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Neural mechanisms linking social status and inflammatory responses to social stress

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Abstract

Social stratification has important implications for health and well-being, with individuals lower in standing in a hierarchy experiencing worse outcomes than those higher up the social ladder. Separate lines of past research suggest that alterations in inflammatory processes and neural responses to threat may link lower social status with poorer outcomes. This study was designed to bridge these literatures to investigate the neurocognitive mechanisms linking subjective social status and inflammation. Thirty-one participants reported their subjective social status, and underwent a functional magnetic resonance imaging scan while they were socially evaluated. Participants also provided blood samples before and after the stressor, which were analysed for changes in inflammation. Results showed that lower subjective social status was associated with greater increases in inflammation. Neuroimaging data revealed lower subjective social status was associated with greater neural activity in the dorsomedial prefrontal cortex (DMPFC) in response to negative feedback. Finally, results indicated that activation in the DMPFC in response to negative feedback mediated the relation between social status and increases in inflammatory activity. This study provides the first evidence of a neurocognitive pathway linking subjective social status and inflammation, thus furthering our understanding of how social hierarchies shape neural and physiological responses to social interactions.

Key words: subjective social status; stress; dorsomedial prefrontal cortex; inflammation; interleukin-6; fMRI

Introduction

The social structures of many species, from insects (Yan *et al.*, 2015) and fish (Fernald and Maruska, 2012) to primates (Ghazanfar and Santos, 2004) and human beings (Hill and Dunbar, 2003), are characterized by their profound hierarchical organization. This social stratification has important implications for health

and well-being, as animals and humans lower in social status are often found to have worse outcomes than those with relatively higher standing in the social hierarchy (Adler *et al.*, 1994; Sapolsky, 2005).

Interestingly, alterations in immune system processes, and particularly heightened levels of inflammation, may provide a biological link between lower social status and poor physical

and emotional outcomes (Kemeny, 2009) . Indeed, mice that are consistently subjected to social defeat (a rodent model of low social status) show greater inflammatory dysregulation (Blanchard *et al.*, 1993; Powell *et al.*, 2009), and lower-ranking female macaques have been shown to have greater expression of genes involved in inflammation than higher-ranking females (Tung *et al.*, 2012). In humans, subjective ratings of social status have been associated with increases in stressor-evoked inflammation, such that lower-status individuals show a more pronounced inflammatory response to a laboratory stressor than individuals who perceive themselves as higher in status (Brydon *et al.*, 2004; Derry *et al.*, 2013). While short-term increases in inflammation in response to injury or infection are an integral part of the innate immune system's response to physical insults, exaggerated inflammatory activation in response to purely psychological threats (Slavich and Cole, 2013) and systemic elevations in inflammation are associated with the development of a number of chronic diseases (Hansson, 2005; Miller *et al.*, 2009), thus providing a possible physiological mechanism linking social status and poor physical and mental health outcomes. However, to date no known studies have investigated the neurocognitive systems that are engaged by those lower in subjective social status during a stressor that may lead to increases in inflammation.

Although no studies have directly investigated the neural mechanisms linking social status and stress-related increases in inflammation, a few studies have explored how status affects neural responses to social threat. For example, subordinate animals have been shown to have greater functional activation of the amygdala following social stress, relative to dominant animals (Kollack-Walker *et al.*, 1997). Results from two human studies have also demonstrated that lower-status individuals show greater neural activity in the amygdala, a key brain region in responding to salience cues and threat, when processing external social threats such as angry facial expressions (Gianaros *et al.*, 2008; Muscatell *et al.*, 2012). Given that the amygdala plays a key role in initiating activation of the sympathetic nervous system during stress (LeDoux *et al.*, 1988), and sympathetic activation is thought to drive inflammatory responses (Powell *et al.*, 2013), the tendency of low status individuals to activate the amygdala during social threat processing may lead to increases in inflammation.

Activity in the dorsomedial prefrontal cortex (DMPFC), a key node of the 'mentalizing network' that is often active during tasks that involve thinking about the thoughts and feelings of others, has also been associated with social status. Specifically, individuals lower in subjective status show greater activity in the DMPFC in response to social information, compared to their higher-status counterparts (Muscatell *et al.*, 2012). Furthermore, research in mice suggests that the prelimbic cortex (the mouse analog of human DMPFC/dorsal anterior cingulate cortex) may play a causal role in establishing social rank (Wang *et al.*, 2014). Combined with behavioral research showing that lower-status individuals tend to be more engaged during social interactions (Kraus and Keltner, 2009) and are better at reading the emotions of others (Kraus *et al.*, 2010), these patterns suggest that DMPFC-related attention to others' thoughts and feelings may also track with lower perceived social status. The DMPFC has strong connections with the amygdala and other brainstem regions whose activity can drive stress-related changes in the cardiovascular system and the hypothalamic-pituitary-adrenal axis (Gianaros and Sheu, 2009; Eisenberger and Cole, 2012; Muscatell and Eisenberger, 2012), and as such, it is possible that the DMPFC may also play a key role in linking social status and inflammation. To date, however, no known research has tested this possibility.

With this background in mind, the aim of this study was to explore neural activity in the amygdala and the DMPFC in response to negative social information as a neural mechanism linking social status and stress-related inflammatory responses. To investigate this, 31 healthy, female participants were exposed to a social stressor while they underwent a functional magnetic resonance imaging (fMRI) scan. We focused on females in this study given that women have been shown to be more reactive than men to social stressors (Rohleder *et al.*, 2001; Stroud *et al.*, 2002) and are at greater risk for some inflammatory-related conditions, such as major depressive disorder (Nolen-Hoeksema, 2001) . Blood samples were taken before and after the scan, and plasma was assayed for two inflammatory markers commonly studied in the acute stress literature: interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α; Steptoe *et al.*, 2007). Participants also completed a measure of subjective social status, and reported their affective responses to the social stressor. Consistent with prior research, we hypothesized that lower subjective social status would be associated with greater stressor-evoked increases in inflammation. We also hypothesized that lower subjective status would be related to greater neural activity in the amygdala and the DMPFC in response to negative social feedback, replicating prior research. Finally, we explored whether the relationship between social status and inflammatory responses was mediated by neural activity in the amygdala and/or DMPFC in response to negative social feedback. This is the first known study to examine the potential neurocognitive mechanisms linking social status and inflammatory responses to stress.

Materials and methods

Participants

Participants were 31 healthy young-adult females (M age = 19 years; range = 18–22 years). The sample self-identified as 32% Asian/Asian American, 23% Hispanic/Latina, 22% Mixed/Other, 13% African American and 10% White (non-Hispanic/Latina). The socioeconomic background of participants was varied: 45.2% (n = 14) of participants' mothers had completed high school education or less, whereas 32.3% (n = 10) of the sample had fathers who had completed high school education or less. All participants provided written informed consent, and procedures were approved by the UCLA Institutional Review Board. Participants were paid $135 for participating.

Procedure

Complete details of the experimental procedure have been previously reported (Muscatell *et al.*, 2015). In brief, prospective participants were excluded during phone screening if they endorsed a number of criteria known to influence levels of inflammation (e.g. acute infection, chronic illness, BMI over 30) or contraindications for the MRI environment (e.g. left-handedness, claustrophobia, metallic implants). Participants were also excluded if they endorsed any current or lifetime history of Axis-I psychiatric disorder, as confirmed by the Structured Clinical Interview for DSM-IV Axis 1 Disorders (First *et al.*, 1995). Individuals who met all inclusion criteria completed a video-recorded 'impressions interview' in the laboratory, in which they responded to questions such as 'What would you most like to change about yourself?' and 'What are you most proud of in your life so far?' Participants were told that in the next session for the study, they would meet another participant, and the

same neural and inflammatory processes operate at the tails of the objective SES distribution, such as among those living in poverty and/or individuals with extremely high SES. It will also be important for future research to examine if subjective perceptions of social status or objective indicators of SES are stronger predictors of neural and inflammatory responses to social stress, or if there are dissociable neural and physiological stress responses as a function of subjective *vs* objective SES. Third, given that participants in this study received negative, neutral and positive feedback, we cannot determine if it was specifically the negative feedback that was driving the observed increases in inflammation among those reporting lower social status. It will also be important for future studies to examine if simply being socially evaluated (even if the feedback one receives is positive) is sufficient to increase inflammation among lower subjective status individuals, or if the presence of negative feedback is necessary. Finally, we note that although the effect size for the mediation analysis indicated a medium effect, only the 90% CI did not include 0, possibly due to a small sample size for detecting these sorts of complex relationships between social status, neural activity and physiological responses. More research in larger samples will be needed to replicate this effect, but given that this is the first known study to link social status, neural and inflammatory reactivity data, we believe it is an important first step in exploring the neural mechanisms linking social status and inflammatory responses to stress.

Despite these limitations, data from the present study are the first to show a neural mediator of the relation between social status and inflammatory responses to stress. Furthermore, we replicate prior work showing that lower subjective status is related to greater neural activation in the DMPFC, and extend this previous work by using a novel social stress task. Finally, we also replicate a number of studies showing that lower subjective social status is related to greater stress-related increases in inflammation, and demonstrate for the first time that this is true even when there is no cognitive, effortful component to the stressor. Together, these findings shed light on possible neurocognitive and immune mechanisms that may contribute to the negative health consequences of low social status, and further our knowledge of how social standing shapes our brain and bodily responses in social interactions.

Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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