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Does general intelligence moderate the association between inflammation and psychological distress?

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ABSTRACT

Research has shown that inflammation is implicated in the pathogenesis of mental health disorders, but not all individuals with such disorders have raised inflammatory markers. This study examined whether general intelligence may be a protective factor for 9666 adults aged 18–97 with elevated inflammation, measured with C-reactive protein (CRP), using data from the UK's Understanding Society. In multigroup analyses for males and females, multiple linear regression was used to model psychological distress dependent upon CRP, adjusting for a host of possible confounders including alcohol consumption, smoking status, history of cardiovascular disease or diabetes, physical exercise and obesity. Moderation by intelligence was tested with a multiplicative interaction term. Results showed that, in adjusted models, CRP was related to an increase in psychological distress in males ($\beta = .049$) but not females. Furthermore, intelligence moderated the effect of CRP on psychological distress in males ($\beta = -.037$), such that males with higher CRP levels were at lower risk with increased intelligence. In conclusion, general intelligence may protect male adults from the negative effects of inflammation on psychological distress.

1. Introduction

The link between inflammation and psychological distress was first made by Robert Smith (1991). His "macrophage theory of depression" proposed that enhanced production of proinflammatory cytokines is related to the pathogenesis of depression. Indeed, empirical studies have found significantly higher levels of circulating inflammatory markers including proinflammatory cytokines [e.g., interleukin 6 (IL-6)], as well as C-reactive protein (CRP), an acute phase protein synthesized in the liver, among clinical patients with psychiatric disorders, especially depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Kiecolt-Glaser, Derry, & Fagundes, 2015). Although few longitudinal studies have examined inflammatory markers and psychiatric problems (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014), a much-cited meta-analysis (Howren, Lamkin, & Suls, 2009) of cross-sectional studies showed that effect sizes for depression are moderate, around $d = 0.25$ (for IL-6) and $d = 0.15$ (for CRP).

There are three main pathways through which inflammation may bring about mental health problems, mainly evidenced by animal models (Dantzer et al., 2008; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Miller, Maletic, & Raison, 2009). Firstly, inflammation has been found to reduce the availability of serotonin and other neurotransmitters in the brain, associated with depression and anxiety. Secondly, it may be related to activation of the hypothalamic-pituitary-adrenal (HPA) axis. Thirdly, it may cause oxidative stress dysfunction in the brain including abnormal total antioxidant capacity, antioxidants, free radicals, oxidative damage and autoimmune response products (Liu et al., 2015 for a review). These effects may contribute to impaired mood, cognition and perception, all of which are associated with depression (Miller et al., 2009).

Although inflammation may be a risk factor for depression, not everyone with high levels of inflammatory markers develop depressive symptoms (Dantzer et al., 2008; Kiecolt-Glaser et al., 2015). Raison and Miller (2011) indicated that inflammatory markers are noticeably higher in roughly a third of depressed patients compared to comparison participants who are non-depressed. Therefore, inflammation is not required nor sufficient to bring on depressive symptoms (Glassman & Miller, 2007).

Intelligence is one individual characteristic that may be associated with such emotional resilience to inflammatory responses to illness, injury or stress, yet, to our knowledge, there has been no attempt to explore this possibility. There are two main reasons why we might see a moderating role for intelligence. Firstly, intelligence has been shown to enhance individuals' care of their own health and well-being through effective learning and good reasoning skills (Deary, Weiss, & Batty, 2010; Deary, Whiteman, Starr, Whalley, & Fox, 2004). Such skills are

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useful in protecting against depressive symptoms through positive behaviours such as exercise, a healthy diet as well as minimizing alcohol and drug consumption. They are also important for adhering to complex treatment regimens to manage appropriately longstanding or other illnesses and physical conditions, also associated with depression. Secondly, stress brought on by negative life events is a cause of inflammation. Individuals with higher intelligence have been found to cope better with such stressors through superior problem-solving abilities and self-regulatory functioning (Breslau, Lucia, & Alvarado, 2006; Masten et al., 1999), which can reduce depressive symptoms or psychological distress, in general.

In the present study, we used data from Understanding Society, an annual longitudinal survey of around 40,000 households in the UK, to explore if, indeed, intelligence buffers the effect of inflammation (measured with CRP) on psychological distress (measured with the General Health Questionnaire). We adjusted for selected characteristics to rule out confounders, including education (Khandaker et al., 2014), age (Franceschi et al., 2000), history of cardiovascular disease or diabetes, smoking status, alcohol consumption, physical exercise and obesity. Elevated inflammation characterises several disorders and diseases (e.g., cardiovascular disease, diabetes, metabolic syndrome) related to a higher risk for depression or psychological distress (Shelton & Miller, 2010). Alcohol dependence and smoking have been found to be comorbid with depression as well as have inflammatory effects (Leclercq, De Saeger, Delzenne, de Timary, & Stärkel, 2014). Physically active individuals have lower inflammatory markers than their sedentary counterparts (Lancaster & Febbraio, 2014) and exercise's benefits for reductions in depressive or anxiety symptoms may be via lowering inflammation levels (Gleeson et al., 2011). Moreover, obesity is associated with depression (Luppino et al., 2010) and has been characterised as a state of chronic inflammation (Shelton & Miller, 2010).

We explored these relationships in males and females separately. Females are more at risk of psychological distress as well as of persistently high levels of CRP (Ishii et al., 2012). On the other hand, males are more susceptible than females to the effects of inflammation on psychological distress (Ramsey et al., 2016). There may be an increased susceptibility among males to dysregulation of acute inflammation and pro-inflammatory immune response (Fairweather, Frisancho-Kiss, & Rose, 2008) and greater proneness to infection. Furthermore, there may be different pathways from stress to inflammation for males and females (Toker, Shirom, Shapira, Berliner, & Melamed, 2005). As well as inflammation and psychological distress, cognitive ability has been shown to differ by gender, especially over time, albeit not consistently or in the same direction. Some studies suggest that women have greater age-related declines (Karlamangla et al., 2009; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008; Wu et al., 2012). Other studies have found that men do (Salthouse, 2014; Zelinski & Gilewski, 2003). Still other research shows similar patterns in both (Ferreira, Ferreira Santos-Galduróz, Ferri, & Fernandes Galduróz, 2014).

2. Method

2.1. Sample

Understanding Society is an annual longitudinal survey of over 40,000 households (at wave 1) in all four UK countries. It comprises the larger General Population Sample (GPS), a stratified (by Government Office Region [GOR], population density and minority ethnic density) clustered (within postal sectors) random sample of households recruited in 2009–2010 (wave 1) and a smaller component from the preexisting British Household Panel Survey (BHPS). There have been six waves of interviews thus far. Biomedical measures including CRP and body mass index were taken during a nurse visit approximately five months after the main wave 2 interview (GPS participants) or wave 3 interview (BHPS participants) (McFall, Conolly, & Burton, 2014). Respondents were eligible to participate in the nurse visit if they had taken part in the corresponding main interview in English, were aged 16+, lived in England, Wales or Scotland and were not pregnant. Of these 35,875, 57.5% took part in the nurse visit. Further details of the sampling and timelines associated with data collection can be found at www.understandingsociety.ac.uk/documentation.

This study used data from GPS and BHPS participants taking part in either wave 2 or 3 (as this was when the inflammatory marker and mental health measures were taken). Our study participants were at least age 18 (ages ranged 18–97), had appropriate data from the nurse health assessment on CRP (see further information in Measures) as well as on the General Health Questionnaire (GHQ) at either wave 2 or 3 and had data on cognitive ability tests (taken in English) at wave 3 ($n = 9666$). In this sample, 4344 participants were male and 5322 were female.

2.2. Measures

C-reactive protein (*CRP*) was analysed from serum using the N latex CRP mono immunoassay on the Behring Nephelometer II Analyzer (Dade Behring, Milton Keynes, UK). Intra and inter assay coefficients of variation were < 2%. Systemic inflammation is defined as CRP > 3 mg/L levels. In line with previous research on CRP and depression (Valkanova, Ebmeier, & Allan, 2013), participants with CRP levels higher than 10 mg/L (likely due to infection) were excluded. We modelled CRP as a continuous indicator. We log transformed the variable for our main regression analyses given that it has a positively skewed distribution. We present the untransformed CRP data in the descriptive tables to aid in interpretation.

Psychological distress was measured with the General Health Questionnaire-12 (GHQ-12; Goldberg, 1972), a self-administered 12-item screening measure for minor psychiatric disorders. The questionnaire detects changes in normal functioning and caseness (the strong probability that an individual has a minor psychiatric disorder). The items focus on the inability to carry out normal activities and the appearance of new and distressing symptoms. They also cover feelings of strain, depression, inability to cope, anxiety-based insomnia and lack of confidence. Each item asks whether the respondent has recently experienced a particular symptom or behaviour, rated on 4-point frequency scales. We created a continuous variable using the established approach (Goldberg & Williams, 1991), as follows. The first two of the four response categories were scored as 0 and the latter two as 1. The total number of times a person indicated that their psychological state was worse than usual was then summed, giving a possible score ranging 0–12.

To measure *general intelligence* (*IQ*), a component score was derived from principal components analysis of the z-transformed scores on the five cognitive ability measures[1] (described below) administered in Understanding Society to those aged 16+. These multiple well-validated assessments are thought to measure general intelligence (or ‘g’), which has been shown not to be dependent on the use of specific mental ability tasks (Johnson, Bouchard, Krueger, McGue, & Gottesman, 2004). Verbal declarative memory was measured with a summary score on tasks measuring immediate and delayed recall. Verbal fluency was measured with a test of semantic or category fluency. Working memory was measured with the Serial 7 Subtraction test (Huppert, Brayne, Gill, Paykel, & Beardsall, 1995). A number series test assessed fluid reasoning (Fisher, McArdle, McCammon, Sonnega, & Weir, 2013). Lastly, numerical problem solving was measured with a test that assesses skills in solving numerical problems encountered in everyday life. (For more details on the tests see Whitley et al., 2016.) The component score (using the first unrotated component) was transformed into a

[1] Only individuals completing the cognitive ability component in English were included in this analysis to avoid issues with comparability of tests in different languages. Roughly 1% of respondents had tests translated into other languages.