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Inhibition is associated with metabolic syndrome and depression through inflammation

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Abstract

Inhibition is the ability to stop one's self from responding, or paying attention, to tempting/distracting stimuli or thoughts. Those with poor inhibition are at greater risk of depression and a variety of diseases of older adulthood than those with better inhibition. Inflammation may be a mechanism underlying these links. A total of 840 participants from the Midlife in the United States study completed a neuropsychological measure of inhibition, a self-report measure of depressive symptoms, and a blood draw. Results indicated that poor inhibition was associated with high interleukin-6 (IL-6). Inhibition was indirectly associated with metabolic syndrome incidence and depressive symptoms through IL-6. Findings suggest that IL-6 may be a mechanism linking inhibition with metabolic syndrome and depression.

KEYWORDS

depression, inflammation, inhibition, metabolic syndrome

1 | INTRODUCTION

Metabolic syndrome (MetS) and depression are notable health concerns that impact many adults in the United States (Greden, 2003; Potenza & Mechanick, 2009). Those with poor cognitive abilities are at greater risk for depression (e.g., Joorman, 2010) and a variety of diseases of older adulthood (e.g., Gottfredson, 2004). Inflammation has been implicated as one mechanism underlying these links (e.g., Esposito & Giugliano, 2004). The aim of this study was to evaluate how inhibition, an important aspect of cognitive ability, is associated with inflammation, MetS, and depressive symptoms.

Inhibition is defined as the ability to stop one's self from responding, or paying attention, to tempting/distracting stimuli or thoughts (Diamond, 2013). Inhibition is a cognitive ability, along with updating/monitoring of information in working memory and cognitive flexibility (i.e., attention switching/shifting), within the broader network of cognitive skills termed *executive functioning* (Suchy, 2009). According to the neurovisceral integration model (e.g., Thayer & Lane, 2009), a common reciprocal inhibitory cortico-subcortical neural circuit

in the prefrontal cortex links inhibition to physical health; however, the theorized mechanisms underlying this association have not been adequately studied.

Better inhibition is associated with improved self-regulation and lower stress than poor inhibition (e.g., Bridgett, Oddi, Laake, Murdock, & Bachmann, 2013). Indeed, those with poor inhibition are more likely to experience stressful thoughts, as well as have greater difficulty shifting attention away from stressful thoughts, than those with better inhibition (e.g., Joorman, 2010). Those with high stress demonstrate enhanced inflammation in comparison to those who are less stressed (e.g., Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013). There are a variety of pathways by which inflammation enhances MetS risk. Inflammation promotes insulin resistance and endothelial dysfunction, two important risk factors for MetS (Esposito & Giugliano, 2004). MetS is characterized by meeting criteria for three of five symptoms (i.e., large waistline, high triglyceride level, low high-density lipoprotein cholesterol level, high blood pressure, and high fasting blood sugar). Interestingly, those who are diagnosed with MetS perform poorly on measures of inhibition in comparison to those without the

syndrome (Yates, Sweat, Yau, Turchiano, & Convit, 2012). Although prospective data have not been provided, the focus in the literature has been on poor inhibition being a consequence of MetS as opposed to a risk factor. Longitudinal evidence has linked childhood self-control, which is closely related to inhibition, with global health in adulthood (Moffitt et al., 2011) indicating the potential for a bidirectional pathway.

Those with poor inhibition tend to ruminate (i.e., focus attention on distress) more often than those with better inhibition, which promotes inflammation (Murdock et al., 2016) and depression (Joorman, 2010). Therefore, inhibition may be a common underlying risk factor for both MetS and depression; however, such constructs have not been well integrated in the literature. We sought to evaluate inflammation as a potential mechanism linking inhibition with MetS and depressive symptoms. It was hypothesized that poorer inhibition would be associated with higher interleukin-6 (IL-6). Furthermore, it was expected that IL-6 would partially mediate the association between inhibition and MetS, as well as the association between inhibition and depressive symptoms.

2 | METHODS

2.1 | Participants and procedure

Data were obtained via the Midlife in the United States (MIDUS) study, a large-scale research study examining predictors of mental and physical health in middle-aged adults. Variables were taken from the Cognitive and Biomarker Projects of the MIDUS study. The Cognitive Project was conducted over the phone, and the Biomarker Project involved an in-person visit to Madison, WI; Los Angeles, CA; or Washington, DC (see Lachman, Agrigoroaei, Tun, & Weaver, 2014). A total of 1,054 individuals participated in the Biomarker Project. Those who did not complete the measure of inhibition described below were removed from the analyses ($n = 214$), yielding a final sample of 840 participants. No significant differences were identified when comparing individuals who had complete versus incomplete data. The Biomarker Project was conducted an average of 23.39 months ($SD = 14.28$) after the Cognitive Project.

3 | MEASURES

3.1 | Inhibition

As described in prior work (Tun & Lachman, 2008), a Stop and Go Switch Task was utilized as a measure of inhibition in the Cognitive Project of the MIDUS study. The Stop and Go Switch Task consisted of three conditions. In the normal condition, which consisted of 20 trials, the experimenter instructed the participants to respond by stating *stop* after being presented with the stimulus words *red* and *go* after being presented with the stimulus word *green*. In the reverse condition, also consisting of 20 trials, participants were asked to respond with the word *go* when presented with the stimulus words *red* and *stop* after being presented with the stimulus word *green*. For the mixed task condition, consisting of 32 trials, participants were provided with a cue of

normal or *reverse* before being presented with a stimulus word. Participant response times were measured in milliseconds. Average response times were calculated across the reverse and mixed task conditions to form an overall indicator of inhibition. Mean response times were reverse coded in order to generate an indicator in which a higher score is associated with better inhibition.

3.2 | Inflammation

Inflammatory markers were determined via immunoassays following the Biomarker Project. Specifically, serum IL-6 levels were determined via Quantikine® High-sensitivity ELISA kit #HS600B (R&D Systems, Minneapolis, MN). Values were log transformed to normalize the distribution of scores.

3.3 | MetS

The criteria published by the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) were utilized to determine a diagnosis of MetS in this study. Specifically, participants met criteria for a diagnosis if they had three or more of the following symptoms: (a) waist circumference greater than 88 cm for females or greater than 102 cm for males, (b) triglycerides greater than 150 mg/dl, (c) high-density lipoprotein cholesterol levels below 50 mg/dl for women or below 40 mg/dl for males, (d) blood pressure $\geq 130/85$ or taking medication for high blood pressure, and (e) fasting glucose ≥ 110 mg/dl. A symptom count was also utilized for each participant in ancillary analyses with a range of 0 to 5. All indicators of MetS were evaluated during the Biomarker Project.

3.4 | Depression

Participants completed the 20-item self-report version of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) during the Biomarker Project. The CES-D is a widely utilized measure of depression in which participants are asked to indicate the degree to which they had experienced symptoms of depression (e.g., feeling sad) on a scale ranging from 1 (*rarely*) to 4 (*most or all of the time*). Internal consistency for the CES-D was good in this study ($\alpha = .88$).

3.5 | Demographics

Participant age, gender, ethnicity, and smoking history were collected via clinical questionnaires and were included as covariates in the analyses described below. Body mass index (BMI) was calculated by measuring height and weight of participants during the Biomarker Project, which was also included as a covariate.

4 | RESULTS

Approximately 32.3% ($n = 271$) of the sample met criteria for MetS and 12.1% ($n = 102$) met criteria for clinical depression (i.e., CES-D score of 16 or greater; see Supporting Information Table S1 for descriptive statistics for study variables). In bivariate correlations, better inhibition was associated with lower IL-6 and fewer symptoms of MetS.

Furthermore, greater IL-6 was associated with a higher MetS symptom count and likelihood of meeting criteria for MetS. Higher IL-6 was also associated with higher depressive symptoms (see Table S2 for a table containing all bivariate correlations for study variables). As seen in Figure 1 in the full structural equation modeling (SEM) model, poorer inhibition was associated with increased IL-6, and greater IL-6 was associated with greater likelihood of meeting criteria for MetS. Moreover, inhibition was indirectly associated with MetS and depressive symptoms through IL-6. Importantly, higher participant age ($\beta = .24, p < .001$), BMI ($\beta = .33, p < .001$), and more time between the cognitive and biological assessments ($\beta = .14, p = .002$) were associated with greater IL-6. Participant SES ($\beta = -.35, p < .001$), ethnicity ($\beta = -.08, p < .05$), and BMI ($\beta = .48, p < .001$) were associated with MetS incidence. Participant age ($\beta = -.16, p < .001$) and smoking history ($\beta = .12, p < .001$) were associated with self-reported depressive symptoms. Findings were consistent in ancillary analyses when using the MetS symptom count (range 0–5) as the dependent variable in the full model.

The fit of the model in Figure 1 was good; however, model fit was improved when removing the direct path from inhibition to MetS, $\chi^2(2, N = 840) = 1.15$; comparative fit index = 1.00; normed fit index = 1.00; root mean-square error of approximation = .01; 90% confidence interval [0, 0.09]. Additionally, a reversed indirect effect model (i.e., IL-6 being associated with inhibition via depressive symptoms and MetS) was evaluated. In this model, MetS and inhibition were not indirectly associated through IL-6 (.01; 95% CI [-.01, .01]). Moreover, depressive symptoms and inhibition were not indirectly associated through IL-6 (.01; 95% CI [-.01, .01]).

5 | DISCUSSION

MetS and depression are notable public health concerns (Greden, 2003; Potenza & Mechanick, 2009). This study sought to evaluate how inhibition and inflammation were related to MetS and depression. Poor inhibition was indirectly associated with a greater likelihood of meeting criteria for MetS through higher IL-6. This finding contributes to the literature in novel ways. For example, low

inhibition was associated with higher levels of IL-6, consistent with the neurovisceral integration model (e.g., Thayer & Lane, 2009). These data can be integrated into existing biopsychosocial models of health as the brain and the immune system clearly have bidirectional communication networks (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Accordingly, it may be that poor inhibition is associated with IL-6, which, if chronic, can exacerbate inhibition deficits leading to further emotional, physiological, and behavioral challenges that enhance inflammation. This cycle may begin prior to meeting criteria for MetS and continue after a diagnosis has been made. However, given the bidirectional associations identified in prior work, such an explanation is speculative and should be evaluated in future longitudinal research.

Inhibition was also indirectly associated with depression through IL-6 in this study. These findings are consistent with the available literature indicating that chronic inflammation promotes depressive symptoms (e.g., reduced social and physical activity, decreased appetite, and sleep difficulties; Dantzer et al., 2008); however, depression and inflammation feed off one another in a bidirectional negative feedback loop (Kiecolt-Glaser, Derry, & Fagundes, 2015). That is, depression clearly enhances inflammation (Fagundes et al., 2013) and chronic inflammation promotes depression (Dantzer et al., 2008). Prior research indicates that childhood self-control, which is closely related to inhibition, predicts global health in adulthood (Moffitt et al., 2011). Therefore, low inhibition and inflammation may trigger a cascade of biopsychosocial effects that are associated with poor health in adulthood, although longitudinal work evaluating the interplay between inhibition, inflammation, and health is clearly needed to determine causality.

The cholinergic system is one pathway through which inhibition may be related to MetS and depressive symptoms (Hasselmo & Sarter, 2011). Indeed, poor inhibition is associated with decreased alpha7-nicotinic acetylcholine receptor (alpha7nAChR) activity (Logue & Gould, 2014). The vagus nerve modulates immune responses, including inflammation, through the nicotinic anti-inflammatory pathway that is largely dependent on alpha7nAChR activation (Ulloa, 2005). Stimulation of immune cells' alpha7nAChRs reduces proinflammatory cytokine production (e.g., de Jonge & Ulloa, 2007).

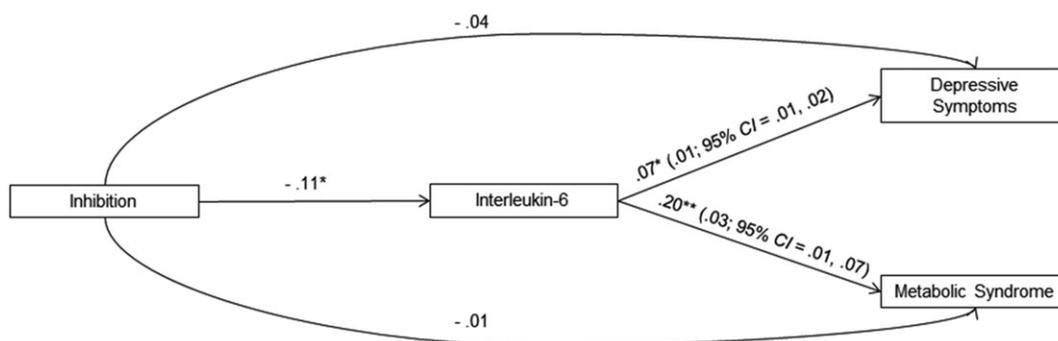


FIGURE 1 A model of associations between inhibition, interleukin-6, metabolic syndrome, and depressive symptoms. Indirect effects, and associated 95% confidence interval, using 5,000 bootstrap samples are presented in parentheses. Control variables (not pictured) include participant age, gender, ethnicity, body mass index, smoking history, and the time lag between the cognitive and biological assessments. Tests of model fit: $\chi^2(1, N = 840) = 2.02, p = .16$; comparative fit index = .98; normed fit index = .97; root mean-square error of approximation = .04, 90% confidence interval = 0, 0.11. * $p < .050$. ** $p < .001$

Accordingly, poor inhibition should be associated with elevated levels of key proinflammatory cytokines such as IL-6 and tumor necrosis factor alpha (TNF-alpha) through the nicotinic anti-inflammatory pathway (Thayer & Lane, 2009), an area for future investigation. Heightened IL-6 and TNF-alpha are known to be associated with an increased likelihood of meeting criteria for MetS and clinical depression (Berthold-Losleben & Himmerich, 2008; Esposito & Giugliano, 2004).

This study is limited by the predominantly white sample. Intermediate mechanisms that may explain the association between inhibition and inflammation (i.e., parasympathetic and sympathetic activity, self-regulation, and health behaviours) were not evaluated in the present analysis, which is an important direction for future research. Furthermore, the strength of effects identified in this study are small; however, as has been demonstrated in prior work, small effect sizes can have remarkable implications at the population level (Martell, Lane, & Emrich, 1996). A small portion of the current sample met criteria for clinical depression. Accordingly, it would be useful to examine whether this study findings can be replicated in a sample of people who meet criteria for clinical depression. Although inhibition was measured prior to other primary study variables, this study was not longitudinal. Accordingly, causality cannot be determined.

6 | CONCLUSIONS

In summary, inhibition was indirectly associated with MetS and depressive symptoms through IL-6. These findings provide support for the premise that inflammation may be an underlying mechanism linking inhibition with physiological and emotional outcomes. Such information is useful for designing future research studies targeting improved prevention and intervention of MetS and depression.

CONFLICT OF INTEREST

None

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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