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Inflammation impairs social cognitive processing: A randomized controlled trial of endotoxin

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ABSTRACT

Neuropsychiatric disorders (e.g., autism, schizophrenia) are partially characterized by social cognitive deficits, including impairments in the ability to perceive others' emotional states, which is an aspect of social cognition known as theory of mind (ToM). There is also evidence that inflammation may be implicated in the etiology of these disorders, but experimental data linking inflammation to deficits in social cognition is sparse. Thus, we examined whether exposure to an experimental inflammatory challenge led to changes in ToM. One hundred and fifteen ($n = 115$) healthy participants were randomly assigned to receive either endotoxin, which is an inflammatory challenge, or placebo. Participants completed a social cognition task, the Reading the Mind in the Eyes (RME) test, at baseline and at the peak of inflammatory response for the endotoxin group. The RME test, a validated measure of ToM, evaluates how accurately participants can identify the emotional state of another person by looking only at their eyes. We found that endotoxin (vs. placebo) led to decreases in performance on the RME test from baseline to the peak of inflammatory response, indicating that acute inflammation can lead to decreases in the ability to accurately and reliably comprehend emotional information from others. Given that deficits in ToM are implicated in neuropsychiatric disorders, including those which may have an inflammatory basis, these results may have implications for understanding the links between inflammation, social cognition, and neuropsychiatric disorders.

Clinical Trials Registration. ClinicalTrials.gov NCT01671150.

1. Introduction

One of the most important aspects of human social interaction is the ability to infer others' mental states and emotions. Indeed, theory of mind (ToM)—defined as the capacity to attribute thoughts, desires, intentions, and beliefs to others (Premack and Woodruff, 1978)—is an aspect of social cognition which is essential for dealing with complex social relationships. This capacity was likely developed in order to allow primates, including humans, to adapt to the complexities that accompany living in organized social groups (Brüne, 2001; Brüne and Brüne-Cohrs, 2006). Impairments or deficits in ToM are implicated in an array of neuropsychiatric disorders, including autism spectrum disorders and schizophrenia (Baron-Cohen et al., 1985; Brüne and Brüne-Cohrs, 2006; Couture et al., 2010; Frith and Corcoran, 1996; Sprong et al., 2007). In fact, deficits in ToM have been hypothesized to underlie the core behavioral symptoms of autism (Baron-Cohen et al., 1985), and social cognitive abilities such as ToM are more strongly related to functional outcomes (e.g., work functioning, living independently) than non-social cognition in individuals with schizophrenia (Fett et al., 2011).

Recent research has also suggested that inflammation, including proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, may play a role in the pathophysiology of autism and schizophrenia (Fineberg and Ellman, 2013; Meyer et al., 2009, 2011; Michel et al., 2012; Onore et al., 2012; Patterson, 2009). It has been hypothesized that prenatal exposure to infection, including the subsequent maternal proinflammatory response, can alter the development of the fetal brain (Fineberg and Ellman, 2013; Meyer et al., 2009, 2011; Michel et al., 2012; Onore et al., 2012; Patterson, 2009). Indeed, elevated levels of maternal inflammatory markers during pregnancy are associated with increased risk for neuropsychiatric disorders such as schizophrenia and autism spectrum disorders (Brown et al., 2004, 2013; Buka et al., 2001; Canetta et al., 2014), and animal work

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has shown that offspring of mothers who were exposed to an inflammatory challenge during pregnancy show long-lasting changes in inflammation persisting through adulthood (Romero et al., 2008). Furthermore, individuals with autism spectrum disorders exhibit elevated levels of proinflammatory cytokines (e.g., IL-6) compared to healthy controls (Ashwood et al., 2011a; Masi et al., 2014; Ricci et al., 2013; Suzuki et al., 2011), and proinflammatory cytokines are also associated with more impaired behavioral outcomes in individuals with autism (Ashwood et al., 2011a,b; Enstrom et al., 2010; Onore et al., 2012). Similarly, a recent meta-analysis of cytokine alterations in schizophrenia found that inflammatory cytokines were elevated during acute exacerbations of the illness (Miller et al., 2011), suggesting that acute changes in proinflammatory cytokines may contribute to the pathogenesis and clinical course of schizophrenia. Thus, disruptions in inflammatory processes may play a critical role in the pathophysiology of schizophrenia and autism.

While prior work has found that proinflammatory cytokines may contribute to the etiology of these disorders characterized by ToM deficits, the literature demonstrating a causal relationship between inflammation and deficits in social cognition, particularly ToM, is sparse. Only one prior study, to our knowledge, has examined the link between inflammation and social cognition, specifically examining the impact of endotoxin, an experimental inflammatory challenge, on the Reading the Mind in the Eyes test, a ToM task in which participants are asked to infer the mental or emotional state of another person by looking at only their eyes (Kullmann et al., 2013). Experimentally-induced inflammation in this study did not impact social cognitive performance as assessed by the ToM task. However, the study had a small sample ($n = 18$) and subjects were administered a very low dose of endotoxin (0.4 ng/kg). Prior work has shown that the effect of endotoxin on physiological responses and neurobehavioral functions in humans is dose-dependent (Grigoleit et al., 2011), suggesting that a higher dose of endotoxin may be necessary to induce effects on social cognition.

Given that inflammation is thought to contribute to disorders marked by social cognitive deficits, but that little is known about the effect of inflammation on social cognition, we aimed to examine the effect of a relatively higher dose of endotoxin (0.8 ng/kg), previously shown to alter socioemotional responding, on social cognitive performance in a large sample ($n = 115$) of healthy adults. We hypothesized that endotoxin, compared to placebo, would lead to decreases in performance on a ToM task.

2. Material and methods

2.1. Participants and procedures

One hundred and fifteen healthy participants (69 female; mean age: 24.2 ± 6.6) completed the study. Participants were recruited from UCLA and the greater Los Angeles community using flyers around the UCLA campus, advertisements in campus and local newspapers, and online postings (i.e., Craigslist, ClinicalTrials.gov NCT01671150). Interested participants were screened for eligibility using a two-step process, consisting of a structured telephone interview and an in-person screening session. During the phone interview, prospective participants were screened for and excluded if they had any of the following conditions: claustrophobia, left-handedness, or metal in their body (relevant for a neuroimaging portion, reported separately); chronic physical or mental health problems; history of allergies, autoimmune, or other severe chronic diseases; current use of prescription medications; or recent nightshift work or time zone shifts greater than 3 h. If participants were still eligible, they completed an additional interview at the UCLA Cousins Center for Psychoneuroimmunology to ensure eligibility. During the in-person session, participants completed the Structured Clinical Interview for DSM-IV Disorders (SCID; First et al., 2012) and were asked about their medical and medication history. In addition, height, weight, and vital signs were assessed. Urine samples were collected to examine drug use (marijuana, opiates, cocaine, amphetamines, methamphetamines), and blood samples were collected to screen for abnormalities (e.g., complete blood cell count, chemistry panel, liver function tests), as well as pregnancy for females. Participants' eligibility was determined by the study physician (M.R.I.). After the in-person screening session, any participant who: (1) had body mass index (BMI) greater than 30, (2) reported physical health problems or medication use, (3) evidenced an Axis I psychiatric disorder based on SCID assessment, (4) showed evidence of drug use from a positive urine test, (5) had a positive pregnancy test, or (6) showed abnormalities on the screening laboratory tests were ineligible for the study. Participants who met study eligibility criteria were then scheduled for the study.

The study was conducted between March 2011 and August 2013 (when the intended sample size of $n = 115$ was reached, which was based on effect sizes from prior research (Eisenberger et al., 2010) regarding the primary aims of the study (reported in Moieni et al., in press) at the UCLA Clinical and Translational Research Center (CTRC) using a randomized, double-blind, placebo-controlled design. Upon arrival to the CTRC, a nurse, who was blind to condition, inserted a catheter with a heparin lock into the dominant forearm (right) for hourly blood draws and one into the non-dominant forearm (left) for a continuous saline flush and for drug administration. Ninety minutes after arrival to the CTRC, each participant was randomly assigned to receive either low-dose endotoxin (0.8 ng/kg of body weight) or placebo (same volume of 0.9% saline), which was administered by the nurse as an intravenous bolus. The endotoxin was derived from *Escherichia coli* (*E. coli* group O:113: BB-IND 12948 to M.R.I.) and was provided by the National Institutes of Health Clinical Center as a reference endotoxin for studies of experimental inflammation in humans (Suffredini et al., 1999b); previous research has demonstrated the safety of this reference endotoxin across many different samples (Andreasen et al., 2008; Suffredini et al., 1999a). The random allocation sequence was generated by a consultant who was not involved in running participants and was kept by the UCLA Pharmacy to ensure proper drug preparation for each participant. Randomization was done using a computerized uniform random number generator; males and females were randomized separately in permuted blocks of 4. Participants were enrolled in the study by a study coordinator (I.J.). The two conditions were not different in appearance or method of administration. However, it is possible that participants in the endotoxin condition who felt very symptomatic may have suspected that they were in the active condition. For this reason, participants who were out of range on self reports of physical sickness symptoms in the endotoxin condition were removed from all analyses (described below).

Throughout the study, vital signs and blood draws (to assess cytokine levels) were collected at baseline and then approximately every hour for the next 6 h. Participants also completed hourly measures of sickness symptoms and socioemotional responses (reported in Moieni et al., in press). The social cognition task, a pre-specified secondary behavioral outcome, was completed at baseline and approximately 2 h post-injection (1 h and 40 min post injection), the peak inflammatory response for the endotoxin group (please see Fig. 1 and Moieni et al. (in press), for further details on timing). Participants were discharged from the CTRC following the last blood draw upon approval from the study's physician; approval was granted once self-reported symptoms returned to baseline levels. The Data Safety Monitoring Board met

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