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To cite this article: Elana M. Gloger & Suzanne C. Segerstrom (2024) Repetitive thought, cognition, and systemic inflammation in the midlife in the United States study, *Psychology & Health*, 39:5, 651-669, DOI: [10.1080/08870446.2022.2092104](https://doi.org/10.1080/08870446.2022.2092104)

To link to this article: <https://doi.org/10.1080/08870446.2022.2092104>

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Repetitive thought, cognition, and systemic inflammation in the midlife in the United States study

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ABSTRACT

Objective: Poor cognition increases risk for negative health outcomes, and this may be explained by associations with systemic inflammation. Previously, amount of repetitive thought (Total RT) interacted with IQ to predict interleukin-6 (IL-6) in older adults. This study continued the investigation of repetitive thought (RT) as an element involved in the effect of cognition on inflammation.

Design: Participants ($N=164$) came from the Midlife in the United States Refresher project ($M_{age}=45.33$, $SD = 11.51$, ranges = 25–74; 48.2% female; 85% Caucasian). Cognition was assessed via telephone, inflammatory biomarkers (IL-6, C-reactive protein (CRP), and tumour-necrosis factor-alpha (TNF- α)) analysed after blood draw, and RT derived from daily diary data.

Results: Cognition significantly interacted with RT valence ($p=.009$) to explain CRP after covariate adjustment. Better cognition and more negative RT valence was associated with lower CRP ($\beta=-0.190$ [-.387, .008]). Worse cognition and more negative RT valence was associated with higher CRP ($\beta=0.133$ [-.031, .297]). No significant effects were found for IL-6 or TNF- α .

Conclusion: RT may interact with cognition to affect different inflammatory biomarkers. Those with worse cognition may benefit more from skills related to regulating thought than those with better cognition.

ARTICLE HISTORY

Received 22 June 2021
Accepted 15 June 2022


KEYWORDS

Repetitive thought; CRP; IL-6; systemic inflammation; MIDUS; cognition

Poor cognition increases risk for negative health outcomes, including smoking, hypertension, psychiatric disorders, poor health behaviours and premature mortality in older adults (Batty et al., 2007; 2007; Deary et al., 2010; Sachs et al., 2011). The relationship between cognition and health may be explained by systemic inflammation, which in turn increases risk for stroke, heart attack, and mortality (Deary et al., 2010; Franceschi et al., 2000; Harris et al., 1999; Luciano et al., 2009; Newman et al., 2009). Cognitive resources may interact with how people think about themselves and their worlds, and this relationship is important in the context of health. Repetitive thought (RT) – ‘the process of thinking attentively, repetitively, or frequently about oneself

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The data that support the findings of this study are openly available in NACDA at <https://doi.org/10.3886/ICPSR36532.v3>

 Supplemental data for this article can be accessed online at <http://doi:10.1080/08870446.2022.2092104>

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and one's world' – may relate to inflammation and health differently for people with different cognitive abilities (Segerstrom et al., 2003, 2017). The aim of the present study is to investigate RT as one element that may influence the effect of cognition on inflammation in adulthood.

Cognition and systemic inflammation

Inflammation is typically an acute, beneficial immune response to injury or infection (Segerstrom & Miller, 2004). However, stress, illness, or ageing can lead to chronic, systemic inflammation that increases risk for multiple morbidities and premature mortality (Franceschi et al., 2000; Franceschi & Campisi, 2014; Michaud et al., 2013; Stolp & Dziegielewska, 2009). Interleukin-6 (IL-6), C-reactive protein (CRP), and tumour necrosis factor alpha (TNF- α) are commonly studied and interrelated inflammatory biomarkers involved in the inflammatory cascade: IL-6 production is induced by TNF- α , and IL-6 and TNF- α regulate the synthesis of CRP, a liver protein that works with the innate immune system (Gabay & Kushner, 1999; Hopkins & Rothwell, 1995; Rothwell & Hopkins, 1995). These biomarkers may not be uniformly pro-inflammatory (Del Giudice & Gangestad, 2018). However, higher serum IL-6 and CRP predict health outcomes consistent with higher systemic inflammation (Ershler & Keller, 2000; Harris et al., 1999; Tuomisto et al., 2006). In the present report, IL-6, CRP, and TNF- α will be referred to as systemic inflammation, recognising that these cytokines may not be uniformly pro-inflammatory and that cytokines in blood are biomarkers of inflammation, which is a state of tissues.

One risk factor for elevated systemic inflammation, and increased risk for poor health outcomes, may be poor cognition. Lower childhood IQ is associated with higher systemic inflammation in middle and older adulthood (Hagger-Johnson et al., 2012; Luciano et al., 2009; Phillips et al., 2011). Among midlife and older adults, poorer cognition (including decline in global cognition, executive functioning, short-term and working memory, vocabulary, visual organisation and attention and task switching) was associated with higher IL-6, CRP, and TNF- α , and premorbid (i.e. resistant to age-related cognitive decline) cognition prospectively predicted IL-6 in older adults (Gimeno et al., 2008; Kuo et al., 2005; Marsland et al., 2006; Schram et al., 2007; Segerstrom et al., 2017; Tegeler et al., 2016). Whereas the previous investigations have focussed on the correlation between cognition and inflammation, little attention has been paid to interactions with other psychological constructs.

Repetitive thought

The advantages of better cognition for health may be influenced by RT. Discrete forms of RT include worry, rumination, and depressive rumination, as well as reflecting, processing, and planning. Across discrete forms, RT qualities can be empirically described with three orthogonal dimensions: Valence (a bipolar dimension anchored by positive and negative thought content), Purpose (a bipolar dimension anchored by searching, uncertain, or questioning thoughts and solving, certain, or affirming thoughts), and Total (the total amount of RT across all forms; Segerstrom et al., 2003, 2010). Poorer executive functions, less cognitive control, and cognitive inflexibility

were associated with more negatively valenced RT, whereas higher IQ was related to more Total RT (Davis & Nolen-Hoeksema, 2000; Mather & Knight, 2005; Segerstrom et al., 2010, 2017). Purpose has generally not correlated with cognition or health (Segerstrom et al., 2003, 2010).

The effects of RT dimensions on health vary. More Total RT, that is, the propensity to engage in RT of all types, correlated with more perceived stress, depression, and lower psychological well-being, but also with personal growth, better emotion coping, and better self-understanding (Segerstrom et al., 2003, 2010, 2015; Watkins, 2008). Negatively valenced RT correlated with markers of poor health, including poorer subjective health, lower cellular immunity, higher cortisol awakening response, higher risk for coronary heart disease, higher resting blood pressure and vulnerability to depression and anxiety; however, specific types may also assist with the future planning (Basevitz et al., 2008; Harrington & Blankenship, 2002; Kubzansky et al., 1997; Segerstrom et al., 1999, 2000; Watkins, 2008). Positively valenced RT types, such as emotional approach coping and trait reflection, are associated with successful cognitive processing and preparation, which is related to better health and lower systemic inflammation (Hoyt et al., 2020; Watkins, 2008; Woody et al., 2016).

Individual differences in RT may be influenced by cognition. Individuals with a higher IQ have the propensity to engage in both positive and negative thought, which may be related to advantageous, as well as detrimental, outcomes (Segerstrom et al., 2010). Conversely, individuals with poorer fluid intelligence and executive functions have the propensity to engage in more negatively valenced RT types, such as worry and rumination (Segerstrom et al., 2010). Neuroticism, or the propensity to experience negative affect, is related to engaging in, and being more reactive to, repetitive thoughts (Segerstrom et al., 2017, 2020). Similarly, better cognition may imply better emotion regulation, general coping, and less affective reactivity to RT (Watkins, 2008). That is to say, individuals at different levels of cognition may have different capacities to use different adaptive or maladaptive RT strategies, such as worry, rumination, or reflection, differently along the spectrum of positive to negative valence, and in different quantities, and these differences may have important implications for future health (Segerstrom et al., 2010, 2017; Watkins, 2008). Thus, relationships between cognition and RT dimensions, as well as robust associations between cognition and future health, implicate RT along the pathway from cognition to health.

In the previous prospective study of older adults, IQ moderated the relationship between Total RT and IL-6. High IQ (estimated IQ = 123) was associated with lower IL-6 regardless of Total RT. At average IQ (estimated IQ = 103), when Total RT was high, predicted IL-6 was equivalent to the low level associated with high IQ. When Total RT was low, predicted IL-6 was higher (by approximately 0.6 SD) (Segerstrom et al., 2017). Although RT Valence did not moderate the effect of IQ in that study, the interaction remains of interest.

The present study

Cognitive resources may interact with how people think about themselves and their worlds, and this relationship is important in the context of health. The present study tested this proposition among midlife adults who reported RT daily, using multiple

measures of systemic inflammation. Moderation and indirect effects were tested; one previous study (Segerstrom et al., 2017) found a significant moderating effect of IQ on the relationship between RT Total and IL-6; hence, moderation was the primary hypothesised effect. However, cognition may also influence systemic inflammation. Thus, if RT does not affect people with different cognitive resources differently, it may be involved in the cognition-systemic inflammation pathway; indirect effects were tested in support of this prospect.

The association between cognition and systemic inflammation was tested to confirm the well-established finding that better cognition would be related to lower systemic inflammation, which we pre-registered as an inflammatory marker composite, and that better cognition would be related to lower levels of each biomarker in post-hoc analyses.

The study tested the following pre-registered hypotheses:

1. Individuals with worse cognition but higher RT Total will have lower systemic inflammation; individuals with better cognition will have lower systemic inflammation regardless of the amount they engage in RT. That is, the relationship between RT Total and systemic inflammation will be moderated by cognition. Post-hoc analyses were conducted with each biomarker as an outcome.
2. Individuals with worse cognition but more positive RT will have lower systemic inflammation; individuals with better cognition will have lower systemic inflammation regardless of RT Valence. In other words, the relationship between RT Valence and systemic inflammation will be moderated by cognition. Post-hoc analyses were conducted with each biomarker as an outcome.
3. In the secondary analysis, in the absence of moderation, individuals with better cognition will report higher RT Total, more positive RT Valence, or both (in separately tested models of indirect effects), which will be associated with lower systemic inflammation. Post-hoc analyses were conducted with each biomarker as an outcome.

Method

Participants

Data were drawn from de-identified participants of the Midlife in the United States (MIDUS) Refresher Project, which collected health and well-being data in midlife adults between 2011 and 2014. The MIDUS Refresher project was approved by the University of Wisconsin Institutional Review Board and followed national, local, and global regulations (Ryff et al., 2017). Participants were selected by random-digit-dialing to noninstitutionalized, English-speaking adults in the United States. All participants completed the initial telephone interview and mail-in questionnaire. From there, participants were eligible to participate in the cognitive assessment over the phone. Participants were later eligible to participate in the daily diary and biomarker projects (Ryff et al., 2017). The MIDUS Refresher project was chosen because it is the only MIDUS project that asked 'How often did you think about this event' following questions about positive events in the Daily Diary Project (Ryff & Almeida, 2020), allowing complete assessment of the Valence dimension.

Initially, 261 participants met inclusion criteria for this study, including completion of the initial MIDUS telephone interview and mail-in questionnaire; cognitive assessment over the phone; IL-6, CRP, and TNF- α assayed following a fasted blood draw; and at least one positive and one negative event reported during at least one day of the 8-day daily diary study. Additional exclusion criteria were applied to reduce extraneous sources of immunomodulation: current smokers of cigarettes, cigars, pipes, use of chewing tobacco or snuff; current chemotherapy or radiation treatment; current pregnancy; a diagnosis of tuberculosis, thyroid disease, AIDS/HIV, or lupus/autoimmune disease; use of immunomodulatory prescription drugs (immunosuppressants, systemic steroids, cytotoxic drugs, TNF- α blockers, opioids) or use of more than two of the following: α or β blockers or ACE inhibitors, hormone replacement, thyroid supplements, or antidepressants, anxiolytic, hypnotics, or antipsychotics ($N=86$). One participant was excluded for BMI > 70 ($N=1$) and 10 participants were excluded for CRP > 10 mg/L, which can indicate acute infection ($N=10$; Pearson et al., 2003). However, eliminating participants solely due to CRP values > 10 mg/mL may reduce generalisability and may not only represent acute infection (Giollabhui et al., 2020). A sensitivity analysis included these participants; results were substantively unchanged (Supplementary material, Table 5). The final analytic sample ($N=164$) ranged in age from 25 to 74 years old ($M=45.33$, $SD=11.51$) and was 48.2% female, 70.1% married, and 85% White/Caucasian (Table 1).

A sensitivity analysis was conducted using the G*Power 3.1 to determine the minimum effect size that may be found in a regression model given a sample size of $N=164$, $\alpha=0.05$, and 80% power. The final sample would be sufficient to achieve 80% power to detect a small-to-moderate effect size of $\eta^2=0.048$. A similar effect size, $\eta^2=0.056$, characterised the interaction between IQ and total RT predicting IL-6 (Segerstrom et al., 2017).

Measures

Demographics

Participants provided demographic information during an initial 45-min telephone interview and a 108-page mail questionnaire, collected November 2011 to September 2014. Relevant demographic information included age, gender, race/ethnicity, BMI, and marital status.

Cognition

Cognition was assessed with the 20-min Brief Test of Adult Cognition by Telephone (BTACT) after completion of the initial telephone interview and mail questionnaire, February 2012 – September 2014 (Ryff & Lachman, 2021). The BTACT includes seven facets: Word List Recall, Digit Span Backward, Category Fluency, Red/Green Task, Number Series, Backward Counting, and Short-Delay Word List Recall (Lachman et al., 2014; Ryff & Lachman, 2021). The BTACT had $\alpha=0.82$ in healthy adults ($N=84$) ranging from 23 to 80 years old and $\alpha=0.71$ in the MIDUS Refresher BTACT subsample (Lachman et al., 2014; Ryff & Lachman, 2021). The BTACT composite score, including all seven factors, was used for analyses. However, five of the seven tasks loaded on an executive

Table 1. Descriptive statistics.

	Mean (SD)	Minimum	Maximum	Skewness
<i>Gender (%)</i>				
Female	48.2			
Male	51.8			
<i>Race (%)</i>				
White	84.8			
Black/African American	6.1			
Native American/Alaska Native	1.2			
Asian	1.2			
Other	6.7			
Age	45.33 (11.51)	25	74	.259
Body Mass Index	28.44 (6.3)	19.41	51.24	1.113
<i>Marital status (%)</i>				
Married	70.1			
Separated	1.2			
Divorced	11.6			
Widowed	3.7			
Never Married	13.4			
<i>Biomarker data collection site (%)</i>				
UCLA	34.1			
UW	31.7			
Georgetown	34.1			

functioning factor, with loadings 0.31–0.81, and only two of the tasks loaded on episodic memory, with loadings 0.88–0.89 (Lachman et al., 2014). This measure is therefore described as capturing general ‘cognition’ abilities, with an emphasis on executive functioning.

Systemic inflammation

Blood for measurement of inflammatory biomarkers was collected during a 24-h hospital stay at one of three sites (University of California, Los Angeles, University of Wisconsin, and Georgetown University), October 2012 to August 2016. Participants were eligible to participate in the biomarker project following completion of the initial telephone interview, mail-in questionnaire, and cognitive project (Weinstein et al., 2019). IL-6, CRP, and TNF- α were assayed following fasted blood draws after an overnight hospital stay. IL-6 was assayed with the Quantikine High-sensitivity ELISA (assay range: 0.156–10 pg/mL; inter-assay CV: 15.66%; intra-assay CV: 3.73%) at MIDUS BioCore Laboratory (University of Wisconsin, Madison, WI). TNF- α was measured by immunoelectrochemiluminescence using a V-plex Custom Human Cytokine Kit (assay range: 0.69–248 pg/mL; inter-assay CV: 7%; intra-assay CV: 3.19%) at MIDUS BioCore Laboratory (University of Wisconsin, Madison, WI). CRP was initially measured in plasma by a BNII nephelometer (assay range: 0.164–800 μ g/mL; inter-assay CV: 1.08–4.3%; intra-assay CV: 2.3–4.4%). Samples with very low levels of this biomarker were re-assayed using a high sensitivity assay (immunoelectrochemiluminescence). However, due to ‘technical difficulties’ of assaying plasma in the immunoelectrochemiluminescence kits, CRP was eventually assayed in serum (assay range: 0.014–216 μ g/mL; inter-assay CV: 4.72–5.16%; intra-assay CV: 2.2–4.1%; (Weinstein et al., 2019, p. Blood, Urine, Saliva Data Documentation, C5). The MIDUS BioCore Laboratory performed re-assay and harmonisation of these data (University of Wisconsin, Madison, WI).

IL-6, CRP, and TNF- α were log-transformed and standardised to Z-scores to satisfy the normality assumption for linear regression and for interpretation purposes (skewness of residuals before and after transformation: IL-6=4.16 to .762; CRP = 2.07 to .277; TNF- α =1.85 to .672). With regard to stability, single TNF- α and CRP measurements are likely to generalise to the surrounding months to years. However, IL-6 is less generalisable (Gloger et al., 2020).

Repetitive thought

RT data were collected as part of the MIDUS Refresher Daily Diary Project: National Study of Daily Experiences (NSDE), an 8-day study of self-reported daily experiences and their effect on daily living, collected October 2012 to November 2014 (Ryff & Almeida, 2020). Most daily diary participants completed all eight days (80.2%). Participants were eligible to participate in the daily diary following completion of the initial telephone interview and mail-in questionnaire. RT was assessed using responses to daily positive and negative event questions and their follow-ups (Table 2).

If the participant endorsed a positively valenced event, then they were prompted with a single follow-up question that asked how often they thought about that event that day and were measured on a scale of 0='Not at all' to 3='A lot'. The response to this question characterised how much positive RT that person endorsed that day. For negative events, participants were asked two questions during each daily diary questionnaire, each measured on a scale of 0='None of the time' to 4='All of the time', and items correlated $r=.54$ ($p < .001$). (Table 2). Positive and negative RT were calculated separately using mean responses to the valenced follow-up questions across the week for each participant. The negative RT items have been validated against a dimensional model of RT (Segerstrom et al., 2016). The Positive RT item, though not formally assessed for validity in previous MIDUS studies, meets the definition of RT (Segerstrom et al., 2003, 2016; Watkins, 2008).

To provide standardisation on a larger sample, RT variables were calculated and standardised on a subsample of the NSDE ($N=625$) that reported at least one positive and one negative event in the same diary day for at least one day. RT Total was calculated as a sum of the standardised ($M=0$, $SD = 1$) means (across events and days) of negative RT and positive RT. RT Valence was calculated as the difference

Table 2. Daily measures of RT in MIDUS National Study of Daily Experiences.

Daily questions about negative events:	Daily questions about positive events:
Did you have an argument or a disagreement today?	Did you have a positive interaction with someone today?
Did you avoid a disagreement today?	Did you have a positive experience at work?
Did anything happen at work or school?	Did you have a positive experience at home?
Did anything happen at home?	Did anything happen to a friend that was positive for you?
Did any discrimination happen to you?	Did anything else positive happen?
Did anything happen to a friend that stressed you?	
Did anything else [negative] happen to you?	
Daily negatively-valenced questions:	Follow-up question to endorsed positive events:
How often have you thought about personal problems/ concerns?	How much have you thought about this event?
How often have you thought about situations that upset you?	

between standardised mean values of negative RT and positive RT (i.e. RT Valence = negative RT – positive RT; a positive value for this variable indicates the participant had more negative RT than positive RT).

Data analyses

All analyses were conducted in the SPSS v27. The data analysis plan and hypotheses were pre-registered on Open Science Framework (Anonymized pre-registration link: https://osf.io/tncmr/?view_only=1cf254a8da9b49a8a9e8b72b01e1e489).

All pre-registered hypotheses were tested to satisfy the pre-registration. However, recent evidence suggests that unidimensional inflammatory composites may not be valid for biomarker data (Moriarity et al., 2021). Thus, all pre-registered analyses and results using the inflammation composite are included in the supplemental material (page 1), and analyses and results using individual biomarkers are reported.

Each log-transformed, standardised inflammatory biomarker (IL-6, CRP, TNF- α) was first regressed on the composite score from the BTACT (cognition) in separate models. Next, each biomarker was regressed on RT Total and RT Valence, centred around their sample mean, then on the interaction between cognition and RT Total and RT Valence. Models then included mean-centred age and BMI and centred statin use (yes/no; centred on proportion of participants reporting statin use). Bonferroni correction was implemented to control for Type I error ($\alpha = 0.05/3 = 0.17$). The Johnson–Neyman technique was used to identify regions of significance using the PROCESS macro in the SPSS.

The tests of indirect effects (cognition to RT Total or RT Valence to systemic inflammation) were conducted using PROCESS in the SPSS (Preacher & Hayes, 2004). The Bonferroni correction was implemented to control for Type I error ($\alpha = 0.05/3 = 0.17$). Mediation analyses in cross-sectional data should always be conducted and interpreted with caution as they generate biased estimates, risk Type I error, and may contradict stable, longitudinal estimates (Fairchild & McDaniel, 2017; Maxwell et al., 2011). Prior evidence suggests that premorbid cognition predicts systemic inflammation (Segerstrom et al., 2017). Further, the theoretical, temporal ordering of these variables, initially suggested that these cross-sectional, mediational analyses could be meaningfully interpreted and supported the choice to pre-register mediation analyses. However, due to the risks of bias in analysing and interpreting cross-sectional mediation analysis, all mediational results are included in Supplemental Materials (page 2) to satisfy pre-registration (for review, see Fairchild & McDaniel, 2017; Maxwell et al., 2011; Maxwell & Cole, 2007).

Results

Descriptive statistics

Table 3 contains correlations among study variables. To compare this sample with the values in the larger MIDUS subsamples, variables were transformed to Z score units and standardised on the entire relevant subsample. The study sample's cognition ($M_z = .53$) was statistically significantly better than the remainder of the BTACT

Table 3. Correlations among study variables (*N* = 164).

	1	2	3	4	5	6	7	8	9	10
1. Cognition	–									
2. Age	–.297 [–.431, –.151]	–								
3. BMI	–.219 [–.130, .177]	.024	–							
4. Statin use	.346 [.204, .474]	.079 [–.076, .229]	–							
5. Negative RT	–.078 [–.229, .076]	–.165 [–.310, .012]	.033 [–.121, .185]	.017 [–.137, .170]	–					
6. Positive RT	–.082 [–.023, .072]	.153 [–.000, .299]	.050 [–.104, .202]	.196 [.044, .339]	.043 [–.111, .195]	–				
7. RT Total	–.111 [–.260, .043]	.000 [–.153, .153]	.058 [–.096, .209]	.152 [–.001, .298]	.698 [.610, .769]	.746 [.669, .807]	–			
8. RT Valence	.007 [–.146, .160]	–.229 [–.369, –.079]	–.015 [–.168, .139]	–.135 [–.282, .019]	.664 [.569, .742]	–.719 [–.786, –.636]	–.073 [–.224, .081]	–		
9. TNF-α	.035 [–.119, .187]	.023 [–.131, .176]	.205 [.053, .347]	.268, .0339 [–.120, –]	–.048 [–.200, .106]	–.037 [–.189, .117]	–.058 [–.209, .096]	–.006 [–.159, .147]	–	
10. IL-6a	–.192 [–.335, –.040]	.274 [.126, .410]	.454 [.323, .568]	.077 [–.077, .228]	–.103 [–.252, .051]	.003 [–.0150, .156]	–.066 [–.217, .088]	–.074 [–.225, .080]	.157 [.004, .303]	–
11. CRPa	–.050 [–.202, .104]	.115 [–.039, .264]	.509 [.386, .614]	–.017 [–.170, .137]	–.102 [–.251, .052]	–.058 [–.209, .096]	–.109 [–.258, .045]	–.027 [–.180, .127]	.127 [–.027, .275]	.627 [.524, .712]

Note: TNF-α = tumour necrosis factor alpha; IL-6 = interleukin-6; CRP = C-reactive protein.

Bold font indicates *p* < .05.

^alog10 transformed values.

subsample ($t=7.05$, 95% CI [.407, .722], $p < .001$). In the study sample, 27% had at average or below-average cognition ($M_z \leq .00$). Negative RT for the study sample ($M_z = -.12$) was not statistically significantly different from the remainder of the NSDE subsample ($t = 1.06$, 95% CI [-.223, .067], $p = .29$). Positive RT for the study sample ($M_z = -.063$) was not statistically significantly different than the remainder of the NSDE subsample ($t = 0.31$, 95% CI [-.174, .126], $p = .75$). RT Total for the study sample ($M_z = -.18$) was not statistically significantly different from the remainder of the NSDE subsample ($t = 0.88$, 95% CI [-.331, .127], $p = .38$). In sum, except for better cognition, the study sample was generalisable to the MIDUS Refresher sample, which itself may only represent more White, female, well-educated individuals from the population (Radler & Ryff, 2010).

IL-6 and CRP ($r = .627$, 95% CI [.524, .712], $p < .001$), and TNF- α and IL-6 ($r = .157$, 95% CI [.004, .303], $p = .045$) were significantly positively correlated; CRP and TNF- α were not significantly correlated ($r = .13$, 95% CI [-.027, .275], $p = .11$). The relative independence of TNF- α in this sample further supports treating these biomarkers individually (Moriarty et al., 2021; see supplemental material, Table 5)

Better cognition was significantly correlated with lower IL-6 ($r = -.192$, 95% CI [-.335, -.040], $p = .014$). Cognition was not significantly correlated with TNF- α ($r = .035$, 95% CI [-.119, .187], $p = .66$) or CRP ($r = -.05$, 95% CI [-.202, .104], $p = .53$).

Hypotheses 1 and 2: Cognition and RT interactions

In unadjusted models, the interaction between cognition and RT Total was not significantly related to TNF- α ($\beta = -0.093$, 95% CI [-.249, .063], $p = .24$), IL-6 ($\beta = -0.024$, 95% CI [-.173, .126], $p = .76$), or CRP ($\beta = -0.028$, 95% CI [-.188, .132], $p = .73$). In adjusted models, the interaction between cognition and RT Total did not significantly relate to IL-6, TNF- α , or CRP (Supplementary material, Tables 3 and 4, and Table 4, respectively).

In unadjusted models, the interaction between cognition and RT Valence did not significantly relate to TNF- α ($\beta = 0.016$, 95% CI [-.142, .175], $p = .84$), IL-6 ($\beta = -0.029$, 95% CI [-.182, .126], $p = .71$), or CRP ($\beta = -0.14$, 95% CI [-.298, .019], $p = .08$). In the adjusted models, however, an interaction between cognition and RT Valence was significantly associated with CRP (interaction $\beta = -0.182$, 95% CI [-.319, -.046], $p = .009$; Table 4), but not IL-6 or TNF- α (Supplemental Tables 3 and 4, respectively). Figure 1 illustrates the relationship between RT Valence and CRP for individuals with better and worse cognition (± 1 SD). There were no statistically significant simple main effects of more negative RT Valence at better (+1 SD; $\beta = -0.190$, 95% CI [-.387, .008], $p = .060$) or worse (-1 SD; $\beta = 0.133$, 95% CI [-.031, .297], $p = .11$) cognition, although the significant interaction indicates that a relationship between more negative valence and higher CRP increased with poorer cognition and reversed with better cognition. The difference between better and worse cognition (Figure 1) was statistically significant when RT valence was less than $Z = -0.0122$, that is, in all regions in which RT was more positive than negative.

Exploratory post-hoc analyses were conducted in May 2021. In the previous multi-dimensional scaling, RT Valence was a bipolar dimension with negative RT and positive RT at its endpoints (Evans & Segerstrom, 2011; Segerstrom et al., 2003, 2010). In the

Table 4. Effects of cognition and RT in adjusted CRP models.

	Model 1 β [95% CI]	Model 2 β [95% CI]	Model 3 β [95% CI]	Model 4 β [95% CI]
<i>RT Total</i>				
Age	.140 [.000, .280]	.178 [.036, .332]	.166 [.024, .320]	.166 [.024, .320]
BMI	.514 [.381, .641]	.540 [.400, .673]	.542 [.408, .676]	.555 [.415, .689]
Statin use	-.106 [-.247, .035]	-.119 [-.261, .023]	-.098 [-.241, .045]	-.105 [-.249, .039]
Cognition		.118 [-.025, .261]	.103 [-.040, .246]	.107 [-.035, .249]
RT Total			-.115 [-.249, .020]	-.118 [-.252, .016]
Cognition \times RT Total				.069 [-.066, .204]
ΔR^2	.280	.012	.013	.005
ΔF (df)	20.736 (3, 160)	2.678 (1, 159)	2.852 (1, 158)	1.026 (1, 157)
<i>RT Valence</i>				
Age	.140 [0, .28]	.178 [.036, .332]	.179 [.024, .334]	.219 [.069, .369]
BMI	.514 [.381, .641]	.540 [.400, .673]	.540 [.400, .673]	.544 [.410, .678]
Statin Use	-.106 [-.247, .035]	-.119 [-.261, .023]	-.118 [-.260, .024]	-.132 [-.272, .008]
Cognition		.118 [-.025, .261]	.118 [-.025, .262]	.140 [-.002, .282]
RT Valence			.005 [-.148, .159]	-.028 [-.166, .109]
Cognition \times RT Valence				-.182 [-.319, -.046]
ΔR^2	.280	.012	.000	.03
ΔF (df)	20.736 (3, 160)	2.678 (1, 159)	.005 (1, 158)	7.008 (1, 157)

Notes: RT, repetitive thought; BMI, body mass index.

Bold font indicates $p < .0125$ (Bonferroni adjusted $\alpha = .05/4$).

present sample, this did not hold empirically (negative and positive RT $r = -.073$, $p = .35$). Therefore, negative RT and positive RT were mean-centred and entered separately (rather than as the calculated RT Valence variable) into the model testing for an effect of RT Valence on cognition and CRP. Entering negative RT and positive RT into the same model simultaneously controls for RT Total. The interaction between cognition and Positive RT on CRP was statistically significant ($\beta = 0.164$, 95% CI [.029, .299], $p = .018$), but the interaction between cognition and negative RT on CRP was not ($\beta = -.068$, 95% CI [-.203, .067], $p = .321$). There was a statistically significant simple main effect of better cognition at higher positive RT (+1 SD; $\beta = .303$, 95% CI [.0931, .5136], $p = .005$) but not lower positive RT (-1 SD; $\beta = -.0395$, 95% CI [-.225, .146], $p = .68$). The difference between better and worse cognition was statistically significant when positive RT was greater than $Z = .0965$, that is, when RT was more positive than average.

Hypothesis 3: Testing indirect effects

Cognition was not significantly correlated with RT Total ($r = -0.11$, 95% CI [-.259, .044], $p = .16$) or RT Valence ($r = -0.007$, 95% CI [-.160, .146], $p = .93$), so further analyses were not performed.

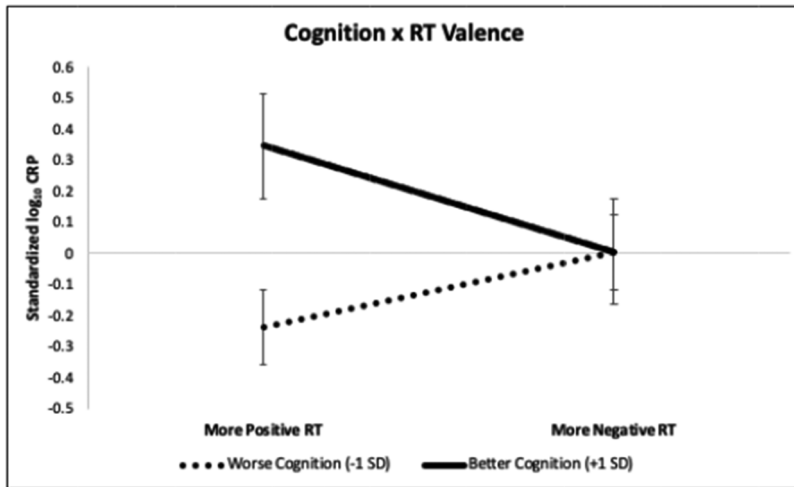


Figure 1. Standardised log₁₀ C-reactive protein for individuals 1 SD above (More Negative RT) and 1 SD below (More Positive RT) RT Valence sample mean at better (+1 SD) and worse (-1 SD) cognition. Model estimates are shown with their standard errors; CRP=C-reactive protein; RT=repetitive thought.

Discussion

Better cognition has been related to lower systemic inflammation, and repetitive thought may play a role (Segerstrom et al., 2017). In the present study, individuals with better cognition had lower IL-6 but no other biomarkers of systemic inflammation. Cognition moderated the relationship between RT Valence and CRP, a liver protein that works with the innate immune system and can act as an indicator of chronic, systemic inflammation and risk for poor health outcomes. With poorer cognition, more positively valenced RT was associated with lower CRP; the opposite was true with better cognition. However, cognition did not significantly interact with RT Total to influence IL-6, as previously found, and the nature of the significant interaction found in the present study was different from the previous study. In the present study, there was not a statistically significant simple main effect of RT Valence at either level of cognition on CRP, but the slopes differed from each other. Previously, there was a simple main effect of RT Total on IL-6 only at lower estimated IQ (Segerstrom et al., 2017).

Together, these findings suggest that cognition may interact with RT differently to affect different inflammatory markers. Similarly, trait-like, retrospectively reported RT may interact with cognition in a different way from RT reported daily. The present study measured cognition with the BTACT, which largely captured executive functioning and fluid intelligence rather than crystallised intelligence or IQ (Lachman et al., 2014; Ryff & Lachman, 2021). Crystallised intelligence is resistant to ageing and organic changes and has been related to more Total RT (Segerstrom et al., 2010, 2017). More fluid EF has been previously related to the valence, rather than the amount, of RT (Blair & Spreen, 1989; Segerstrom et al., 2010). It may be that two cognitive systems are functioning differently: RT Valence may be related to EF and fluid intelligence,

whereas RT Total may be related to crystallised intelligence. In turn, these two systems may relate to circulating biomarkers of systemic inflammation, with the dominant influence depending on sample age, average cognitive ability, or other demographic factors.

The dimensional model of RT is similar for older and younger adults (Segerstrom et al., 2010). However, older adults differ from younger and middle-aged adults in executive functioning and cognitive abilities and experience an increase in systemic inflammation over time (i.e. 'inflammaging') that directly contributes to the development of age-related disease. How RT relates to the cognition-to-health pathway may differ in young, midlife, or older age and potentially influenced by other health phenomena (Franceschi & Campisi, 2014; Kray et al., 2004; Prull, 2000; Reed et al., 2020; Segerstrom et al., 2017). Significant findings related to cognition, RT, and health in an advantaged population, such as the present sample, highlights the importance of broadening the consideration of these effects to populations with less advantage. Cognition and RT may have stronger or different effects on biomarkers of long-term health in less-advantaged populations at higher risk of negative effects of health inequities and may necessitate different, population-wide solutions (Marmot et al., 1997; Paradies et al., 2015; Williams & Mohammed, 2009).

In exploratory post-hoc analyses, positive RT drove the interaction effect between cognition and RT Valence on CRP. Positive and negative RT were poles of a single RT Valence dimension in multidimensional scaling of trait and 'lately' measures (Evans & Segerstrom, 2011; Segerstrom et al., 2003, 2010) but were orthogonal in the present study. The finding implies that positively valenced RT such as reminiscing, processing, or reflecting may provide benefit above and beyond the absence of negatively valenced RT such as worry or rumination. Individuals with worse cognition may benefit more (with regard to CRP) from positively valenced thought content. Individuals with better cognition may already have more positive health behaviours and better capacity to self-regulate (Hofmann et al., 2012; Scheier & Carver, 1987). In turn, positive health behaviours, such as more physical activity and less smoking, are associated with lower systemic inflammation (O'Connor et al., 2009). On the other hand, individuals with poorer cognitive ability may need environmental structures and contingencies that do not rely on exerting self-regulation (Hofmann et al., 2012; Milyavskaya & Inzlicht, 2017). For individuals with this vulnerability, more positive RT may buffer against other risks. Continued investigation should focus on positive RT as another form of health behaviour that may influence systemic inflammation and health.

It is also possible that cognition does not influence systemic inflammation, and systemic inflammation may instead influence cognition. For example, higher levels of CRP and more negative RT valence may combine to predict poorer cognition. Consistent with this interpretation, neuroticism, a personality facet characterised by a disposition for negative affect, combines with neuropathology (e.g. morphological changes, tau protein tangles) to predict risk for Alzheimer's disease (Segerstrom, 2020). The possibility that inflammation was exerting a causal effect on cognition could not be ruled out with the present data (Marioni et al., 2009; Mooijaart et al., 2013; Schram et al., 2007). Future longitudinal research should investigate the directionality of these mechanisms to better understand the cause, and potential modifiable risk factors, influencing increased systemic inflammation and cognitive decline.

Strengths of the present study included a large age range, multiple biomarkers of systemic inflammation, and daily RT measurement. However, there were also limitations. First, the inclusion criteria for this study required that participants complete the MIDUS survey, Cognitive Project, Daily Diary Project (National Study of Daily Experiences), Biomarker Project, and meet exclusion criteria (necessary to avoid immunomodulatory confounding on biomarker data). From a sample of 3,577 people, only 164 participants fit these criteria. Statistical comparisons of the study sample with other subsamples and the full MIDUS Refresher sample revealed that the present sample had better cognition but similar RT. Although selection bias may be at play, this sample is otherwise representative of the MIDUS Refresher sample. Next, positively and negatively valenced RT were not measured in the same way in the daily diary and were not strictly parallel for the purpose of calculating RT Valence. Finally, serum CRP and serum TNF- α are stable across weeks and months from single-time point measurements and thus generalise to the time period around a single measurement (for review, see Gloger et al., 2020; Navarro et al., 2012). However, serum IL-6 requires 3 measurements to achieve adequate generalisability to longer periods of time, and as such, findings for IL-6 may be over- or underestimates (Gloger et al., 2020; Navarro et al., 2012).

Conclusion

Immune function may constitute an important element of the pathway between cognition and health across the lifespan (Batty et al., 2007; 2007; Calvin et al., 2011). The present study asked what dimension(s) of RT may intervene along this pathway to influence systemic inflammation and for whom? The finding that cognition and RT interacted to explain CRP indicates that for this sample, positive RT was most beneficial for people with poorer cognition. The relationships between RT dimensions and fluid and crystallised intelligence and their relationships to health and immune function are a fruitful direction of study.

Author contributions

Study conceptualisation and report writing were completed by Elana Gloger and Suzanne Segerstrom. Data preparation, and data analysis were completed by Elana Gloger with mentorship and guidance from Suzanne Segerstrom.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The Midlife in the United States Study investigators received funding from the following sources: John D. and Catherine T. MacArthur Foundation Research Network, National Institute on Ageing (P01-AG020166), National Institute on Ageing (U19-AG051426), NIH National Centre for Advancing Translational Sciences (NCATS) Clinical and Translational Science Award (CTSA) program as follows: UL1TR001409 (Georgetown), UL1TR001881 (UCLA), 1UL1RR025011 (UW).

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