Peripheral Inflammation Acutely Impairs Human Spatial Memory via Actions on Medial Temporal Lobe Glucose Metabolism

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Background: Inflammation impairs cognitive performance and is implicated in the progression of neurodegenerative disorders. Rodent studies demonstrated key roles for inflammatory mediators in many processes critical to memory, including long-term potentiation, synaptic plasticity, and neurogenesis. They also demonstrated functional impairment of medial temporal lobe (MTL) structures by systemic inflammation. However, human data to support this position are limited.

Methods: Sequential fluorodeoxyglucose positron emission tomography together with experimentally induced inflammation was used to investigate effects of a systemic inflammatory challenge on human MTL function. Fluorodeoxyglucose positron emission tomography scanning was performed in 20 healthy participants before and after typhoid vaccination and saline control injection. After each scanning session, participants performed a virtual reality spatial memory task analogous to the Morris water maze and a mirror-tracing procedural memory control task.

Results: Fluorodeoxyglucose positron emission tomography data demonstrated an acute reduction in human MTL glucose metabolism after inflammation. The inflammatory challenge also selectively compromised human spatial, but not procedural, memory; this effect that was independent of actions on motivation or psychomotor response. Effects of inflammation on parahippocampal and rhinal glucose metabolism directly mediated actions of inflammation on spatial memory.

Conclusions: These data demonstrate acute sensitivity of human MTL to mild peripheral inflammation, giving rise to associated functional impairment in the form of reduced spatial memory performance. Our findings suggest a mechanism for the observed epidemiologic link between inflammation and risk of age-related cognitive decline and progression of neurodegenerative disorders including Alzheimer's disease.

Key Words: Alzheimer's disease, imaging, inflammation, memory, parahippocampus, PET

Although previously considered an immune-privileged site, it is now clear that the immune system plays an integral role in many fundamental neuronal processes, including long-term potentiation (LTP) (1,2), synaptic plasticity (3), and neurogenesis (4), that are critical to learning and memory. In health, immune mechanisms regulate each of these processes and assist in the remodeling of neural circuits that promote learning and memory (5). However, during systemic infection or injury (6), this positive regulatory function is disrupted, resulting in acute memory impairments: When inflammation is severe, cognitive impairment may become persistent (7), and when chronic inflammation is present, age-related cognitive impairment is accelerated (8). Inflammation may drive the rapid progression of neurodegenerative diseases such as Alzheimer's disease (9).

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Structures in the medial temporal lobe (MTL) appear to be particularly sensitive to effects of inflammation. This increased sensitivity may be related to their relatively high receptor and messenger RNA expression for proinflammatory cytokines (10,11) and their neural connectivity to regions such as the insula (12) that support cortical representations of peripheral inflammatory states (13). Rodent studies emphasized the role of the hippocampus; direct administration of inflammatory cytokines, particularly interleukin (IL)-1, into the hippocampus selectively impaired spatial and contextual memory processes, including radial arm and Morris water maze performance, and contextual, but not auditory-cued, fear conditioning (5,14,15). Similarly, overexpression of IL-1 messenger RNA within the hippocampus is associated with delayed acquisition of spatial memory on the Morris water maze task (14). For synaptic plasticity underlying the encoding and recall of memories, LTP is arguably the key neuronal mechanism. The cytokine IL-1 compromises both hippocampal and dentate gyrus LTP (1,17,18) and may mediate both age-dependent decreases in LTP (19) and the modulation of LTP by Aβ amyloid (20). Cytokine-induced inhibition of neurogenesis within the dentate gyrus is also alleviated by the microglial inhibitor minocycline (4). Together, these data highlight the central action of inflammatory mediators (cytokines such as IL-1) on MTL-dependent memory processes.

Inflammatory challenges administered outside the central nervous system also induce IL-1 expression within brain regions, including the MTL (21). Peripherally induced inflammation also replicates many of the direct actions of inflammatory cytokines on MTL-dependent memory (5,22,23). There are numerous mechanisms through which peripheral inflammation can engender changes in cytokine levels within sensitive brain regions. Circulating cytokines may be actively transported across the blood-brain barrier

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(24) or activate microglia via the circumventricular organs (25) and vascular endothelium (26). However, local synthesis of IL-1 is suggested by the rapid upregulation of IL-1α and IL-1β gene expression and the central predominance of the short half-life IL-1 isoform in the context of mild systemic inflammatory challenge (21). Vagus nerve afferents show sensitivity to peripheral cytokines (27) and mild inflammatory challenge (28) indicating an additional neurally mediated immune-brain pathway. Central vagus nerve targets show enhanced activity within 2–3 hours of peripheral inflammatory challenge in both rodents and humans (29,30). Electrical stimulation of vagus nerve afferents results in a rapid increase in IL-1β expression within the hippocampus (31). Humoral and neurally mediated routes may communicate peripheral inflammatory responses centrally to regions supporting memory processes.

These data from animal studies suggest mechanisms to account for human epidemiologic data linking increased peripheral inflammation to accelerated cognitive aging and neurodegeneration. However, it is unknown whether systemic inflammation modulates MTL function in humans. We used an experimental inflammatory model, typhoid vaccination, together with sequential fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning to quantify hypothesized effects of peripheral inflammation on human MTL function and spatial memory. In 20 healthy participants, three FDG-PET scans were performed immediately before and 4 hours and 8 hours after typhoid vaccination or control (saline) injection (Figure 1). After each of the first two scanning sessions, participants performed a spatial memory task in which they learned and then recalled the identity and location of two sets of 16 objects positioned within a virtual reality environment. This virtual reality task is analogous to the Morris water maze (32), which is sensitive to inflammatory effects on object-location accuracy in rodents, and to the hidden tracer task, which is sensitive to lesions in discrete MTL structures in humans (33). Recall of the spatial location and identity of both sets of objects was tested again after the third scan to investigate differential effects of inflammation on early encoding and later consolidation processes. Participants also performed a mirror-tracing procedural memory task to test general effects of inflammation on psychomotor responses and motor learning.

Methods and Materials

Participants

We recruited 20 healthy male nonsmokers (mean age, 24.7 ± 6.8 years old) and screened them for relevant physical or psychiatric illness; all were medication-free. Volunteers who had received typhoid vaccine within 3 years or other vaccine within 6 months were excluded. Participants were advised to avoid caffeinated beverages, alcohol, high-fat meals, and excessive exercise for 24 hours and steroidal or nonsteroidal drugs for 2 weeks before testing. All participants fasted for 8 hours and consumed only water until study completion. Written informed consent was obtained from all participants, and procedures were approved by the Brighton East National Research Ethics Committee.

Study Design

A randomized, double-blind, repeated measures crossover design was used in which all participants underwent three FDG-PET imaging sessions each separated by 4 hours. After each of the first two scanning sessions, participants randomly received intramuscular injections of either 0.025 mg *Salmonella typhi* vaccine (Typhim Vi; Aventis Pasteur MSD Ltd., Lyon, France) or 0.5 mL normal saline. Of participants, 13 were randomly assigned to the early inflammation group and received vaccination after the first PET scan 1, and 7 were randomly assigned to the late inflammation group and received vaccination after the second PET scan. This study design enabled us to control for nonspecific time effects as well as have sufficient participants ($n = 13$) scanned 8 hours after typhoid vaccination to test late effects of inflammation. After each scan, participants performed a laptop-based spatial memory task and a mirror-tracing procedural memory task that took 35 min to complete. Vaccination or saline injection was given after the PET scan immediately before memory testing; this was done to minimize an already long testing day. We are aware of no data to suggest that peripherally induced inflammation can impair memory at such a short latency, and if this were the case, it would increase the risk of false-negative rather than false-positive findings. A high-resolution inversion recovery echo planar image was obtained to aid image registration.

Inflammatory Model

We used a *S. typhi* vaccination model known to induce low-grade inflammation without body temperature change (34). Blood (10 mL) was drawn into ethylenediamine tetraacetic acid BD Vacutainer tubes (Franklin Lakes, New Jersey) and centrifuged at 1250 × *g* for 10 min, and plasma was removed, aliquoted, and frozen at −80°C. Plasma IL-6, IL-1 receptor antagonist, and tumor necrosis factor alpha were assessed using high-sensitivity enzyme-linked immunosorbent assays (R&D Systems, Abingdon, United Kingdom). Limits of detection were .039 pg/mL, 6.26 pg/mL,

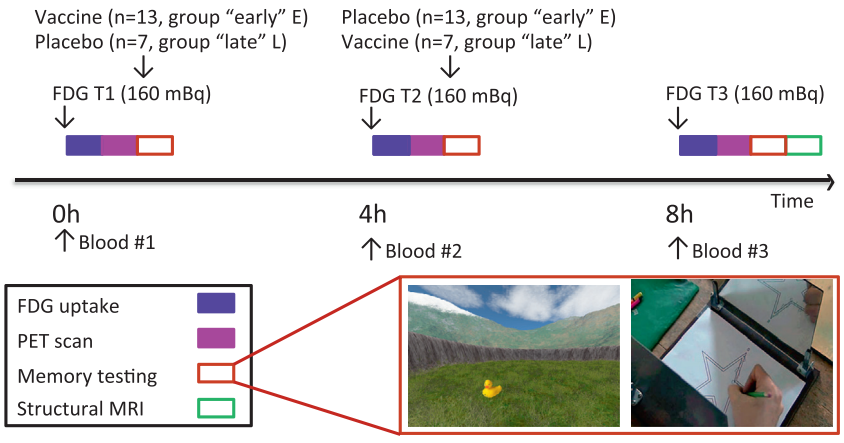

Figure 1. Study timeline. All participants completed three fluorodeoxyglucose (FDG) positron emission tomography (PET) scans. Each scan was preceded by a blood draw and followed by a memory testing session. The "early" inflammation group received the typhoid vaccination after the first PET scan (and saline injection after the second PET scan), and the "late" inflammation group received the typhoid vaccination after the second PET scan (saline injection after the first scan). In the first two sessions (T1 and T2), participants encoded and then recalled the identity and spatial location of two sets of objects (object set 1 and set 2). In the third session (T3), participants recalled the identity and spatial location of the two sets of objects encoded at T1 and T2. The mirror-tracing task was performed at each of the three testing sessions. MRI, magnetic resonance imaging. (Photo credit, copyright WGBH Educational Foundation.)