years dropped by -0.15 points. In regards to rates of change, the interaction between MaxStress and MaxAge was associated with significant additional declines in cognitive performance on the Symbol Digit test prior to 75 years of age(-0.010 points, $p = 0.0214$). Moreover, the later the occurrence of MaxStress after age 65 (MaxAge) the flatter the rate of decline after 75 years of age (0.027 points, $p = 0.002$). As the timing of the peak stress approached 75 years of age, individuals had worse cognitive performance at and after 75 years of age (see Figure 11, Tables 16-17).

Similarly, model 5 was also the best fitting model for the association between MaxStress with MaxAge and Synonyms performance ($p = 0.0002$). Higher MaxStress scores were associated with significantly steeper rates of decline prior to age 75 on the Synonyms test, such that each logged unit of stress contributed -0.04 points to the rate of change expected before age 75 ($p = 0.024$). Additionally, for each log unit increase in peak stress, rate of decline in performance after age 75 was associated with a gain of +0.24 points ($p = .0125$) for an individual's rate of decline. With respect to MaxAge effects, for every year past age 65 that the MaxStress occurred, performance at age 75 on the Synonyms test dropped by -0.10 points ($p < .001$). In addition, the interaction between MaxStress and MaxAge was associated with significant acceleration in rate of decline after 75 years of age, resulting in a loss of -0.015 points on the test ($p = 0.033$). Altogether, the model estimates suggest that the closer the peak stress occurred to age 75, the worse the expected Synonyms performance was at age 75. However, with higher but earlier-occurring peak stress, long-term negative impacts on Synonyms performance after

age 75 were less evident, and indeed, performance was relatively improved (see Figure 12, and Tables 16-17).

Lastly, model 5 was the best fitting model for the relationship between MaxStress and Maxage on Thurstone Picture Memory performance ($p = 0.0118$). Within this model, only MaxAge significantly predicted performance at age 75. Controlling for MaxStress levels, for every year after age 65 years that the MaxStress occurred (MaxAge), a loss of -0.06 points on the Thurstone test resulted at age 75 ($p = 0.0026$). Thus, the closer the peak stress was to age 75, the worse the expected episodic memory performance was at age 75 years (see Figure 13, Tables 16-17).

To summarize, we found different associations between chronic stress and cognitive performance in late adulthood based upon the manner in which chronic stress was conceptualized. The uniform effect of chronic stress across time (AveStress) was associated with lower levels of memory and perceptual speed performance. Higher maximum negative life events scores (MaxStress) and the age at which MaxStress occurred (MaxAge) were associated with differences in levels and rates of cognitive performance across all domains. For spatial and memory abilities (Block Design and Thurstone Picture Memory, respectively), the later the occurrence of the peak stress after age 65 (MaxAge), the lower the expected performance at age 75, with marginal effects after age 75 evident for spatial abilities. For perceptual speed abilities, the later the age at which the peak stress occurred (MaxAge), the lower the levels of cognitive performance expected at and after age 75; moreover, increasing levels of stress seemed to intensify this pattern. For verbal abilities, the closer the peak stress occurred to age 75, the worse

the expected performance was at age 75. However, with higher but earlier-occurring peak stress, longer-term detrimental impacts on Synonyms performance after age 75 years were less evident, and indeed improved performance after age 75 could be expected.

Research Question 4

For Research Question 4, we examined relations among chronic psychological stress, the process of inflammation, and cognitive decline in late adulthood. We intended to use latent class analysis to classify individuals into subgroups within the sample based on their negative life events scores across time. Once individuals were classified into subgroups, we intended to examine how group membership was related to the association between chronic psychological stress, the process of inflammation, and cognitive decline in late adulthood.

We attempted to classify participants into meaningful groups based on their total negative life events score across multiple time points for a subset of 760 individuals belonging to SATSA. A 3-class model was determined to be the best fitting model based on the BIC value (5586.055) and the Lo-Mendell-Rubin test (239.942, p=0.0168). The 3 class model was also ideal, since it classified the 760 individuals into 3 classes, in which each class included more than 1% (approximately 8 people) of the aforementioned sample of 760 participants from SATSA. Group 1 included 40% (n=306) of the entire sample. The natural log transformed mean negative life events scores across 5 time points were 1.16, 1.196, 1.013, 1.453, and 0 across group 1. Group 2 included 19% (n=143) of the entire sample. The mean negative life events score across group 2 for these 5 time points was 1.48, 1.308, 0.917, 1.328, and 1.24. Lastly, group 3 included 41% of the

complete sample. For group 3, the mean negative life events scores across the 5 time points were 1.796, 1.557, 1.296, 1.254, and 2.028. Although the 3 class model best explained the negative life events scores across time, the entropy score was 0.502. The entropy score is an indication of how well a model predicts class membership, and the closer the entropy score is to 1, the better. Also, from a theoretical perspective it did not explain any distinct patterns of psychological stress in late adulthood. Upon further examination, the correlations between negative life events and inflammatory biomarkers were negligible; hence, we decided not to pursue the relationship between class membership with psychological stress, inflammation, and cognitive decline (See Table 18 for Latent Class Analysis Fit Statistics, and Table 19 for Latent Class Analysis Group Classifications).

The complex association between psychological stress, inflammatory biomarkers and cognitive performance was examined via three nested dual change growth curve models in SAS PROC MIXED that included a smaller sample of SATSA twins. There were165 individuals with stress, CRP values, and cognitive performance scores, and 160 individuals with stress, IL-6 values, and cognitive performance scores. The relationship between the maximum negative life events scores, the age at which the maximum negative life events score occurred, and CRP protein levels were examined as predictors of cognitive performance across four cognitive tests. In addition, the relationship between the maximum negative life events scores, the age at which the maximum negative life events score occurred, and IL-6 levels were also examined as predictors of cognitive performance. Based on model fit comparisons, only one significant chi-square difference

test was found between psychological stress and CRP levels as predictors of Thurstone Picture Memory performance. Model 3, the fullest model, was the best fitting and most significant model (p=0.0000000468). This model included CRP, the maximum negative life events score (MaxStress), and the age at which the maximum negative life events occurred (MaxAge) as predictors of Thurstone Picture Memory performance and rate of change before and after age 75. Lastly, interactions between CRP, MaxAge and MaxStress were included in this model as well. Upon closer examination of the predictors within this model, no individual parameters were above trend level of significance (p<0.10*)*. Thus, it is possible that model convergence across models tested was not fully achieved or that the parameters were highly correlated, perhaps given the small sample available for the analyses which was limited to SATSA participants with available biomarker and psychological stress scores. Thus, the parameters estimates will not be discussed. No significant associations were found between IL-6 levels, psychological stress and cognitive performance in these analyses. (See Tables 20-21 for model fit statistics, and Tables 22-23 for fixed effects).

To summarize, initial analyses suggested a meditational relationship may exist between peak stress scores (MaxStress), CRP levels, and episodic memory performance. Follow-up analyses with larger sample sizes must be examined to better understand the observed relationship.

DISCUSSION

The primary goal of the present study was to gain a better understanding of how psychological stress and the process of inflammation may affect cognitive decline in late

adulthood. This study examined the varying impact of quantitative measures of psychological stress and inflammatory biomarkers on trajectories of cognitive decline across late adulthood.

Research question 1 examined whether chronic psychological stress had an effect on inflammatory biomarker levels in late adulthood. We predicted self-reported psychological stress would be associated with greater inflammatory response, as indexed by higher levels of inflammatory biomarkers levels. The results suggested that the association between psychological stress and inflammatory biomarkers were weak.

Research question 2 considered whether inflammatory biomarkers may be related to changes in cognitive abilities in late adulthood. We predicted that individuals with higher inflammatory biomarker levels would evidence lower levels and rates of cognitive performance. Higher levels of C-Reactive Protein (CRP) and Interleukin-6 levels (IL-6) were associated with decrements in levels and rates of change for some, though not all cognitive measures.

Research Question 3 focused on whether chronic psychological stress was associated with changes in cognitive performance in late adulthood. We hypothesized that those individuals who reported more chronic psychological stress would be more susceptible to more rapid cognitive decline in late adulthood. The results suggested that psychological stress affected cognitive performance in late adulthood, but that the peak and timing of the psychological stress experienced had varying effects on levels and rates of decline across cognitive measures.

Lastly, research question 4 investigated the relationship among psychological stress, the process of inflammation, and cognitive performance in adulthood. We predicted that levels of psychological stress would predict inflammatory levels and these two processes would share an inverse relationship with cognitive performance in late adulthood. The results suggested that inflammatory biomarkers did not mediate the relationships between psychological stress and levels or rates of decline across cognitive tasks.

Research Question 1

The findings from this study suggest that the influence of psychological stress on the process of inflammation was weak. Specifically, whether stress was conceptualized as a constant uniform effect (AveStress) or in terms of peak stress (MaxStress), higher psychological stress was associated with non-significant elevations in inflammatory biomarker levels.

An individual's maximum negative life events score (MaxStress) was associated at trend significance with higher IL-6 levels, while no significant association was found between an individual's MaxStress score and CRP levels. We expected stronger relationships between psychological stress and higher inflammatory biomarker levels. Many research studies have found higher levels of psychological stress to be associated with elevations in CRP levels (e.g. Bitton et al, 2008; Blum et al, 2009; Janicki-Deverts et al, 2008; Kiecolt-Glaser et al, 2003; McDade et al, 2006; Veldhuijizen van Zanten et al, 2005) and IL-6 levels (e.g. Homer et al, 2007; Kop et al, 2008; Maes et al, 1998; Von Kanel et al, 2006; Von Kanel et al, 2008; Yasui et al, 2007). Our results were consistent

in direction through the small, but positive correlations we observed between CRP levels with negative life events scores (r=0.061) and the IL-6 levels with negative life events scores (r=0.063).

The limited findings between psychological stress (AveStress and MaxStress) with inflammatory biomarker levels were unexpected. Even though we treated psychological stress as a fixed effect time varying predictor (i.e. one uniform effect of stress measured longitudinally) or as the peak occurrence of stress experienced, the dynamic nature of stress was not fully captured in these analyses. A meta-analysis by Segerstrom and Miller (2004) noted no significant relationships between life events (i.e. caring for a spouse or living with a handicap) with IL-6 levels, but two studies that examined the influence of the stress associated with one specific life event, caring for a spouse with AD or dementia suggest otherwise (Kiecolt-Glaser et al, 2003; Von Kanel et al, 2006). Both studies showed that greater chronic stress was associated with the burden of caring for a spouse with AD or dementia; however Von Kanel and colleagues (2006) showed that this relationship disappeared when the caregiver's age and health were controlled. Also, there is evidence in the literature for an association between greater psychological stress and higher CRP levels; however, this is especially true for studies using subjective stress measures, such as the Perceived Stress Scale (e.g. Bitton et al, 2008; McDade et al, 2006) compared to studies using objective life events measures, such as the UCLA Life Stress Interview (e.g. Marin et al, 2007).

The limited findings between negative life events scores and inflammatory biomarker levels suggest that there was not a uniform effect of psychological stress on

inflammatory biomarker levels. It is possible that steady exposure to psychological stress in late adulthood may not be as detrimental to one's immune system in comparison to psychological stress that may have been experienced earlier in the lifespan. That is, the experience of significant negative life events in late adulthood may not lead to the theorized biological responses to stress and associated dysregulation in immune response. There may be non-linear effects of stress that were not examined in this study (see Aldwin & Levensen, 2001). It is also probable that the experience of psychological stress earlier in life may be more predictive of inflammatory response in late adulthood. For instance, O'Mahony and colleagues (2009) examined the relationship between early life stress and inflammatory health changes in rat pups. Maternal separation was an early life stressor that was related to trend significant elevations in IL-6 and an upregulation in HPA function. Perhaps the level of psychological stress a person experiences prior to late adulthood affects their sensitivity to cortisol within the body and ultimately immune response later in life. In the present study, we only had inflammatory biomarker levels at one time point and none prior to late adulthood, thus it is difficult to investigate such patterns of inflammatory response in late adulthood. Moreover, we were unable to distinguish between early and late incidence of life events at the first questionnaire wave.

In addition, the relationship between stress response and inflammatory response may be moderated by factors, such as exercise, medication, and genes, which were not investigated in the present study. For example, Starkweather (2009) stated that in an elderly sample, a moderate exercise program was associated with lower psychological stress and a decrease in IL-6 levels. Von Kanel and colleagues (2008) found that taking

aspirin decreased IL-6 levels after experiencing an acute stressor, and vitamin use was associated with decreased CRP levels in a study conducted by Harpuarachichi and colleagues (2003). Although genetic factors were not controlled in any of the studies discussed, it is possible that they may account for the variability observed in our study. For instance, genetic influences stemming from the presence of genes may affect inflammatory response. Single nucleotide polymorphisms of inflammatory genes such as the *CRP* gene and *IL-6* gene that code their respective protein levels may moderate the observed relationship between stress response and inflammatory biomarker levels. For instance, prior research suggests that some *CRP* single nucleotide polymorphisms may be associated with lower biomarker levels of CRP. In the Women's Health Initiative Observational Study, the minor alleles for *CRP*_rs1205 (allele G) and CRP_rs1800947 (allele C) were associated with lower CRP levels ($p < 0.0001$) (Lee et al, 2009). Lastly, Teng and colleagues (2009) found that the *CRP*_rs1205 minor allele (allele G) was associated with decreased CRP levels ($p=0.003$) at one time point in a sample of healthy Taiwanese adults with no history of cardiovascular disease. These studies suggest that the influence of stress on inflammatory response in late adulthood could be moderated by various health factors.

Research Question 2

The results from this study indicate that the inflammatory pathway may be important to cognitive performance in late adulthood such that higher levels of CRP and particularly IL-6 were associated with declines in levels and/or rates of change across the cognitive domains examined.

Our findings between CRP levels and cognitive performance were mixed though no more so than prior studies. In the current study, higher C-Reactive Protein (CRP) levels were associated with lower levels of performance, but not differences in rates of decline on the Block Design test, which is a measure of spatial ability. Higher CRP levels were marginally associated with lower levels of performance but slight gains in performance before 75 years of age on the Synonyms test, a test of verbal ability. No associations were found between elevated CRP levels and cognitive performance on the Symbol Digit (perceptual speed measure) and the Thurstone Picture Memory (memory measure).

Overall, our mixed findings of associations with CRP mirror the mixed findings the literature. Few studies have examined the relationship between CRP levels and spatial ability, and usually this cognitive measure belongs to a composite score (Hoth et al, 2009; Weaver et al, 2002). In a cross sectional study, Hoth and colleagues (2009), noted that higher CRP levels were associated with declines on an attention-executive psychomotor composite score, which included a test of visual spatial ability. Weaver and colleagues (2002) found that higher CRP levels were related to decreases in cognitive decline on a cognitive score that included performance on a test of spatial ability, the Geometric Figures Test in a cross-sectional study. Previously, two studies have reported decrements in verbal learning ability performance on a word learning task (Teunission et al, 2005) or change across 6 months (Gimeno et al, 2009) in individuals with higher CRP levels on a vocabulary test; our findings were weak but in a similar direction. While non-significant relationships between CRP levels and perceptual speed and memory

performance (Derby et al, 2008; Dik et al, 2005) have been reported similar to our findings, others have reported higher CRP levels predict poorer processing speed performance (Marioni et al, 2009) or poorer memory performance (Komulainen et al, 2007).

Our findings between IL-6 levels and cognitive decline were more consistent in suggesting an association. Higher Interleukin-6 (IL-6) levels were associated with lower levels of performance, but not differences in rates of decline on the Block Design test (a measure of spatial ability), the Symbol Digit test (a measure of perceptual speed), and the Synonyms test (a measure of verbal ability). Higher IL-6 levels were also related to lower levels of performance, and higher rates of decline before and after age 75 on the Thurstone Memory Test (episodic memory). Some previous longitudinal cross-sectional studies have reported no associations between IL-6 levels and cognitive performance (e.g. Teunissen et al, 2003; Dik et al, 2005). While other longitudinal studies have found similar associations between elevated IL-6 levels and cognitive decline as those observed in the current study. For instance, Weaver and colleagues (2002) found that higher IL-6 levels were associated with decreased spatial ability performance. Rafnsson and colleagues (2007) reported decrements in perceptual speed in those individuals with higher IL-6 levels. Marsland and colleagues (2006) also noted that higher IL-6 levels were associated with decreases in working memory performance. Lastly, declines in verbal abilities have been previously reported for those with higher IL-6 levels (Derby et al, 2009; Gimeno et al, 2009).

The findings from the current study suggest that the inflammatory pathway may explain some aspects of normal cognitive change in late adulthood, but that chronic inflammation is most likely not the sole process that is contributing to both decreases in levels and rates of cognitive decline during late adulthood. Prior research (e.g. McEwen, 2006; Rosenberg, 2005) suggests that elevated levels of CRP and IL-6 would be associated with worse cognitive performance. Higher levels of CRP and IL-6 were indicative of lower levels of cognitive performance on the Block Design Test, suggesting that elevations in these inflammatory proteins may affect the brain regions that mediate these cognitive processes. Elevations in CRP and IL-6 appear to be more related to effects on levels of cognitive performance more than differential change in late adulthood.

In addition, the mixed findings across studies may also be due to the variability in methodology used to investigate these associations (Gimeno et al, 2009). The studies described above (e.g. Dik et al, 2005; Gimeno et al, 2009; Marsland et al, 2006; Rafnsson et al, 2007; Teunnisson et al, 2003;Weaver et al, 2002) have examined the relationship between inflammatory biomarker levels and cognitive performance. However, many other studies have investigated the association between inflammatory biomarker levels and cognitive functioning, thus suggesting that higher levels of inflammatory biomarkers may serve as an indication of cognitive impairments (e.g. Laurin et al, 2009; Weuve et al, 2006; Yaffe et al, 2003; Xu et al, 2009). For instance, in the Honolulu Aging Study, Laurin and colleagues (2009) found that higher inflammatory biomarker levels at midlife were predictive of declines in cognitive functioning on the Cognitive Abilities Screening

Instrument (CASI) up to 25 years later. However, once individuals with incidence dementia were excluded from analyses, there was no association between higher CRP levels and cognitive decline. Since the current study included participants with dementia (approximately 6%) this may explain our mixed findings. As a result, we re-ran analyses for CRP levels predicting Block Design performance while excluding individuals with dementia. The results for Block Design performance were still significant ($p=0.011$). This suggests that higher CRP levels may be predictive of cognitive declines in cognitive performance, not just dysfunction.

Research Question 3

Our findings from this study suggested that psychological stress was associated with some aspects of cognitive decline in late adulthood. When the average negative life events score was examined as a predictor of cognitive performance, it was evident that it was associated with lower levels of performance, but not differential cognitive change, for perceptual speed (Symbol Digit Test) and episodic recognition memory (Thurstone Memory Test). No significant relationships were found between the average negative life events score and cognitive performance on the Synonyms and Block Design Tests. Most prior research has found relationships between cognitive tasks that are dependent on hippocampal brain activity (de Kloet, 2008; McEwen et al, 1999; McEwen, 2000b; Pardon et al, 2008) that include spatial learning, memory, and short term memory abilities. In the current study, we did not find any associations between chronic stress and spatial abilities (Block Design), but as mentioned we did observe effects on episodic memory performance (Thurstone Picture Memory).

In addition, we looked at the relationship between the maximum negative life events score (MaxStress) with the age at which the MaxStress occurred (MaxAge) and cognitive performance in late adulthood. When both MaxStress and MaxAge were examined as predictors of cognitive decline, significant differences in performance for spatial (Block Design), perceptual speed (Symbol Digit), verbal (Synonyms), and memory (Thurstone Picture Memory) abilities were observed. In general, peak stress was associated with poorer performance as the timing of peak stress approached 75 years, the age at which the growth trajectory was centered. Earlier occurring peak stress tended to have a lesser effect on trajectories, or if one survived into old-old age a potential resiliency effect (e.g., Synonyms).

For Block Design performance, individuals with peak stress (MaxStress) occurring after 65 years of age (MaxAge) had significantly lower spatial performance at age 75 years, with trend effects after age 75 where those experiencing stress closer to age 75 maintained lower performance after age 75. Indeed, the age at which the peak stress occurred, not the actual peak stress experienced (MaxStress), was associated with cognitive performance on the Block Design test. This suggests that the timing at which peak stress occurred was more predictive of spatial ability performance levels than the magnitude of the stressor experienced. A similar case was observed for episodic memory with respect to performance at age 75: individuals with peak stress (MaxStress) occurring after 65 years of age (MaxAge) had significantly lower Thurstone Picture Memory performance at age 75 years.

For Symbol Digit performance, the level and timing of peak negative life events scores (MaxStress and MaxAge, respectively) predicted significant differences in levels and rates of perceptual speed performance. Specifically, the later the age at which the peak stress occurred, the lower the levels of cognitive performance expected at age 75 and maintenance of lower performance some years after; while increasing levels of stress predicted poorer performance.

For Synonyms performance, the closer the peak stress occurred to age 75, the worse the expected performance was at age 75. However, with higher but earlier-occurring peak stress, longer-term detrimental impacts on Synonyms performance after age 75 years was less evident, and indeed improved performance after age 75 could be expected. However, we note the relative sparseness of longitudinal data in the old-old age period in the SATSA study.

It is interesting to note that the average stress score (AveStress) as well as peak stress (MaxStress) significantly predicted perceptual speed and episodic memory performance. Thus, a definition of psychological stress indicating stress levels across time showed relationships as well as one more indicative of acute stress. While the Thurstone Picture Memory task tends to show high and stable performance until after age 70 (e.g., Finkel et al, 2003; Reynolds et al, 2005), perceptual speed performance tends to show steadily accelerating change with age after age 60 (Finkel et al, 2003). In both these cases, acute or continuing or chronic psychological stress may be impactful to overall performance in late life.

Our findings with the maximum negative life events scores (MaxStress) and the age at which MaxStress occurred (MaxAge) suggest that the peak, duration, and timing of a stressor is differently associated with various cognitive abilities in late adulthood. Cohen (1993) has pointed out that an acute stressor can have a direct effect on a person's health and or well-being. For instance, Peters and colleagues (2010) found that the report of one stressful event occurrence was associated with significant decrements in cognitive functioning as assessed via MMSE scores. Yet, higher perceived stress scores were not associated with decrements in MMSE in this same study. In a Greek sample, individuals who were diagnosed with dementia reported one or more stressful life events prior to dementia diagnosis (Tsolaki et al, 2010). Also, prior research (e.g. Rosnik et al, 2009, Von Dras et al, 2005) suggested that more than chronic stress across time, the experience of specific negative life events may be better predictors of declines in cognitive performance.

In our analyses, the maximum negative life event could be interpreted as a period of acute stress, possibly explaining some of the observed relationships. However, overall our analyses indicated strong relationships between MaxAge with cognitive performance in late adulthood suggesting that the timing and occurrence of peak stress after age 65 years of age was associated with worse levels and rates of cognitive performance later in life.

Research Question 4

Our initial findings suggest no significant mediation of the relationship between psychological stress and cognitive performance via inflammatory biomarker levels in late

adulthood. Based on model fit comparisons, we only found one significant relationship with a measure of episodic memory (Thurstone Picture Memory); however, no individual parameters reached above trend significance. The limited sample size may have hindered our opportunity to find more associations between psychological stress, inflammatory biomarkers and their impact on cognitive performance in late adulthood. Thus, further work is needed before ruling out inflammatory biomarker levels as a mediator of the relationship between psychological stress and cognitive performance.

Limitations

Negative Life Events (Psychological Stress)

Life events questionnaires, such as the modified version of the Social Readjustment Rating Scale (created by Holmes and Rahe) allow researchers to quantify the experience of psychological stress by asking individuals to report the occurrence of life events at a certain point in time which is helpful in understanding the type and chronology life events experience. However, in many instances the effect of psychological stress may vary for those who become widows. For instance, a spouse's death resulting from a terminal illness may be associated with more stress prior to the actual death of a spouse for an individual and dissipate after (Lichtenstein et al, 1998). Diagnosis of the illness, caring for the spouse, financial difficulties, and certainty of impending death are all factors that may occur prior to the death of a spouse and lead to the experience of increased psychological stress prior to the occurrence of the negative life event. For one or more of the aforementioned reasons, it is possible that an individual may be relieved or at ease once the spouse has passed away. On the other hand, the

unexpected death of an individual's spouse could be followed with an increase in psychological stress for reasons including unresolved financial situations, the timing and nature of the event.

In addition, based on an examination of standard life events inventories, Aldwin and Levensen (2001) have reported that there is no significant correlation between age and the self-report of negative life events from midlife to late adulthood. However, older individuals tend to report more health related life events changes. These same researchers suggest that in comparison to older adults, younger adults tend to report more life events changes. This may explain the decrease in negative life events scores across time in the SATSA sample. However, more events may have been reported at the first wave (Q1), since individuals were asked to report the presence of any or all events that occurred prior to the first wave of data collection. However, at subsequent waves the experience of new life events that occurred since the last wave of testing was coded. Thus, individuals may have been more likely to report a higher number of life events at Q1 given the longer span of time in which such events could have occurred prior to entry into the SATSA study. This explanation is supported by the fact that the most common wave at which participants reported their peak stress was at Q1 at 28%. However, the percentage reporting peak stress at the next wave, IPT2, follows closely at 26%.

In addition, there are other factors that may buffer or exacerbate the impact of negative life events on the brain and body. For instance, social support and social networks, may influence the impact that psychological stress has on cognitive performance and inflammatory response in late adulthood. For instance, individuals who

lack social support and or an extensive social network may be more susceptible to the adverse effects associated with the experience of negative life events; thus, leading to more profound declines in cognitive abilities or greater dysregulation in immune response. A review conducted by Fratiglioni and colleagues (2004) reported that across five out of seven studies, lower cognitive performance and or a greater risk of cognitive decline was predicted by smaller, more sparse networks among the participants. In addition, in a study of individuals with Alzheimer's Disease (AD), belonging to the Rush Memory and Aging Project, social networks seemed to have a protective effect for some aspects of cognition and some global measures of pathology underlying AD (Bennett et al, 2006). The relationship between semantic, episodic, and working memory performance with the amount of tangles in the brains of AD patients was altered based on the extent of social networks. It is also possible that having a source of social support or having an extensive social network may buffer the deleterious effects of psychological stress.

Inflammatory Biomarkers –C-Reactive Protein and Interleukin-6 levels

In the current study, we have inflammatory biomarkers at only 1 time point. If inflammatory biomarker levels were assayed at more than one time point it would enable us to examine variability in biomarker levels within and across individuals over time. More than one time point would allow us to see if participants have consistently low, medium, or high levels of inflammation.

Although our study includes participants from 3 major studies of aging ranging from young-old to old-old age, all participants were not the same age when blood serum

analysis was conducted. In addition, participants' age at blood serum analysis did not always precede a person's age at cognitive testing.

The current analyses did not account for the presence of inflammatory diseases, which would most likely be related to increased levels of inflammatory biomarkers. For instance, higher levels of C-Reactive Protein are associated with a greater risk of some types of cancer, cardiovascular disease, and rheumatoid arthritis (Black et al, 2004; de Maat et al, 2004; Hurme et al, 2007). A closer examination of individual's inflammatory health in late adulthood will help us understand if an individual's inflammatory biomarker levels result from the presence of a chronic health condition such as diabetes. Although CRP and IL-6 are thought to be indicative of chronic inflammation, an acute inflammatory stressor such as a stroke or a cold may boost a person's level of inflammatory response or change their biomarker levels and possibly relationship with psychological stress and cognitive performance in late adulthood (Bourdel-Marchasson et al, 2010).

Lastly, medication like non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, which may be taken for inflammatory health conditions such as rheumatoid arthritis may moderate the relationship between inflammatory biomarker levels with psychological stress or cognitive decline in late adulthood. Studies conducted by Stewart and colleagues (1997) initially reported a reduced risk of Alzheimer's Disease (AD) in those with rheumatoid arthritis who reported taking NSAIDs. More recently studies suggest that the relationship between NSAID use and AD may be more complex than initially supposed: the type of NSAID taken, the neurological target, duration of use,

APOE-4 status, and date of initial use may affect the strength of the association between NSAID use and the cognitive deficits associated with AD (McGeer and McGeer, 2007).

Cognitive Measures

In some cases, cognitive performance is concurrent with the ages at inflammatory biomarker levels and self-report of negative life events. It is possible that our observed relationships between psychological stress, inflammation, and cognitive decline may be more significant if inflammatory biomarker levels always preceded cognitive performance.

Strengths

A primary strength of this study includes our ability to examine the aims of this research study in a sample that includes participants that range in age from young-old to old-old age through inclusion of participants from three major Swedish studies of aging. As a result, inflammatory biomarker levels were assessed in individuals ranging in age from young-old to old-old age. In addition, in these same participants we were able to examine cognitive performance longitudinally for a maximum of 3-5 waves of in person testing based upon which study an individual belonged to. Unlike most studies, we were able to examine psychological stress across 5 time points in individuals who belong to the Swedish Adoption/Twin Study of Aging.

Implications and Future Directions

The findings from this study suggest that psychological stress and inflammation are both related to cognitive performance and cognitive change in late adulthood. However, more studies must be conducted to better understand the impact of psychological stress on both

inflammation and cognitive decline in late adulthood. Our results suggest that inflammatory health and exposure to major psychological stressors after 65 years of age may be more predictive of cognitive performance in late adulthood.

Our findings suggest that both the experience of negative life events *and* the age at which these negative life events occur are important influences on cognitive performance in late adulthood. The experience of greater psychological stress later in life may put an individual at a higher risk for decrements in cognitive performance in late adulthood, particularly as a function of how late in life the peak stress occurs. It is impossible to avoid most negative life events (e.g. losing a spouse or being diagnosed with a serious health condition) a person may experience in late adulthood. However, the occurrence of such life events in later-life may be relatively more impactful. This could result in the risk of or progression of inflammatory health conditions that may impact changes in cognitive performance.

Importantly, however, there are a range of factors that may buffer the adverse effects associated with psychological stress in late adulthood. A strong social network, a positive personality/outlook on life, and exercise are examples of factors that could help an individual overcome the negative effects psychological stress may have on inflammatory response and cognitive performance in late adulthood (e.g. Cohen and Hoberman, 1983; McEwen, 2006; Seeman et al, 2001). Hence, the impact of psychological stress on inflammatory response and cognitive performance is quite intricate, given the various factors that may lessen or worsen the strength of association between these various processes.

In addition, our findings suggest that inflammatory health may be predictive of cognitive change in late adulthood. In the current study, higher levels of CRP and IL-6 were associated with level and in some cases changes in cognitive performance. As a result, further investigation must be done to better understand what health conditions may contribute to the observed elevations in inflammatory biomarker levels. In addition, these elevated biomarker levels and inflammatory health conditions may give insight to other aspects of an individual's well-being and health.

In subsequent analyses, we hope to further examine psychological stress as a time varying covariate that varies in effect both across time and individuals. This will allow us to see if the role of psychological stress is more dynamic or if its impact is still most profound after age 65. In addition, we would like to examine the role of inflammatory genes (single nucleotide polymorphisms) on the observed relationships in this study. It is possible that genotype status may moderate an individual's response to psychological stress, inflammatory response, and or cognitive performance in late adulthood.

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Table 1: Average Ages in SATSA, GENDER, and OCTO-twin studies

Variable	N	Mean	Std. Dev	Minimum	Maximum
SATSA					
Age1	618	66.43	7.61	50.18	87.98
Age2	576	66.51	8.61	50.08	91.00
Age3	567	68.90	9.10	50.23	94.00
Age5	541	70.59	10.00	51.20	96.40
Age6	445	72.16	9.26	54.26	95.21
Gender					
Age1	472	74.49	2.63	69.74	80.71
Age 2	330	78.05	2.70	73.21	84.62
Age 3	254	82.07	2.62	77.66	88.28
OCTO-twin					
Age 1	589	83.41	3.11	79.37	97.91
Age 2	445	85.24	2.89	81.55	99.90
Age 3	326	87.05	2.70	83.53	101.84
Age 4	238	89.85	2.77	85.48	103.78
Age 5	180	90.63	2.47	87.50	100.96

Table 2: Correlations between Negative Life Events and Cognitive Measures in SATSA

Cognitive Trait	Negative Life Events Q1	Negative Life Events IPT2	Negative Life Events IPT3	Negative Life Events IPT5	Negative Life Events IPT6
Block Design 1	-0.05	-0.14	-0.14	0.01	-0.12
Block Design 2	-0.06	-0.21	-0.1	-0.14	-0.07
Block Design 3	-0.08	-0.22	-0.15	-0.14	-0.13
Block Design 4	-0.1	-0.25	-0.08	-0.1	-0.12
Block Design 5	-0.14	-0.21	-0.18	-0.06	-0.09
Synonyms 1	0.02	-0.17	-0.11	-0.12	0.01
Synonyms 2	0.06	-0.22	-0.09	-0.1	0.02
Synonyms 3	0.07	-0.17	-0.08	-0.1	0.03
Synonyms 4	0.06	-0.2	-0.09	-0.11	-0.8
Synonyms 5	0.07	-0.2	-0.06	-0.07	-0.01
Thurstone 1	-0.1	0.05	-0.1	-0.11	-0.06
Thurstone 2	-0.03	-0.05	-0.11	-0.05	-0.01
Thurstone 3	0.04	-0.0002	-0.06	-0.06	0.04
Thurstone 4	-0.07	-0.1	-0.1	-0.1	-0.09
Thurstone 5	-0.08	-0.14	-0.17	-0.09	-0.07
Symbol Digit 1	-0.14	-0.14	-0.18	-0.08	-0.16
Symbol Digit 2	-0.17	-0.24	-0.21	-0.16	-0.15
Symbol Digit 3	-0.16	-0.25	-0.19	-0.12	-0.17
Symbol Digit 4	-0.13	-0.2	-0.2	-0.1	-0.16
Symbol Digit 5	-0.17	-0.27	-0.14	-0.11	-0.12
Average Correlation					
Block Design	-0.09	-0.12	-0.14	-0.13	-0.14
Synonyms	-0.07	-0.07	-0.05	-0.23	-0.05
Thurstone	-0.06	-0.05	-0.01	-0.10	-0.11
Symbol Digit	-0.14	-0.19	-0.18	-0.16	-0.16

Table 3: Correlations between Uncontrollable Negative Life Events and Cognitive Measures in SATSA

Cognitive Trait	Negative Life Events Q1	Negative Life Events IPT2	Negative Life Events IPT3	Negative Life Events IPT5	Negative Life Events IPT6
Block Design 1	-0.07	-0.09	-0.14	-0.0003	-0.17
Block Design 2	-0.07	-0.15	-0.15	-0.12	-0.1
Block Design 3	-0.07	-0.12	-0.18	-0.12	-0.18
Block Design 4	-0.12	-0.16	-0.12	-0.09	-0.17
Block Design 5	-0.16	-0.16	-0.15	-0.06	-0.15
Synonyms 1	-0.03	-0.16	-0.12	-0.08	-0.03
Synonyms 2	0.05	-0.13	-0.12	-0.07	-0.02
Synonyms 3	0.02	-0.13	-0.11	-0.11	-0.04
Synonyms 4	-0.03	-0.14	-0.13	-0.11	-0.15
Synonyms 5	-0.02	-0.13	-0.08	-0.08	-0.09
Thurstone 1	-0.1	0.03	-0.08	-0.11	-0.12
Thurstone 2	-0.02	-0.08	-0.09	-0.06	-0.08
Thurstone 3	0.04	-0.05	-0.1	-0.04	-0.05
Thurstone 4	-0.09	-0.09	-0.14	-0.04	-0.12
Thurstone 5	-0.03	-0.14	-0.15	-0.09	-0.09
Symbol Digit 1	-0.18	-0.1	-0.22	-0.08	-0.16
Symbol Digit 2	-0.16	-0.17	-0.25	-0.11	-0.15
Symbol Digit 3	-0.15	-0.17	-0.22	-0.13	-0.16
Symbol Digit 4	-0.2	-0.16	-0.22	-0.12	-0.17
Symbol Digit 5	-0.23	-0.21	-0.2	-0.14	-0.14
Average Correlation					
Block Design	-0.09	-0.12	-0.13	-0.13	-0.14
Synonyms	-0.08	-0.06	-0.07	-0.11	-0.08
Thurstone	-0.08	-0.07	-0.04	-0.10	-0.11
Symbol Digit	-0.14	-0.19	-0.18	-0.16	-0.16

Table 4: Negative Life Events Scores (Stress) in SATSA

Variable	N	Mean	Std. Dev	Minimum	Maximum
Negative Life Events Score (Q1)	475	6.01	5.81	0	31.41
Negative Life Events Score (IPT2)	488	4.41	4.07	0	20.50
Negative Life Events Score (IPT3)	416	3.19	3.75	0	22.55
Negative Life Events Score (IPT5)	477	4.68	5.06	0	45.56
Negative Life Events Score (IPT6)	376	2.88	3.26	0	19.18
Log Maximum Negative Life Events Score	760	1.96	0.70	0	3.84
Age at Log Maximum Negative Life Events Score	760	65.90	10.90	36.08	92.62

Table 5: Cognitive Measures in the SATSA Study

Variable	N	Mean	Std. Dev	Minimum	Maximum
Block Design 1	598	18.406	18.406	0	37
Block Design 2	541	19.054	19.054	0	37
Block Design 3	526	19.086	19.086	0	41
Block Design 4	497	20.201	20.201	3	41
Block Design 5	414	19.652	19.652	0	39
Synonyms 1	604	18.555	18.555	2	30
Synonyms 2	530	19.179	19.179	6	30
Synonyms 3	515	19.179	19.351	3	30
Synonyms 4	500	19.940	19.940	5	30
Synonyms 5	409	20.455	20.455	5	30
Thurstone 1	600	20.598	20.598	7	28
Thurstone 2	531	20.819	20.819	4	28
Thurstone 3	521	21.497	21.497	5	28
Thurstone 4	481	21.466	21.466	3	28
Thurstone 5	398	21.631	21.631	8	28
Symbol Digit 1	598	38.142	38.142	0	66
Symbol Digit 2	519	37.981	37.981	6	71
Symbol Digit 3	494	38.415	38.415	7	74
Symbol Digit 4	497	36.406	36.406	2	75
Symbol Digit 5	414	36.381	36.382	3	72

Table 6: Cognitive Measures in the GENDER study

Variable	N	Mean	Std. Dev	Minimum	Maximum
Block Design 1	484	17.244	6.290	0	35
Block Design 2	355	16.823	6.744	0	34
Block Design 3	258	16.616	6.873	0	33
Synonyms 1	477	18.868	6.013	0	30
Synonyms 2	354	19.201	6.589	0	30
Synonyms 3	253	18.964	6.718	0	30
Thurstone 1	454	21.170	3.996	9	28
Thurstone 2	308	20.701	4.557	4	28
Thurstone 3	180	20.767	4.388	9	28
Symbol Digit 1	345	32.762	10.414	2	60
Symbol Digit 2	253	34.534	10.166	2	62
Symbol Digit 3	133	34.338	8.712	12	55

Table 7: Cognitive Measures in the Origins of Variance in the Oldest-Old (OCTO-twin) Study

Variable	N	Mean	Std. Dev	Minimum	Maximum
Block Design 1	555	10.665	7.414	0	33
Block Design 2	449	10.388	7.483	0	30
Block Design 3	351	10.285	7.486	0	31
Block Design 4	250	10.444	7.333	0	27
Block Design 5	167	9.808	7.375	0	25
Synonyms 1	484	15.017	7.341	0	30
Synonyms 2	399	14.576	7.439	0	29
Synonyms 3	296	14.365	7.680	0	30
Synonyms 4	204	14.279	8.156	0	30
Synonyms 5	139	14.259	7.736	0	29
Thurstone 1	436	17.709	5.606	0	28
Thurstone 2	379	16.092	6.724	0	28
Thurstone 3	302	15.411	7.265	0	28
Thurstone 4	209	15.593	7.506	0	28
Thurstone 5	136	14.919	7.775	0	27
Symbol Digit 1	468	23.194	11.683	0	59
Symbol Digit 2	367	23.213	11.460	0	58
Symbol Digit 3	290	23.238	12.031	0	56
Symbol Digit 4	199	22.844	12.616	0	52
Symbol Digit 5	141	21.106	11.588	0	51

Table 8: Inflammatory Biomarkers – C-RP (mg/Liter) and IL-6 (ng/Liter)

CRP (mg/Liter)					
Study	**N**	**Mean**	**Std. Dev**	**Minimum**	**Maximum**
SATSA	237	3.72	6.38	0.19	53.20
Gender	289	4.59	9.25	0.19	130.00
OCTO-twin	344	5.45	14.08	0.19	207.60
TOTAL (across all 3)	870	4.69	10.87	0.19	207.60
IL-6 (ng/Liter)					
Study	**N**	**Mean**	**Std. Dev**	**Minimum**	**Maximum**
SATSA	221	2.64	2.29	0.29	16.12
Gender	278	2.86	2.28	0.19	15.50
OCTO-twin	335	3.58	2.79	0.65	15.44
TOTAL (across all 3)	834	3.09	2.53	0.19	16.12

Note. CRP= C-Reactive Protein; IL-6= Interleukin-6

Table 9: Correlations between CRP and Cognitive Measures by Study

Cognitive Trait	SATSA		GENDER	OCTO-twin	
Block Design 1	-0.09		-0.02	-.13	*
Block Design 2	-0.16	*	0.01	-.15	*
Block Design 3	-0.16	*	-0.01	-.18	**
Block Design 4	-0.17	*	------	-0.18	
Block Design 5	-0.12		------	-0.10	
Synonyms 1	-0.01		-0.05	-.14	*
Synonyms 2	-0.02		0.01	-.14	*
Synonyms 3	0.04		-0.03	-.16	*
Synonyms 4	-0.10		------	-0.06	
Synonyms 5	0.01		------	-0.01	
Thurstone 1	0.05		-0.01	-.21	***
Thurstone 2	0.01		0.12	-0.01	
Thurstone 3	-0.01		0.04	-.17	**
Thurstone 4	-0.06		------	-.18	*
Thurstone 5	0.01		------	-0.17	
Symbol Digit 1	-0.03		-0.02	-.12	*
Symbol Digit 2	-0.04		0.01	-0.06	
Symbol Digit 3	-0.10		0.02	-.12	*
Symbol Digit 4	-0.10		------	-.17	*
Symbol Digit 5	-0.16		------	-0.12	

Average Correlation

Cognitive trait	SATSA	GENDER	OCTO-twin
Block Design	-0.14	-0.04	-0.15
Synonyms	-0.02	-0.02	-0.10
Thurstone	-0.02	0.05	-0.15
Symbol Digit	-0.09	0.00	-0.12

*= $p \leq 0.05$; **= $p \leq 0.01$; ***= $p \leq 0.001$; ----- = no cognitive data at time point

Note. CRP= C-Reactive Protein.

Table 10: Correlations between IL-6 and Cognitive Measures by Study

Cognitive Trait	SATSA		GENDER		OCTO-twin	
Block Design 1	-0.04		-.18	**	-0.10	
Block Design 2	-0.09		-.13	*	-.17	**
Block Design 3	-0.13		-.16	*	-0.13	
Block Design 4	-0.24	**	------		-0.11	
Block Design 5	-0.01		------		-0.04	
Synonyms 1	0.04		-0.10		-0.13	*
Synonyms 2	-0.04		-0.10		-0.06	
Synonyms 3	0.02		-0.07		-0.10	
Synonyms 4	-0.14		------		0.00	
Synonyms 5	-0.02		------		0.04	
Thurstone 1	-0.01		-0.02		-0.04	
Thurstone 2	-0.03		0.05		-0.05	
Thurstone 3	0.01		0.02		-0.13	
Thurstone 4	-.19	*	------		-0.24	*
Thurstone 5	0.12		------		-0.02	
Symbol Digit 1	-0.06		-0.10		-.14	*
Symbol Digit 2	-0.09		-0.07		-0.08	
Symbol Digit 3	-0.09		-0.11		-0.17	*
Symbol Digit 4	-0.08		------		-0.12	
Symbol Digit 5	-0.13		------		-0.10	

Average Correlation

Cognitive trait	SATSA	GENDER	OCTO-twin
Block Design	-0.10	-0.16	-0.11
Synonyms	-0.03	-0.09	-0.05
Thurstone	-0.02	0.02	-0.09
Symbol Digit	-0.09	-0.09	-0.12

*= $p \leq 0.05$; **= $p \leq 0.01$; ***= $p \leq 0.001$; ----- = no cognitive data at time point

Note. IL-6=Interleukin 6

Table 11: Correlations between Negative Life Events and Inflammatory Biomarkers in (SATSA)

	Negative Life Event (Q1)	Negative Life Event (IPT2)	Negative Life Event (IPT3)	Negative Life Event (IPT5)	Negative Life Event (IPT6)	Average Correlation
CRP	0.161	0.136	-0.068	0.031	0.045	0.061
IL-6	0.157	0.129	0.079	0.068	-0.119	0.063

Note. CRP=C-Reactive Protein; IL-6= Interleukin-6; Inflammatory Biomarkers are log transformed.

Table 12: Fit Statistics for Negative Life Events and Inflammatory Biomarker Levels

Inflammatory Biomarker	Model	-2ln(L)	#parms	Δχ2	Δdf	Sig	
Average Negative Life Events							
CRP	Age	1364.40	4	--	--	--	
	w/ AveStress	1364.40	5	2.20	1	0.157	
	w/ Age*		6		2		
	AveStress	1362.40		0.80		1.00	
IL-6	Age	1362.40	4	--	--	--	
	w/ AveStress	1364.40	5	0.50	1	0.480	
	w/ Age*		6		2		
	AveStress	1362.40		0.10		0.752	
Maximum Total Negative Life Events							
CRP	Age	670.10	5	--	--	--	
	w/ MaxStress	669.30	6	0.80	1	0.371	
	w/ Difference in Ages	668.70	7	0.60	1	0.439	
	w/ Slope* MaxStress, Difference in Ages* MaxStress	668.40	9	0.30	2	0.584	
IL-6	Age	406.10	5	--	--	--	
	w/ MaxStress	403.10	6	3.00	1	0.083	t
	w/ Difference in Ages	402.20	7	0.90	1	0.343	
	w/ Age* MaxStress, Difference in Ages* MaxStress	398.30	9	3.90	2	0.143	

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001.

Note. CRP= C-Reactive Protein; IL-6= Interleukin-6; Age= age at sampling of blood serum; AveStress=average stress score; MaxStress= maximum stress score; parms=number of parameters estimated; -2ln(L)=deviance statistic

Table 13: Fixed and random effects for Negative Life Events and Inflammatory Biomarker Levels

Average Negative Life Events				
Parameter	CRP		IL-6	
	B		B	
Intercept	0.670	***	0.876	***
Age	0.012		0.024	***
AveStress	--		--	
AveStress *Age	--		--	
$\sigma^2_{\text{within-pair}}$	1.094		0.308	
Maximum Negative Life Events				
Parameter	CRP		IL-6	
	B		B	
Intercept	0.805	***	0.593	**
Age	0.027	*	0.024	***
MaxStresss	--		0.138	t
Differences in Ages	--		--	
MaxStress*Age	--		--	
MaxStress* Differences in Ages	--		--	
$\sigma^2_{\text{within-pair}}$	0.500		0.046	

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001.

Note. CRP= C-Reactive Protein; IL-6= Interleukin-6; AveStress=average stress score; MaxStress= maximum stress score; Age= age at sampling of blood serum; the Sex covariate was coded as 0=male, 1=female.

Table 14: Fit Statistics for Cognitive Measures: Inflammatory Biomarkers

CRP							
Cognitive Trait	Model	-2ln(L)	#parms	Δχ2	Δdf	P	
Block Design	Dual Slope	16760.70	16	--		--	
	w/ CRP	16752.60	17	8.10	1	0.004	***
	w/ S1*CRP	16752.60	18	0.00	1	1.00	
	w/ S2*CRP	16751.70	19	0.90	1	0.343	
Symbol Digit	Dual Slope	16406.10	16	--		--	
	w/ CRP	16402.80	17	3.30	1	0.067	t
	w/ S1*CRP	16401.70	18	1.10	1	0.294	
	w/ S2*CRP	16401.30	19	0.40	1	0.527	
Synonyms	Dual Slope	15306.20	16	--		--	
	w/ CRP	15303.40	17	2.80	1	0.094	t
	w/ S1*CRP	15299.80	18	3.60	1	0.058	t
	w/ S2*CRP	15297.40	19	2.40	1	0.121	
Thurstone	Dual Slope	14086.60	16	--		--	
	w/ CRP	14086.30	17	0.30	1	0.584	
	w/ S1*CRP	14084.50	18	1.80	1	0.180	
	w/ S2*CRP	14083.50	19	1.00	1	0.317	
IL-6							
Block Design	Dual Slope	15986.30	16	--		--	
	w/ IL-6	15964.10	17	22.20	1	0.00000246	***
	w/ S1* IL-6	15960.40	18	3.70	1	0.054	t
	w/ S2* IL-6	15958.80	19	1.60	1	0.206	
Symbol Digit	Dual Slope	15651.30	16	--		--	
	w/ IL-6	15636.80	17	14.50	1	0.00014	***
	w/ S1* IL-6	15636.30	18	0.50	1	0.480	
	w/ S2* IL-6	15636.30	19	0.00	1	1.00	
Synonyms	Dual Slope	14583.40	16	--		--	
	w/ IL-6	14574.10	17	9.30	1	0.002	***
	w/ S1* IL-6	14574.10	18	0.00	1	1.00	
	w/ S2* IL-6	14572.80	19	1.30	1	0.254	
Thurstone	Dual Slope	13451.80	16	--		--	
	w/ IL-6	13451.40	17	0.40	1	0.527	
	w/ S1* IL-6	13450.60	18	0.80	1	0.371	
	w/ S2* IL-6	13443.90	19	6.70	1	0.010	**

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001.

Note. CRP= C-Reactive Protein; IL-6= Interleukin-6; S1=rate of change before 75 years; S2=rate of change after 75 years; parms=number of parameters estimated; -2ln(L) = deviance statistic

Table 15: Fixed and random effects for Cognitive Measures and Inflammatory Biomarkers

CRP								
Parameter	Block Design		Symbol Digit		Synonyms		Thurstone	
Intercept	16.923	***	32.490	***	18.808	***	21.555	***
S1	-0.227	***	-0.807	***	-0.002		0.046	t
S2	-0.460	***	-0.801	***	-0.270	***	-0.409	***
CRP	-0.507	**	-0.540	t	-0.224	t	--	
CRP *S1	--		--		0.058	*	--	
CRP *S2	--		--		--		--	
σ^2_{Wint}	18.737		50.402		16.588		5.180	
σ^2_{Ws1}	0.031		0.102		0.001		0.0001	
σ^2_{Ws2}	0.078		0.148		0.168		0.138	
$r_{WInt,S1}$	1.000		0.955		1.000		1.000	
$r_{WInt,slopeB}$	-0.187		-0.161		-0.328		-0.145	
σ^2_{Bint}	17.566		54.898		17.405		5.762	
σ^2_{Bs1}	0.025		0.030		0.001		3.96e-27	
σ^2_{Bs2}	0.019		0.138		0.039		0.061	
$r_{BInt,s1}$	-1.000		0.334		1.000		1.00	
$r_{BInt,s2}$	-0.338		-0.647		-1.000		-0.435	
IL-6								
Parameter	Block Design		Symbol Digit		Synonyms		Thurstone	
Intercept	16.689	***	31.994	***	18.645	***	21.487	***
S1	-0.250	***	-0.799	***	-0.012		0.050	
S2	-0.442	***	-0.759	***	-0.256	***	-0.410	***
Il-6	-1.514	***	-2.033	***	-0.945	*	0.276	
Il-6*S1	--		--		--		0.052	
Il-6*S2	--		--		--		-0.118	**
σ^2_{Wint}	18.491		56.229		16.288		5.806	
σ^2_{Ws1}	0.026		0.164		0.002		0.003	
σ^2_{Ws2}	0.060		0.165		0.124		0.143	
$r_{WInt,S1}$	1.000		0.914		1.000		1.000	
$r_{WInt,s2}$	-0.166		-0.284		-0.268		-0.184	
σ^2_{Bint}	17.626		51.069		16.715		4.954	
σ^2_{Bs1}	0.025		0.001		0.00002		0.001	
σ^2_{Bs2}	0.031		0.126		0.043		0.043	
$r_{BInt,s1}$	-1.000		1.000		1.000		-1.00	
$r_{BInt,s2}$	-0.324		-0.610		-0.045		-0.231	

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001.

Note. CRP= C-Reactive Protein; IL-6= Interleukin-6; S1=rate of change before 75 years; S2=rate of change after 75 years.

Table 16: Fit Statistics for Cognitive Measures: Negative Life Events (Stress)

Cognitive Trait	Model	-2ln(L)	parm	Δχ2	Δdf	P	
Average Total Negative Life Events							
Block Design	Dual Slope	11645.90	16	--	1	--	
	w/ AveStress	11645.90	17	0.00	1	1.000	
	w/ S1* AveStress	11645.50	18	0.40	1	0.527	
	w/ S2* AveStress	11645.00	19	0.50	1	0.480	
Symbol Digit	Dual Slope	13395.90	16	--	1	--	
	w/ AveStress	13390.60	17	5.30	1	0.021	*
	w/ S1* AveStress	13390.50	18	0.10	1	0.752	
	w/ S2* AveStress	13390.30	19	0.20	1	0.655	
Synonyms	Dual Slope	10165.60	16	--	1	--	
	w/ AveStress	10164.80	17	0.80	1	0.371	
	w/ S1* AveStress	10164.40	18	0.40	1	0.527	
	w/ S2* AveStress	10163.30	19	1.10	1	0.294	
Thurstone	Dual Slope	10458.00	16	--	1	--	
	w/ AveStress	10453.60	17	4.40	1	0.036	*
	w/ S1* AveStress	10451.30	18	2.30	1	0.129	
	w/ S2* AveStress	10449.90	19	1.40	1	0.237	
Maximum Total Negative Life Events							
Block Design	Dual Slope	14316.10	17	--	--	--	
	w/ MaxStress	14316.00	18	0.10	1	0.951	
	w/ S1*MaxStress	14315.80	19	0.20	1	0.655	
	w/ S2* MaxStress	14315.70	20	0.10	1	0.992	
	w/ S1* MaxStress*MaxAge, S2* MaxStresss*MaxAge	14286.30	26	29.4	6	1.84e-6	***
Symbol Digit	Dual Slope	16275.00	17	--	--	--	
	w/ MaxStress	16274.70	18	0.30	1	0.861	
	w/ S1*MaxStress	16272.00	19	2.70	1	0.100	t
	w/ S2* MaxStress	16267.60	20	4.40	1	0.221	
	w/ S1* MaxStress*MaxAge, S2* MaxStresss*MaxAge	16244.10	26	23.5	6	3.17e-5	***
Synonyms	Dual Slope	12439.20	17	--	--	--	
	w/ MaxStress	12438.80	18	0.40	1	0.527	
	w/ S1*MaxStress	12435.90	19	2.90	1	0.089	t
	w/ S2* MaxStress	12434.00	20	1.90	1	0.168	
	w/ S1* MaxStress*MaxAge, S2* MaxStresss*MaxAge	12407.30	26	26.7	6	0.0002	***
Thurstone	Dual Slope	12748.60	17	--	--	--	
	w/ MaxStress	12748.50	18	0.10	1	0.951	
	w/ S1*MaxStress	12747.20	19	1.30	1	0.254	

w/ S2* MaxStress	12747.00	20	0.20	1	0.978	
w/ S1* MaxStress*MaxAge, S2* MaxStresss*MaxAge	12730.60	26	16.4	6	0.0118	*

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001.

Note. AveStress=average stress score; MaxStress= maximum stress score; MaxAge= age at maximum stress score; S1=rate of change before 75; S2=rate of change after age 75.

Table 17: Fixed and random effects for Cognitive Measures and Negative Life Events

Average Total Negative Life Events								
Parameter	Block Design		Symbol Digit		Synonyms		Thurstone	
Intercept	18.304	***	33.136	***	19.598	***	20.942	***
S1	-0.196	**	-0.667	***	-0.010		-0.049	**
S2	-0.489	***	-0.974	***	-0.148	***	-0.260	***
AveStress	--		-0.382	*	--		-0.164	*
AveStress*S1	--		- -		--		--	
AveStress*S2	--		- -		--		--	
σ^2_{Wint}	17.471		37.989		13.041		8.074	
σ^2_{Ws1}	0.008		0.018		0.004		0.005	
σ^2_{Ws2}	0.085		0.086		0.043		0.093	
$r_{WInt,S1}$	0.667		0.539		0.459		0.625	
$r_{WInt,S2}$	-0.432		-0.559		0.006		-0.137	
σ^2_{Bint}	20.338		59.528		12.757		6.561	
σ^2_{Bs1}	0.002		0.060		0.00005		5.02e-6	
σ^2_{Bs2}	0.026		0.048		0.025		0.004	
$r_{BInt,slope1}$	-1.000		0.564		-1.000		1.000	
$r_{BInt,slope2}$	-0.073		-1.000		-0.044		-1.000	
Maximum Total Negative Life Events								
Intercept	18.640	***	32.736	***	19.700		20.521	***
Sex	-0.327		1.343	t	0.014		1.176	***
S1	-0.156	***	-0.642	***	0.005		-0.020	***
S2	-0.586	***	-1.343	***	-0.164	**	-0.291	***
MaxStress	-0.199		0.152		-0.393		-0.050	
MaxAge	-0.120	***	-0.149	**	-0.098	***	-0.061	**
MaxAge *S1	0.001		-0.005	t	-0.001		-0.024	
MaxStress *S1	-0.038		-0.042		-0.043	*	0.000	
MaxAge*S2	0.012	t	0.027	**	0.002		0.003	
MaxStress*S2	0.152		-0.190		0.237	*	0.038	
MaxAge* MaxStress	0.042		-0.154	*	0.013		0.002	
MaxAge* MaxStress* S1	0.00001		-0.010	*	-0.0001		0.000	
MaxAge* MaxStress*S2	-0.013	t	0.005		-0.015	*	-0.007	
σ^2_{Wint}	15.946		37.872		12.557		6.995	
σ^2_{Ws1}	0.169		0.494		0.021		0.090	
σ^2_{Ws2}	0.009		0.025		0.0003		0.005	
$\sigma_{WInt,S1}$	-0.616		-0.412		-0.002		-0.100	
$\sigma_{WInt,s2}$	0.001		0.021		0.027		-0.030	
$\sigma_{Ws1,s2}$	0.112		0.044		0.007		0.088	

σ^2_{Bint}	19.201	57.121	12.052	5.861
σ^2_{Bs1}	-0.209	0.980	-0.035	-0.015
σ^2_{Bs2}	7.2e-19	0.053	0.002	7.4e-6
$\sigma_{BInt,s1}$	-0.089	-1.708	0.039	-0.014
$\sigma_{BInt,s2}$	0.008	0.022	-0.006	-0.175
$\sigma_{Bs1,s2}$	0.0002	6e-18	0.014	0.026
$\sigma^2_{Residual}$	9.770	26.193	3.882	6.591

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001.

Note. AveStress=average stress score; MaxStress= maximum stress score; MaxAge= age at maximum stress score; S1=rate of change before 75; S2=rate of change after age 75; B=between pair; W=within pair; the Sex covariate was coded as 0=male, 1=female. For MaxStress analyses, the type=UN function was used and the covariance between S1 and S2 was estimated.

Table 18: Latent Class Analysis: Group Classifications by Total Negative Life Events Scores

	total N	BIC	Lo-Mendell-Rubin Test	Entropy
1 class model	760	5946.778	----	----
2 class model	760	5792.226	189.588 (0.0000)	0.535
3 class model	760	5586.055	239.942 (0.0168)	0.502
4 class model	760	5369.141	251.302 (0.0651)	0.527

Note: Classification made with log transformed total negative life events scores

Table 19: Latent Class Analyses: Classifications by Group

Two Class Solution				
	Group 1	Group 2		
	n=578 (76%)	n=182 (24%)		
Wave	Mean Negative Life Events Score	Mean Negative Life Events Score		
Q1	1.637	1.161		
IPT2	1.434	1.192		
IPT3	1.112	1.014		
IPT5	1.291	1.453		
IPT6	1.629	0.007		
Three Class Solution				
	Group 1	Group 2	Group 3	
	n=306 (40%)	n=143 (19%)	n=311 (41%)	
Wave	Mean Negative Life Events Score	Mean Negative Life Events Score	Mean Negative Life Events Score	
Q1	1.16	1.48	1.796	
IPT2	1.196	1.308	1.557	
IPT3	1.013	0.917	1.296	
IPT5	1.453	1.328	1.254	
IPT6	0	1.24	2.028	
Four Class Solution				
	Group 1	Group 2	Group 3	Group 4
	n=200 (26%)	n=401 (53%)	n=67 (0.08%)	n=92 (12%)
Wave	Mean Negative Life Events Score	Mean Negative Life Events Score	Mean Negative Life Events Score	Mean Negative Life Events Score
Q1	1.506	1.163	1.467	2.115
IPT2	1.322	1.198	1.457	1.632
IPT3	0.926	1.016	1.108	1.462
IPT5	1.345	1.453	1.272	1.192
IPT6	1.225	0	1.802	2.303

Table 20: Fit Statistics for Cognitive Measures: Psychological Stress and Inflammatory Biomarkers (CRP)

Cognitive Measure	Model	-2ln(L)	parm	Δχ2	Δdf	*p*
Block Design	w/ Dual Slope, CRP, S1*CRP, S2*CRP	4834.20	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	4827.00	26	7.20	6	0.303
	w/ CRP*MaxStress, CRP*MaxAge, CRP*MaxStress*S1, CRP*MaxAge*S1, CRP*MaxStress*S2, CRP*MaxAge*S2,	4822.40	32	4.60	6	0.596
Symbol Digit	w/ Dual Slope, CRP, S1*CRP, S2*CRP	5399.00	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	5396.70	26	2.30	6	0.890
	w/ CRP*MaxStress, CRP*MaxAge, CRP*MaxStress*S1, CRP*MaxAge*S1, CRP*MaxStress*S2, CRP*MaxAge*S2,	5392.40	32	4.30	6	0.636
Synonyms	w/ Dual Slope, CRP, S1*CRP, S2*CRP	4228.30	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	4223.60	26	4.70	6	0.583
	w/ CRP*MaxStress, CRP*MaxAge, CRP*MaxStress*S1, CRP*MaxAge*S1, CRP*MaxStress*S2, CRP*MaxAge*S2,	4220.10	32	3.50	6	0.744
Thurstone	w/ Dual Slope, CRP, S1*CRP, S2*CRP	4342.20	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	4333.80	26	8.40	6	0.210
	w/ CRP*MaxStress, CRP*MaxAge,	4288.80	32	45.00	6	.0000 0005

	CRP*MaxStress*S1, CRP*MaxAge*S1, CRP*MaxStress*S2, CRP*MaxAge*S2,	***

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001

Note. CRP = C-Reactive Protein, S1= rate of change before 75 years; S2=rate of change after 75 years; parms=number of parameters estimated; -2ln(L)=deviance statistic; MaxStress= maximum stress score; MaxAge= age at maximum stress score.

Table 21: Fit Statistics for Cognitive Measures: Psychological Stress and Inflammatory Biomarkers (IL-6)

Cognitive Measure	Model	-2ln(L)	parms	$\Delta\chi 2$	Δdf	*p*
Block Design	w/ Dual Slope, IL6, S1* IL6, S2* IL6	4552.80	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	4543.40	26	9.40	6	0.152
	w/ IL6*MaxStress, IL6*MaxAge, IL6*MaxStress*S1, IL6*MaxAge*S1, IL6*MaxStress*S2, IL6*MaxAge*S2,	4539.10	32	4.30	6	0.636
Symbol Digit	w/ Dual Slope, IL6, S1* IL6, S2* IL6	5099.90	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	5097.40	26	2.50	6	0.868
	w/ IL6*MaxStress, IL6*MaxAge, IL6*MaxStress*S1, IL6*MaxAge*S1, IL6*MaxStress*S2, IL6*MaxAge*S2,	5092.40	32	5.00	6	0.544
Synonyms	w/ Dual Slope, IL6, S1* IL6, S2* IL6	3987.40	20	--	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	3976.70	26	10.70	6	0.102
	w/ IL6*MaxStress, IL6*MaxAge, IL6*MaxStress*S1, IL6*MaxAge*S1, IL6*MaxStress*S2, IL6*MaxAge*S2,	3974.30	32	2.40	6	0.879
Thurstone	w/ Dual Slope, IL6, S1* IL6, S2* IL6	4044.50	20	7.00	--	--
	w/ MaxStress, MaxAge, S1* MaxStress, S2* MaxStress, S1* MaxAge, S2*MaxAge	4037.50	26	5.70	6	0.321
	w/ IL6*MaxStress, IL6*MaxAge, IL6*MaxStress*S1, IL6*MaxAge*S1, IL6*MaxStress*S2, IL6*MaxAge*S2	4031.80	32	7.00	6	0.457

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001

Note: IL-6= Interleukin-6; S1=rate of change before 75 years; S2=rate of change after 75 years; parms=number of parameters estimated; -2ln(L)=deviance statistic; MaxStress= maximum stress score; MaxAge= age at maximum stress score.

Table 22: Fixed and random effects for Cognitive Measures: Psychological Stress and Inflammatory Biomarkers (CRP)

Parameter	Block Design		Symbol Digit		Synonyms		Thurstone	
Intercept	17.568	***	31.578	***	17.907	***	18.567	***
Sex	-0.689		1.115		0.169		1.572	*
Slope 1 (S1)	-0.053		-0.543	*	-0.014		0.047	
Slope 2 (S2)	-0.221		-0.864	*	-0.234		-0.090	
CRP	0.271		-0.985		-1.014		-0.112	
CRP*S1	0.213		0.247		0.059		0.156	
CRP*S2	0.173		-0.080		0.104		-0.096	
MaxStress	0.531		0.387		0.543		0.752	t
MaxStress*S1	-0.079		-0.129		-0.004		-0.015	
MaxStress*S2	-0.111		-0.069		0.071		-0.080	
MaxAge	-0.079		-0.037		-0.043		0.004	
MaxAge *S1	0.007		0.004		0.002		0.007	t
MaxAge*S2	0.005		0.006		-0.005		-0.002	
CRP* MaxStress	-0.267		0.248		0.557		0.029	
CRP* MaxAge	-0.048		0.048		-0.003		-0.001	
CRP* MaxStress*S1	-0.104		-0.103		-0.007		-0.069	
CRP* MaxAge*S1	-0.0004		0.012		0.002		-0.006	
CRP* MaxStress*S2	-0.013		0.043		-0.031		0.059	
CRP* MaxAge*S2	-0.004		-0.008		-0.005		-0.005	
σ^2_{Wint}	18.193		32.740		13.815		3.325	
σ^2_{Ws1}	0.027		0.060		0.0004		6.11e-6	
σ^2_{Ws2}	0.077		0.003		0.011		0.019	
$r_{WInt,S1}$	1.000		0.950		1.000		-1.000	
$r_{WInt,slopeB}$	-0.685		-1.000		-0.666		1.000	
σ^2_{Bint}	17.307		63.331		12.928		6.362	
σ^2_{Bs1}	0.031		0.067		0.0001		0.0001	
σ^2_{Bs2}	0.00002		0.079		0.002		0.005	
$r_{BInt,s1}$	-1.000		0.529		-1.000		1.000	
$r_{BInt,s2}$	1.000		-1.000		1.000		-1.000	

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001

Note. CRP= C-Reactive Protein; S1=rate of change before 75 years; S2=rate of change after 75 years; ; MaxStress= maximum stress score; MaxAge= age at maximum stress score; B=between pair; W=within pair; the Sex covariate was coded as 0=male, 1=female.

Table 23: Fixed and random effects for Cognitive Measures: Psychological Stress and Inflammatory Biomarkers (IL-6)

Parameter	Block Design		Symbol Digit		Synonyms		Thurstone	
Intercept	17.424	***	32.358	***	17.268	***	18.716	***
Sex	-0.540		1.157		0.282		1.669	*
Slope 1 (S1)	-0.091		-0.577	t	0.017		0.023	
Slope 2 (S2)	-0.518	t	-0.797	t	-0.265		-0.035	
IL-6	2.667		1.319		0.189		0.169	
IL-6*S1	0.268		0.144		0.031		0.165	
IL-6*S2	-0.042		0.850		-0.148		0.154	
MaxStress	0.516		-0.179		0.799		0.027	
MaxStress*S1	-0.076		-0.095		-0.022		0.593	
MaxStress*S2	-0.001		-0.121		0.095		-0.009	
MaxAge	-0.097		-0.026		-0.066		-0.119	
MaxAge *S1	0.006		0.004		-0.0004		-0.007	
MaxAge*S2	0.011		0.014		-0.0006		0.002	
IL-6* MaxStress	-1.570		-1.208		0.003		0.003	
IL-6* MaxAge	-0.092		0.038		-0.100		-0.054	
IL-6* MaxStress*S1	-0.156		-0.047		-0.010		-0.054	
IL-6* MaxAge*S1	-0.006		0.008		-0.003		-0.014	
IL-6* MaxStress*S2	0.069		-0.345		0.059		-0.064	
IL-6* MaxAge*S2	-0.0003		-0.003		0.002		0.02	
σ^2_{Wint}	17.967		40.048		13.130		3.444	
σ^2_{Ws1}	0.021		0.155		0.003		0.0003	
σ^2_{Ws2}	0.082		0.009		0.005		0.009	
$r_{WInt,S1}$	1.000		0.839		1.000		1.000	
$r_{WInt,slopeB}$	-0.640		-1.000		-1.000		1.000	
σ^2_{Bint}	16.430		56.004		13.832		5.556	
σ^2_{Bs1}	0.037		0.017		0.002		0.0004	
σ^2_{Bs2}	2.91E-19		0.063		0.012		0.0001	
$r_{BInt,s1}$	-1.000		0.669		-1.000		-1.000	
$r_{BInt,s2}$	0.1488		-1.000		0.534		-1.000	

t=p<0.10;*=p<.05; **=p<.01; ***=p<.0001

Note. IL-6= Interleukin-6;S1=rate of change before 75 years; S2=rate of change after 75 years; MaxStress= maximum stress score; MaxAge= age at maximum stress score; B=between pair; W=within pair.

Appendix

Negative Life Events Score Coding (Stress):

Participants were given a list of questions about a range of major life events. Since the Swedish Adoption/Twin Study of Aging consists of older individuals, a modified version of the Social Readjustment Rating Scale created by Holmes and Rahe was administered (Holmes and Rahe, 1967;Persson, 1980) to better assess the extent of psychological stress experienced during later adulthood. At the first wave, Q1, individuals were asked to indicate whether each event had occurred (Yes/No). If yes, they were asked to check mark how important the event was to them (Little importance/ Some importance/ Great Importance). If the participant indicated "No" the event had not occurred, they were asked to indicate how important the event would have been to them if it occurred (Little importance/ Some importance/ Great Importance).

Life Events

1. Retirement
2. Major deterioration in financial status
3. Serious illness in child
4. Death of a child
5. Serious conflicts with child
6. Somatic illness, self
7. Forced change in residence because one can't manage to look after oneself
8. Divorce
9. Home care of spouse by proband

10. Getting Married

11. Deterioration in married life

12. Somatic illness, spouse

13. Death of spouse

14. Nursing home care, spouse

15. Mental Illness, spouse

16. Improvement in married life

17. Home care, self

18. Forced change in residence with reduced contacts

19. Mental illness, self

20. Death of siblings or friends

21. Changes in relations with grandchildren

22. Loss of sexual ability or interest

23. Paying fines for minor violation of the law

24. Major improvement in financial status

25. Making a new acquaintance

In this study, we chose to examine only negative life events; hence, we constructed negative life events scores at each time point (Q1, IPT2, IPT3, IPT5, and IPT6) based on a weighted sum of a subset of the aforementioned life events that were negative in nature at each time point. The mean importance ratings for each negative life event at wave 1 (Q1) were used to weigh negative life events across all waves -- Q1, IPT2, IPT3, IPT5, and IPT6.

For each negative life event, the mean importance rating it was weighted by is listed.

The following 18 life events comprise the negative life events score:

2. Major deterioration in financial status (C) {2.13}

3. Serious illness in child (U) {2.88}

4. Death of a child (U) {2.96}

5. Serious conflicts with child (C) {2.83}

6. Somatic illness, self (--) {2.41}

7. Forced change in residence because one can't manage to look after oneself (U) {2.77}

8. Divorce (C) {2.85}

9. Home care of spouse by proband (U) {2.78}

11. Deterioration in married life (C) {2.80}

12. Somatic illness, spouse (U) {2.56}

13. Death of spouse (U) {2.96}

14. Nursing home care, spouse (U) {2.91}

15. Mental Illness, spouse (U) {2.81}

17. Home care, self (--) {2.64}

18. Forced change in residence with reduced contacts (U) {2.59}

20. Death of siblings or friends (U) {2.75}

22. Loss of sexual ability or interest (--)

23. Paying fines for minor violation of the law (C) {1.93}

Note. U= uncontrollable; C=controllable; -- = not defined as Controllable or Uncontrollable

Figure 1: Mediational model of psychological stress, inflammatory biomarkers and cognitive change.

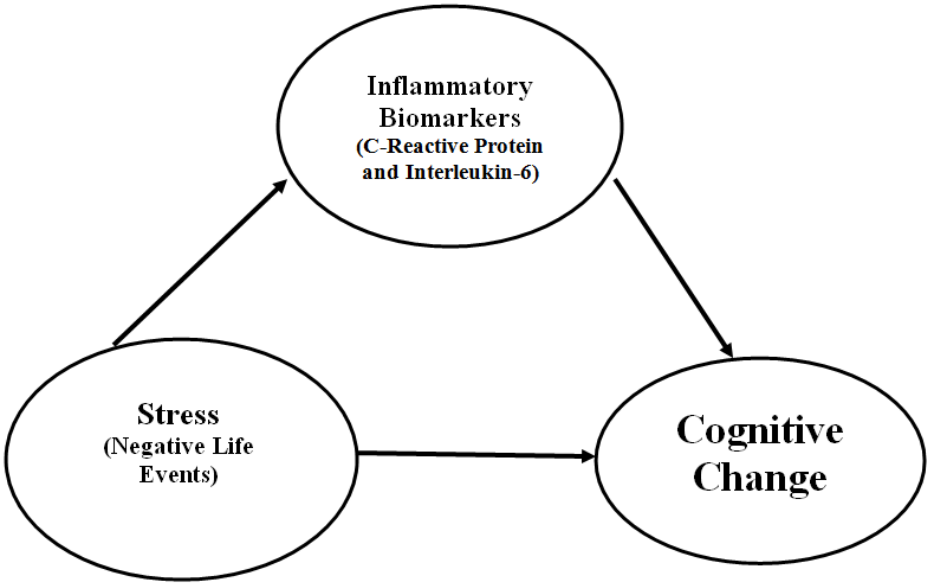

Figure 2: Predictors of an expected prototypical growth process

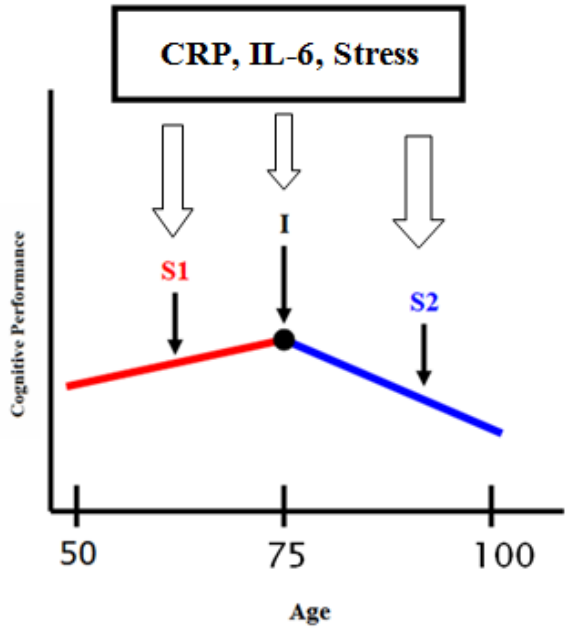

Figure 3: Maximum Total Negative Life Events and IL-6 levels

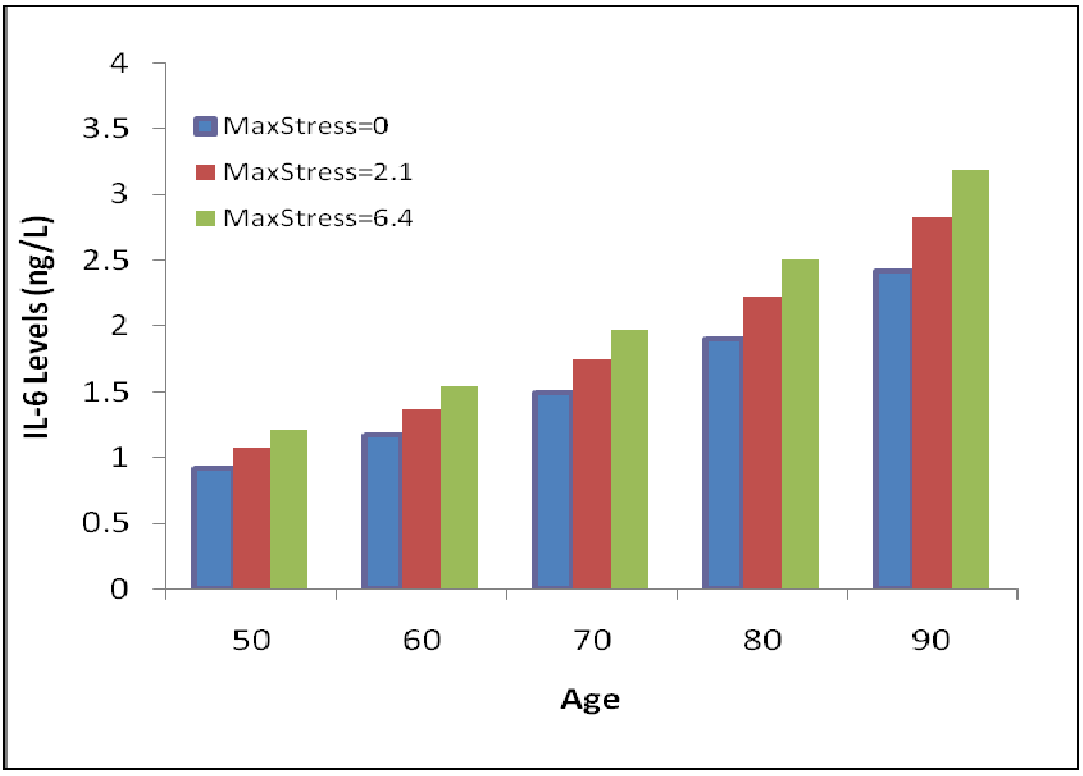

Figure 4: CRP levels and Block Design Performance

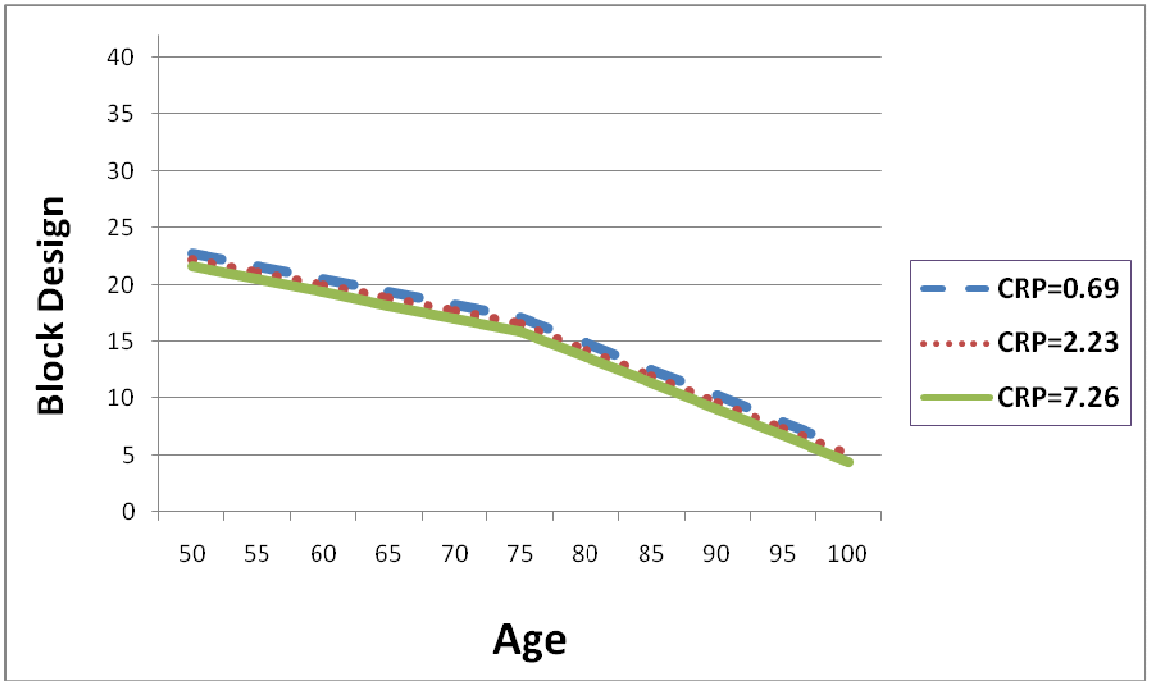

Figure 5: CRP levels and Synonyms Performance

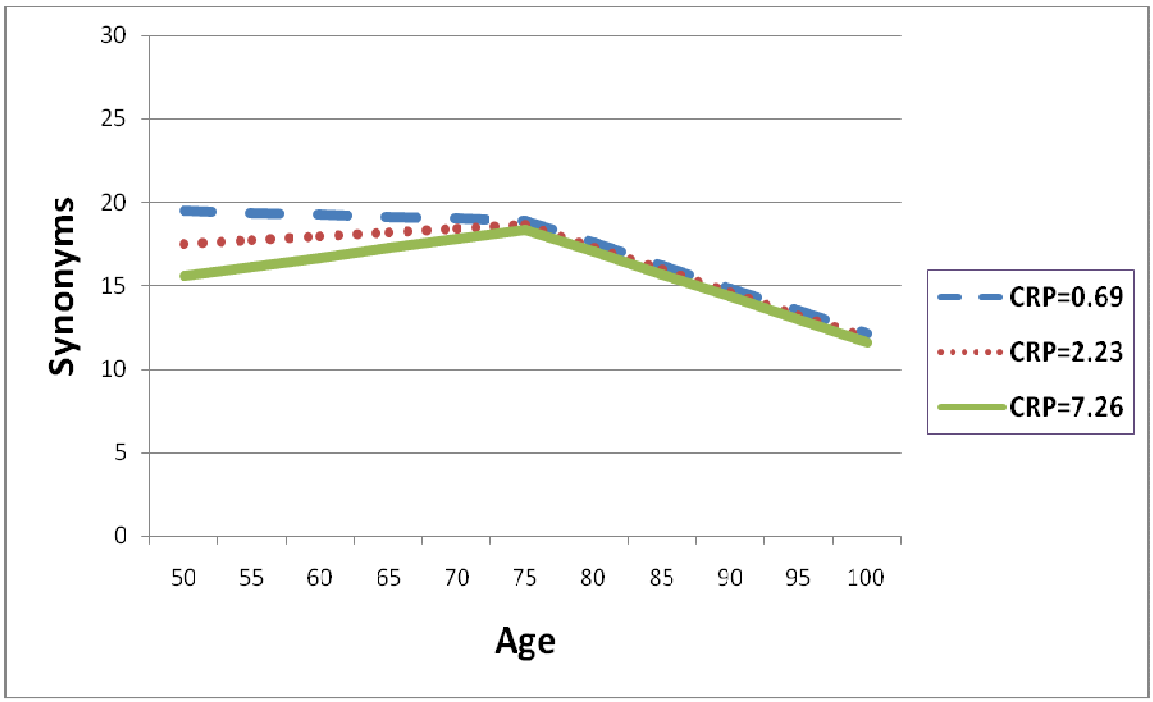

Figure 6: IL-6 levels and Block Design Performance

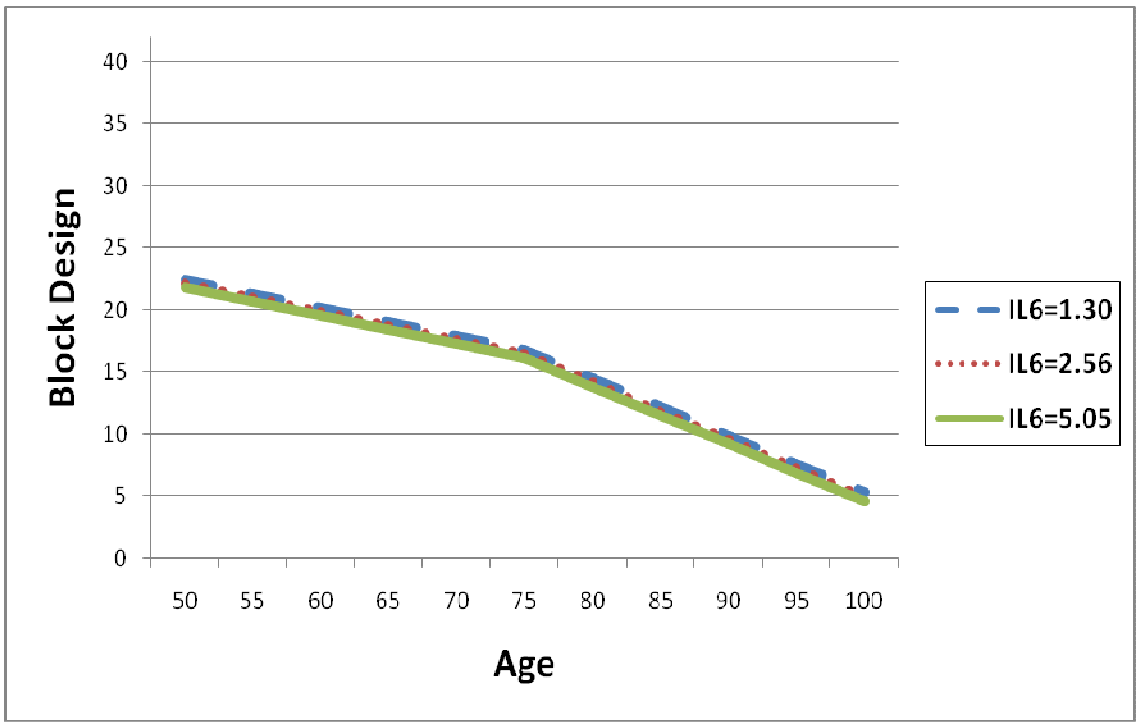

Figure 7: IL-6 levels and Symbol Digit Performance

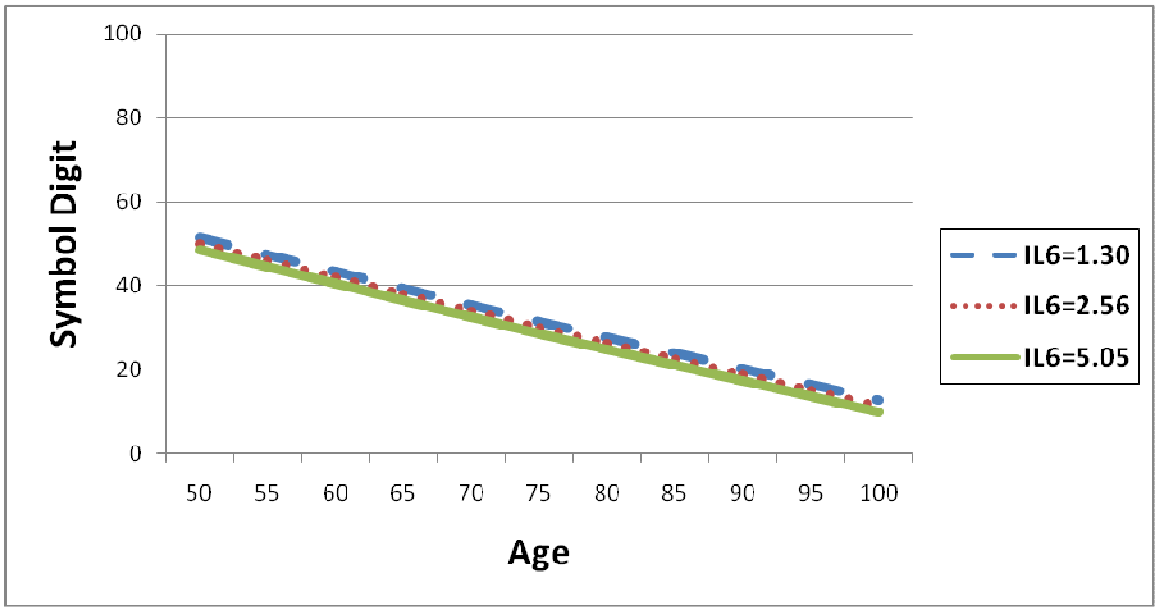

Figure 8: IL-6 levels and Synonyms Performance

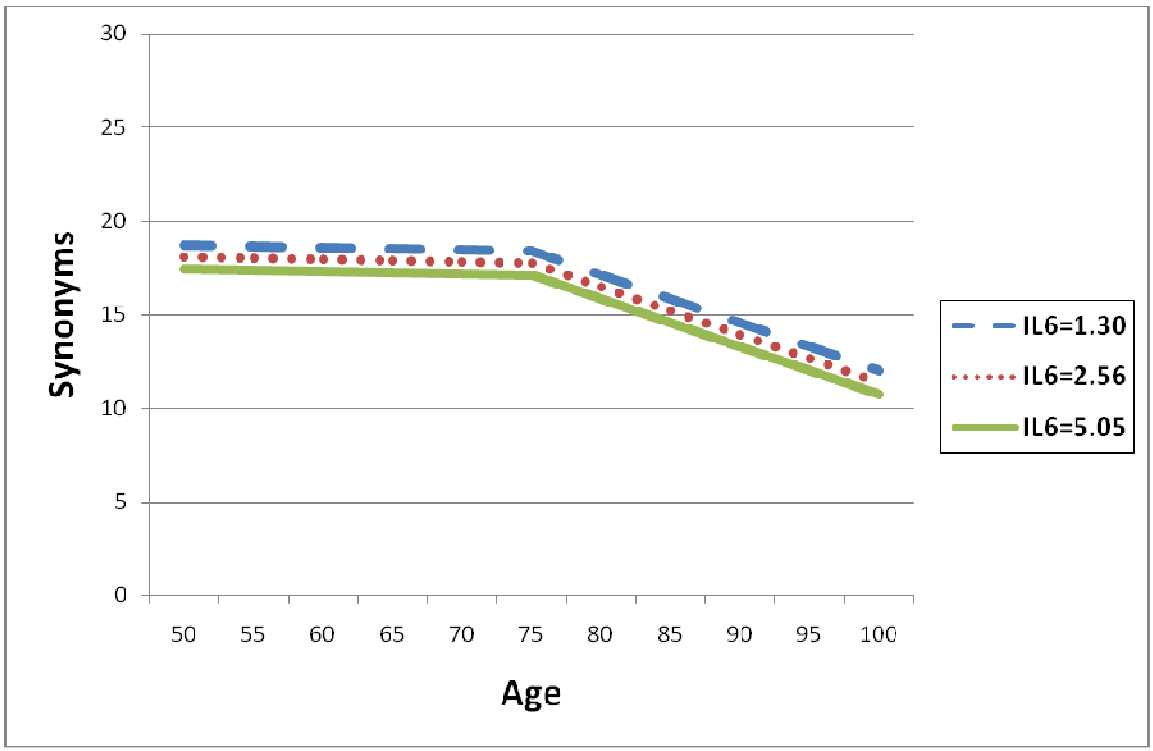

Figure 9: IL-6 levels and Thurstone Picture Memory Performance

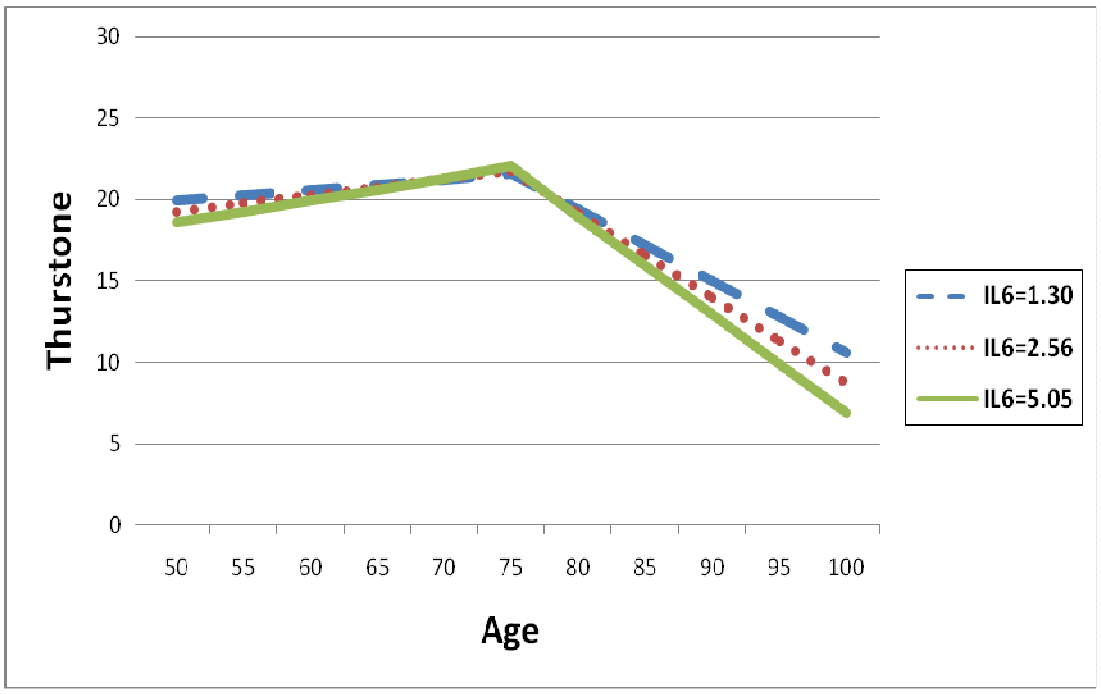

Figure 10: Maximum Negative Life Events and Block Design Performance

Note. Lines in black indicate those at the averge logged MaxStress score. Lines in red indicate those with MaxStress scores one log unit higher than the average.

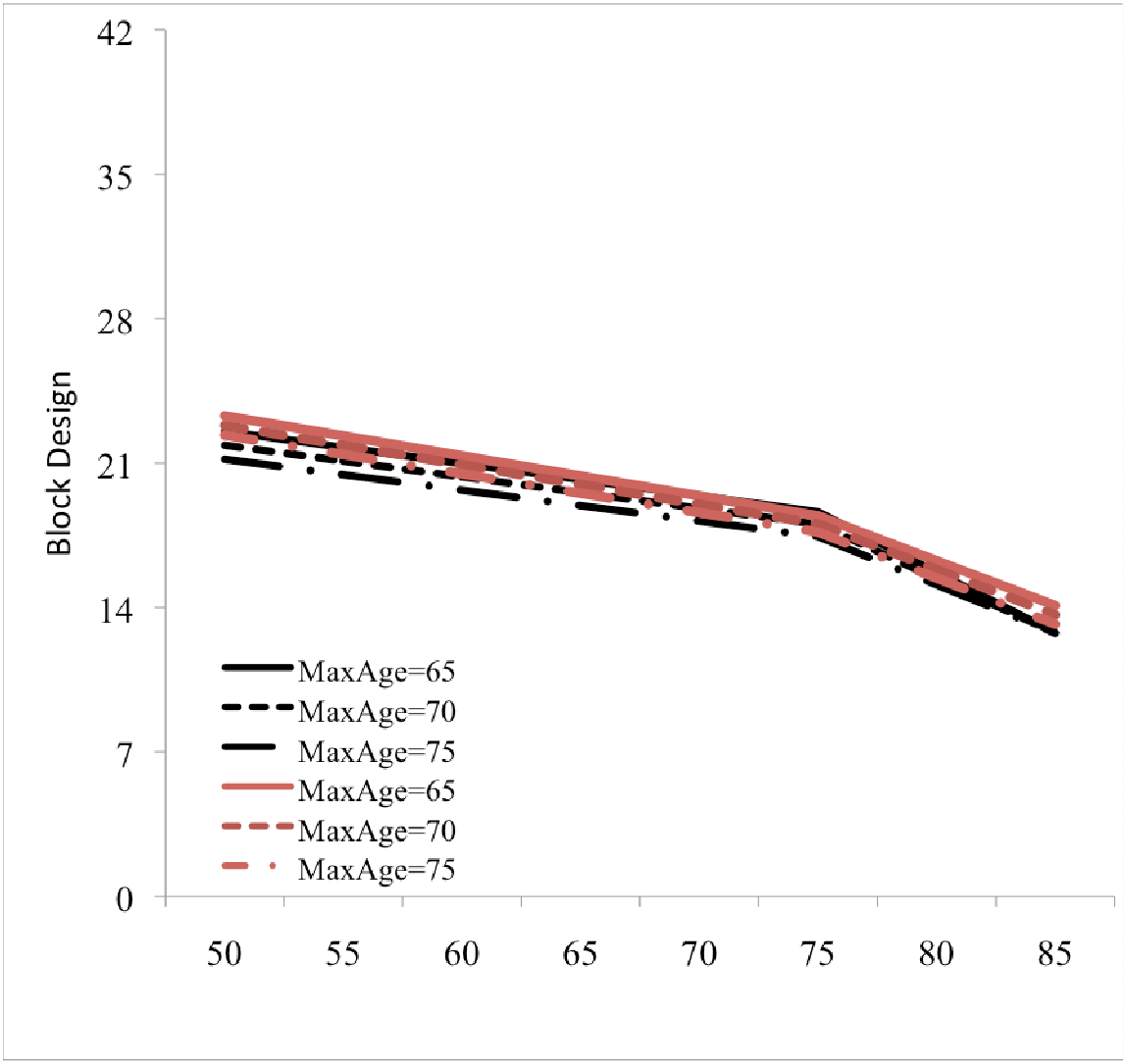

Figure 11: Maximum Negative Life Events and Symbol Digit Performance

Note. Lines in black indicate those at the averge logged MaxStress score. Lines in red indicate those with MaxStress scores one log unit higher than the average.

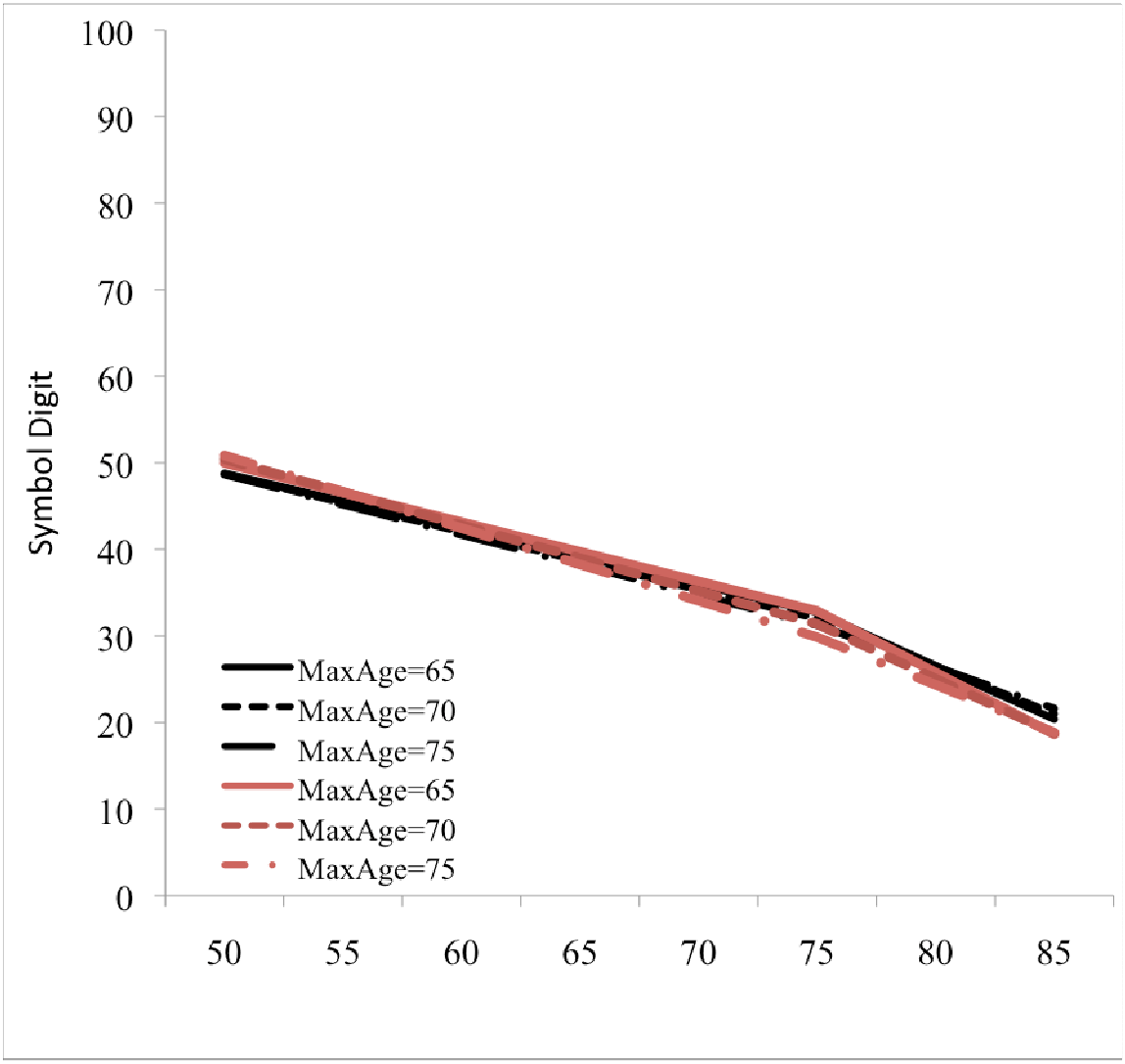

Figure 12: Maximum Negative Life Events and Synonyms Performance

Note. Lines in black indicate those at the averge logged MaxStress score. Lines in red indicate those with MaxStress scores one log unit higher than the average.

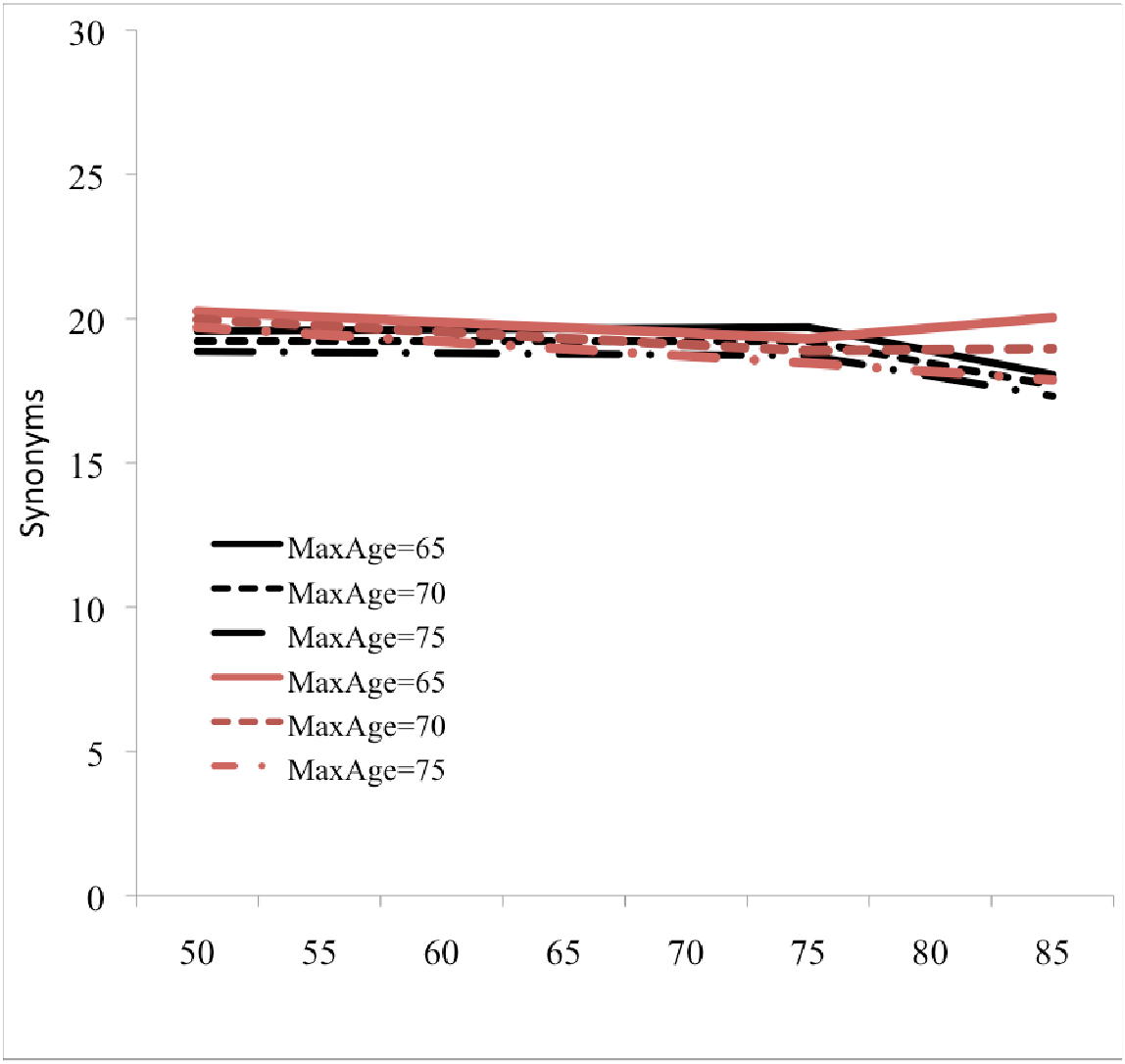

Figure 13: Maximum Negative Life Events and Thurtone Picture Memory Performance

Note. Lines in black indicate those at the averge logged MaxStress score. Lines in red indicate those with MaxStress scores one log unit higher than the average.