Archival Report

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Hippocampal Neuroinflammation, Functional Connectivity, and Depressive Symptoms in Multiple Sclerosis

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ABSTRACT

BACKGROUND: Depression, a condition commonly comorbid with multiple sclerosis (MS), is associated more generally with elevated inflammatory markers and hippocampal pathology. We hypothesized that neuroinflammation in the hippocampus is responsible for depression associated with MS. We characterized the relationship between depressive symptoms and hippocampal microglial activation in patients with MS using the 18-kDa translocator protein radioligand [^{18}F]PBR111. To evaluate pathophysiologic mechanisms, we explored the relationships between hippocampal neuroinflammation, depressive symptoms, and hippocampal functional connectivities defined by resting-state functional magnetic resonance imaging.

METHODS: The Beck Depression Inventory (BDI) was administered to 11 patients with MS and 22 healthy control subjects before scanning with positron emission tomography and functional magnetic resonance imaging. We tested for higher [^{18}F]PBR111 uptake in the hippocampus of patients with MS relative to healthy control subjects and examined the correlations between [^{18}F]PBR111 uptake, BDI scores, and hippocampal functional connectivities in the patients with MS.

RESULTS: Patients with MS had an increased hippocampal [^{18}F]PBR111 distribution volume ratio relative to healthy control subjects ($p = .024$), and the hippocampal distribution volume ratio was strongly correlated with the BDI score in patients with MS ($r = .86$, $p = .006$). Hippocampal functional connectivities to the subgenual cingulate and prefrontal and parietal regions correlated with BDI scores and [^{18}F]PBR111 distribution volume ratio.

CONCLUSIONS: Our results provide evidence that hippocampal microglial activation in MS impairs the brain functional connectivities in regions contributing to maintenance of a normal affective state. Our results suggest a rationale for the responsiveness of depression in some patients with MS to effective control of brain neuroinflammation. Our findings also lend support to further investigation of the role of inflammatory processes in the pathogenesis of depression more generally.

Keywords: Depression, Hippocampus, Multiple sclerosis, Neuroimaging, Neuroinflammation, TSPO

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There is a higher prevalence of depression in patients with multiple sclerosis (MS) than in the general population (1). The association between MS and depression is stronger than associations observed in patients with other long-term disabling conditions, suggesting common pathophysiologic mechanisms (2). Activation of the brain innate immune response has been proposed as one such potential common causal factor (3).

Magnetic resonance imaging (MRI) studies have reported associations between depressive symptoms in patients with MS and measures of disease burden, including lesion load and accompanying tissue destruction, more diffuse abnormalities of the normal-appearing white matter, and brain atrophy (4). However, each of these associations accounted for only a small amount of total variance in depressive symptoms, and specific associations have not been consistent across studies. These findings suggest that the association arises from a common underlying factor that contributes to pathophysiologic changes for both MS and depression.

Elevated inflammatory markers are associated with depressive symptoms in medically healthy individuals (5), and increased levels of depression and anxiety have been documented in clinical and experimental settings after challenges that activate an innate immune response (6,7). We hypothesized that the high prevalence of depressive symptoms in patients with MS is a direct consequence of chronic innate immune activation in functionally relevant regions of their brains.

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Convergent lines of research implicate the hippocampus in the pathophysiology of depression. Hippocampal atrophy is a consistently reported finding in patients with depression and has been suggested as a biomarker of risk for depression (8). Hippocampal activity modulates the hypothalamus-pituitary-adrenal stress hormone axis and regulates the function of prefrontal, ventral tegmental, and striatal areas that appear to contribute to the genesis or maintenance of depressive symptoms (9). The hippocampus may be particularly susceptible to neuroinflammatory triggers; for example, it has a high density of interleukin-1 receptors (10). Hippocampal pathology in MS, including extensive demyelination, neuronal loss atrophy, and microglia activation, has been confirmed by postmortem and imaging studies (11–13). Studies using MRI demonstrated that hippocampal volume loss and altered morphology are associated with depressive symptoms in MS (14–16). Hippocampal neuroinflammation in the rodent experimental allergic encephalomyelitis (EAE) model is associated with dysfunctional neurogenesis (17), and hippocampal neurogenesis in humans may be critical to recovery from depression (18). Therefore, we hypothesized that innate immune responses specifically in the hippocampus are responsible for the genesis of depressive symptoms associated with MS.

We previously demonstrated that positron emission tomography (PET) with the second-generation 18-kDa translocator protein (TSPO) radioligand [^{18}F]PBR111 enables the characterization of microglial activation in the white matter of patients with MS (19). Although TSPO is not seen exclusively in activated microglia, we interpret increased TSPO signal as arising largely from activated microglia/macrophages based on previous immunohistochemical observations in postmortem brains with MS and in EAE rodents (20–22). Studies in patients with MS using first-generation and second-generation TSPO radioligands reported focally increased TSPO radioligand uptake associated with gadolinium-enhancing lesions (23,24), some T2-hyperintense lesions (19,25), in the thalamus (23,25), and in some cortical gray matter areas, particularly in patients with secondary progressive MS (26).

In the present study, we used [^{18}F]PBR111 PET to quantify hippocampal microglia activation and characterize its relationship to depressive symptoms in patients with MS in vivo. We also investigated whether the strength of hippocampal functional connectivity assessed with resting-state functional MRI is related to the expression of depressive symptoms and to hippocampal microglia activation in patients with MS.

METHODS AND MATERIALS

Study Design and Subjects

The study was conducted at Imperial College London and the Imanova Centre for Imaging Sciences and was approved by the Essex 1 Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee. The clinical, demographic, and radiologic characteristics of study subjects are summarized in Supplemental Table S1 and Table 1. The study subjects included 22 healthy control subjects and 13 patients with relapsing-remitting MS who underwent MRI and [^{18}F]PBR111 PET scans on the same day. The MRI scan was conducted approximately 2 hours before the PET scan. All healthy control subjects underwent a PET scan, and 14 of 22 also underwent a resting-state functional MRI scan. Of 13 patients with MS, 2 were subsequently excluded from the PET cohort because of failure of metabolite analysis, which precluded the kinetic modeling using arterial input function with metabolite correction.

The mean age of patients with MS was younger than healthy control subjects (MS group, 44.23 ± 8.42 years [mean

Table 1. Clinical and Demographic Characteristics of Study Participants

Case	Age (Years)/ Sex	TSPO Gene Group	Disease Duration (Years)	EDSS	BDI	MDE
Healthy Control Subjects						
1	45/F	MAB	—	—	6	None
2	36/F	MAB	—	—	0	None
3	33/F	HAB	—	—	9	None
4	52/F	LAB	—	—	0	None
5	61/F	MAB	—	—	0	None
6	42/F	HAB	—	—	0	None
7	52/F	HAB	—	—	1	None
8	43/M	MAB	—	—	0	None
9	50/F	HAB	—	—	4	None
10	28/M	HAB	—	—	1	None
11	52/F	HAB	—	—	0	None
12	51/M	LAB	—	—	0	None
13	65/M	LAB	—	—	8	None
14	28/M	HAB	—	—	2	None
15	57/M	MAB	—	—	—	None
16	59/F	HAB	—	—	—	None
17	59/M	HAB	—	—	—	None
18	62/M	HAB	—	—	—	None
19	60/F	MAB	—	—	—	None
20	60/F	MAB	—	—	—	None
21	56/F	MAB	—	—	—	None
22	44/F	LAB	—	—	—	None
Patients With MS		—	—	—	—	—
1	48/F	HAB	8	6.5	23	Current
2	39/F	LAB	20	4	9	Recent
3	40/F	HAB	11	4	24	Current
4	55/F	HAB	20	2	5	None
5	53/F	LAB	20	7	30	Current
6	50/F	HAB	2	4	10	Current
7	59/F	MAB	16	3	8	Recent
8[a]	42/M	MAB	11	5.5	20	Current
9	41/F	HAB	14	1.5	3	None
10	28/M	HAB	7	2	14	Recent
11	41/F	MAB	4	5.5	7	None
12	42/F	HAB	1.5	6	19	Current
13[a]	37/F	—	9	7	23	Current

BDI, Beck Depression Inventory; EDSS, Expanded Disability Status Scale; HAB, high-affinity binder; LAB, low-affinity binder; MAB, mixed-affinity binder; MDE, major depressive episode; TSPO, 18-kDa translocator protein.

[a]These patients were not included in the positron emission tomography analysis.