Peripheral Inflammation is Associated with Altered Substantia Nigra Activity and Psychomotor Slowing in Humans

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Background: Systemic infections commonly cause sickness symptoms including psychomotor retardation. Inflammatory cytokines released during the innate immune response are implicated in the communication of peripheral inflammatory signals to the brain.

Methods: We used functional magnetic resonance brain imaging (fMRI) to investigate neural effects of peripheral inflammation following typhoid vaccination in 16 healthy men, using a double-blind, randomized, crossover-controlled design.

Results: Vaccination had no global effect on neurovascular coupling but markedly perturbed neural reactivity within substantia nigra during low-level visual stimulation. During a cognitive task, individuals in whom typhoid vaccination engendered higher levels of circulating interleukin-6 had significantly slower reaction time responses. Prolonged reaction times and larger interleukin-6 responses were associated with evoked neural activity within substantia nigra.

Conclusions: Our findings provide mechanistic insights into the interaction between inflammation and neurocognitive performance, specifically implicating circulating cytokines and midbrain dopaminergic nuclei in mediating the psychomotor consequences of systemic infection.

Key Words: Cytokines, fMRI, peripheral inflammation, psychomotor slowing, substantia nigra

In healthy mammals, systemic infections typically engender a set of behavioral, psychological, and physiological changes collectively known as "sickness behavior." Cognitive and affective symptoms include psychomotor retardation, impaired memory, confusion, decreased motivation (e.g., anorexia, adipsia, fatigue), anxiety, and depression (1). Sickness behavior may be conceptualized as an adaptive reorganization of the host's homoeostatic and behavioral priorities to facilitate an immune response, rather than simply a detrimental consequence of infection per se (2).

Animal and human studies suggest that inflammatory cytokines play a pivotal role in mediating sickness-related behaviors by communicating peripheral inflammation to the brain (1,3). The rapid activation of tissue macrophages early in the innate immune response to infection causes the release of cytokines interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), along with other proinflammatory mediators. Systemic administration of IL-1β or bacterial lipopolysaccharide (LPS) (a potent stimulant of cytokine release) induces sickness symptoms in rodents (1). In humans, cytokine immunotherapy for cancer or hepatitis C frequently produces sickness-related symptoms including psychomotor retardation and depressed mood (3). Similarly, elevated circulating IL-6 levels are associated with depressed mood and memory deficits in healthy volunteers following peripheral injection with bacterial endotoxins (4–6). Peripheral cytokines may access and influence the brain through passive diffusion (at the level of circumventricular organs and choroid plexus), active transport (at the level of brain endothelium), and through the activation of interoceptive afferents, particularly in the vagus nerve, that project to the nucleus of the solitary tract and higher viscerosensory centers (1). Within the brain, there exists a network of cells that produce cytokines and express cytokine receptors (1), where central cytokine production can profoundly influence catecholamine neurotransmission, synaptic plasticity, and neuronal survival (7).

Beyond this evidence, the mechanisms through which peripheral inflammation engenders sickness-related psychomotor and behavioral symptoms remain poorly understood. The current investigation set out to address these issues by assessing the impact of a low-grade peripheral immune stimulus, *Salmonella typhi* polysaccharide, on cognitive performance and brain activity in healthy young men.

Methods and Materials

Study Population

Sixteen male student volunteers between 18 and 35 years of age were recruited from University College London. Volunteers were screened by structured interview to ensure that they were healthy, had no previous history of any relevant physical or psychiatric illness, were taking no medication, and were nonsmokers. Volunteers who had received typhoid vaccine in the past 3 years or any other vaccine in the previous 6 months were excluded. Participants were advised not to consume caffeinated beverages or alcohol and to refrain from excessive exercise during the 12 hours prior to testing. They were also advised not to take aspirin, ibuprofen, or antibiotics for 14 days prior to testing. All participants gave their informed consent, and the study was approved by the joint University College London/University College London Hospital Committee on the Ethics of Human Research.

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General Procedure

The study was performed in a double-blind, randomized, crossover-controlled manner. Participants were assessed individually in two separate sessions, a mean of 7 days apart. In session one, a baseline blood sample was drawn and the participant was randomly assigned to one of two experimental conditions (typhoid vaccine or placebo). Injections of *Salmonella typhi* capsular polysaccharide vaccine (.025 mg in .5 mL; Typhim Vi, Aventis Pasteur S.A., Lyon, France) or control saline placebo (.5 mL) were administered intramuscularly into the nondominant deltoid muscle. Typhoid vaccine was selected as a low-grade proinflammatory stimulus, since this vaccine is known to induce increases in circulating proinflammatory cytokine levels with no significant effect on body temperature, a potentially confounding factor (4). To investigate the effect of peripheral inflammation on cognitive and cerebral function, participants performed two tasks during simultaneous functional magnetic resonance brain imaging. The first was a low-grade visual stimulation task and the second was a mentally challenging color-word Stroop task. Tasks were performed 2 hours postinjection, around the time of peak cytokine responses to typhoid vaccine (8). A second blood sample was drawn after scanning (at 3 hours postinjection) for assessment of inflammatory cytokines. Subjective ratings of mood and illness symptoms were taken at baseline, 2 hours, and 3 hours, and body temperature was assessed using a sublingual digital thermometer. The second session was identical to the first except that participants were injected with saline placebo if they had received typhoid vaccine in session one or vice versa.

Assessment of Mood and Illness Symptoms

Mood and symptoms of illness were assessed with a modified, 36-item version of the Profile of Mood States (POMS) (9), as described previously (4). Six high-loading items were taken from the vigor, tension-anxiety, depression-dejection, and confusion scales of the original POMS, and five items were taken from the fatigue scale. Four extra items were added to assess symptoms associated with mild infection (fever, aching joints, nausea, and headache). Participants were asked to rate how they felt at that moment on a 5-point scale from 0 = not at all to 4 = extremely.

Low-Grade Visual Stimulation Task

First, to test for a general perturbation of neurovascular coupling during systemic inflammation, each participant underwent a low-level visual stimulation task involving the intermittent presentation of a high-contrast flickering black and white checkerboard stimulus (Figure 1). The stimulus was presented in alternating blocks of 21.6 seconds (on) and 15.1 seconds (off).

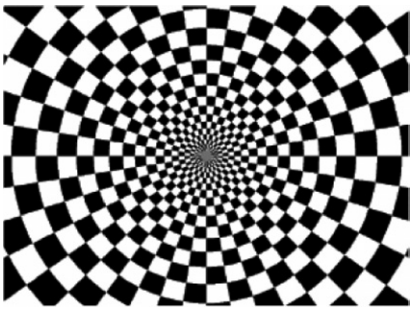

Figure 1. High-contrast flashing checkerboard task used as a potent stimulus of primary visual cortical regions. Participants fixated on a cross at the center of the screen and pressed a key whenever the brightness of the cross changed.

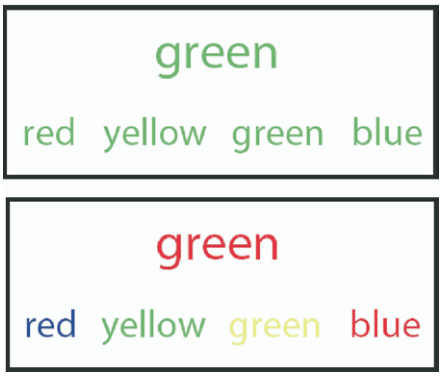

Figure 2. Cognitive color-word Stroop task. Participants pressed a key to select the response word that correctly identified the print color of the target word. Congruent and incongruent conditions were presented separately and examples of these are illustrated here. In the congruent example (upper panel), the correct response is green. In the incongruent example, requiring greater cognitive effort (lower panel), the correct response is red.

A total of 20 on blocks and 20 off blocks were presented in two sessions of 6.4 minutes. Participants responded with a right-handed button press to changes in the brightness of a central fixation cross, ensuring attention to the center of the screen. This low-level visual stimulation paradigm is known to induce potent blood oxygenation level-dependent (BOLD) responses in striate and extrastriate visual cortices (V1; Brodmann areas 17 and 18).

Color-Word Stroop Task

Participants performed a second task during fMRI, the color-word Stroop task (Figure 2). This is a very well established task for assessing high-demand cognitive processing, including attentional and executive control processes, via effects of stimulus conflict on psychomotor responses. These functions are known to be compromised by sickness. The task requires the participant to name the ink color of word stimuli, in this case by making a four-choice button press response. The target color word was presented with four possible response words (red, yellow, green, and blue) below. Target words and the order of response words were displayed randomly. Participants were instructed to respond as rapidly as possible to the color of the target word, using a four-button response pad corresponding to the response words below. In the congruent condition, the font color of all words matched both the ink color and semantic meaning of the target word, whereas in the incongruent condition, words were printed in a color incongruent with the color and meaning of the target word. Thus, in incongruent trials, the participant had to overcome distraction from the meaning of the target and ink color of the response choices (Figure 2). Both targets and response words were displayed for 3000 msec, preceded by a central fixation cross presented for 2000 msec. No feedback was given. Trials were presented in five blocks of 36 events with 10,000-msec breaks between blocks. The percentage of incongruent trials varied between blocks and ranged from 14% (two blocks), 28% (one block), to 42% (two blocks), with 17% null events per block.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) was performed using a 1.5T Siemens Sonata magnetic resonance scanner (Siemens, Erlangen, Germany) equipped with a standard head coil. Mild external head restraint was used to minimize head movement during scanning. Visual stimuli were projected onto a screen visible via a mirror on the head coil. Functional brain