Inflammation after Trauma: Microglial Activation and Traumatic Brain Injury

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Objective: Patient outcome after traumatic brain injury (TBI) is highly variable. The underlying pathophysiology of this is poorly understood, but inflammation is potentially an important factor. Microglia orchestrate many aspects of this response. Their activation can be studied in vivo using the positron emission tomography (PET) ligand [11C](R)PK11195 (PK). In this study, we investigate whether an inflammatory response to TBI persists, and whether this response relates to structural brain abnormalities and cognitive function.
Methods: Ten patients, studied at least 11 months after moderate to severe TBI, underwent PK PET and structural magnetic resonance imaging (including diffusion tensor imaging). PK binding potentials were calculated in and around the site of focal brain damage, and in selected distant and subcortical brain regions. Standardized neuropsychological tests were administered.
Results: PK binding was significantly raised in the thalami, putamen, occipital cortices, and posterior limb of the internal capsules after TBI. There was no increase in PK binding at the original site of focal brain injury. High PK binding in the thalamus was associated with more severe cognitive impairment, although binding was not correlated with either the time since the injury or the extent of structural brain damage.
Interpretation: We demonstrate that increased microglial activation can be present up to 17 years after TBI. This suggests that TBI triggers a chronic inflammatory response particularly in subcortical regions. This highlights the importance of considering the response to TBI as evolving over time and suggests interventions may be beneficial for longer intervals after trauma than previously assumed.

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The underlying pathophysiology of traumatic brain injury (TBI) remains poorly understood.[1] Patient outcomes are highly variable,[2] for reasons that are often unclear. Although TBI is usually thought to involve a static pathological insult from a single event, new clinical effects can emerge many years after the injury. Patients often clinically improve or deteriorate long after TBI[2] and may develop unexpected consequences such as post-traumatic epilepsy[3] or late cognitive decline including Alzheimer disease.[4] These observations suggest the presence of a dynamic element to the underlying pathophysiology of TBI.

An important factor is likely to be the inflammatory response produced by TBI.[5–7] The initial insult results in neuronal injury and can disrupt the blood–brain barrier. Microglial cells resident in the central nervous system react to this injury within minutes, and become chronically activated.[8,9] Once transformed, microglia become indistinguishable from peripheral macrophages, secreting cytokines and acting as antigen-presenting cells.[10] In animal models, the initial inflammatory process has been shown to persist for at least a year, particularly within the thalamus.[5,7,11] In humans, post-mortem studies have shown microglial activation many

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TABLE 1: Demographics and Clinical Data of All Traumatic Brain Injury Patients

Age, yr	Sex	Education Level	Etiology	Lowest GCS	PTA, h	Medication	Interval since Trauma, mo
45	M	Postgraduate	Unknown	4	24	Gabapentin, modafinil, amitriptyline	72
55	M	Postgraduate	Fall	4	UK	Nil	36
42	M	School to 18 years	Pedestrian hit by a car	4	432	Nil	72
36	M	Postgraduate	Cycling accident	6	24	Nil	24
42	M	School to 16 years	Motorcycle accident	4	UK	Trospium chloride, folic acid	204
40	M	Graduate degree	Motorcycle accident	4	1,008	Nil	132
42	F	Postgraduate	Pedestrian hit by a car	3	144	Codeine, paracetamol	72
45	M	School to 16 years	Assault	4	5,040	Thiamine	11
49	M	School to 18 years	Probable assault	4	2	Nil	11
38	M	Graduate	Motorcycle accident	6	UK	Citalopram, modafinil, omeprazole	108

GCS = Glasgow Coma Scale; PTA = post traumatic amnesia; UK = unknown.

years after TBI.[12] Sites of activation often coincide with those of neuronal degeneration and axonal abnormality, and include disconnected nuclei such as the thalamus.[6,13]

The inflammatory response to brain injury can be studied in vivo using the positron emission tomography (PET) ligand [11C](R)PK11195 (PK).[14,15] PK binds to the translocator protein (TSPO) expressed by the mitochondria of activated microglia. This acts as a cholesterol transporter protein and was formerly known as the peripheral benzodiazepine receptor.[16] In humans, PK PET detects subacute microglial activation at the site of strokes, as well as in remote white matter connected to the lesion.[14,15] Later, thalamic and brainstem microglial activation becomes evident due to the disconnection of these areas. Autoradiographic studies in rat models of TBI demonstrate an increased thalamic uptake of [3H]PK11195 linked to a 31-fold increase in microglial numbers in the thalamus ipsilateral to a cortical injury.[17]

Here we employ PK PET to study in vivo the inflammatory response following TBI. In a preliminary investigation of this issue, we selected a group of patients in the chronic phase after TBI to test whether a persistent inflammatory response is present in injuries of varying severity. Motivated by the findings of previous reports, we investigated PK binding in a number of regions of interest. These include cortical structures such as the hippocampi, subcortical structures such as the thalami, and large white matter tracts frequently damaged by TBI. We also investigated whether microglial activation is related to measures of disease severity derived from structural magnetic resonance imaging (MRI), and whether persistent microglial activation is associated with more pronounced cognitive impairment.

Subjects and Methods

Patients: Demographic and Clinical Details

Eleven patients with a history of TBI were recruited, and 10 were included in the analysis (mean age ± standard deviation [SD] 43±5.3 years, range 36-54 years, and mean time since injury ± SD 6.2±5.3 years, range 0.9-17 years; see Supplementary Methods). All had suffered moderate to severe TBI based on the Mayo Clinic criteria.[18] Patients were recruited at least 11 months after their injury (Table 1). Conventional neuroimaging was reviewed by a senior neuroradiologist. Five patients had no abnormalities visible on T1 MRI. The remaining 5 had significant focal lesions with damage seen mostly in the frontal (n = 4) or temporal (n = 3) lobes (Fig 1). Two patients had evidence of microbleeds on gradient echo imaging. One patient had undergone a parietotemporal lobectomy following TBI. All patients and control subjects gave written

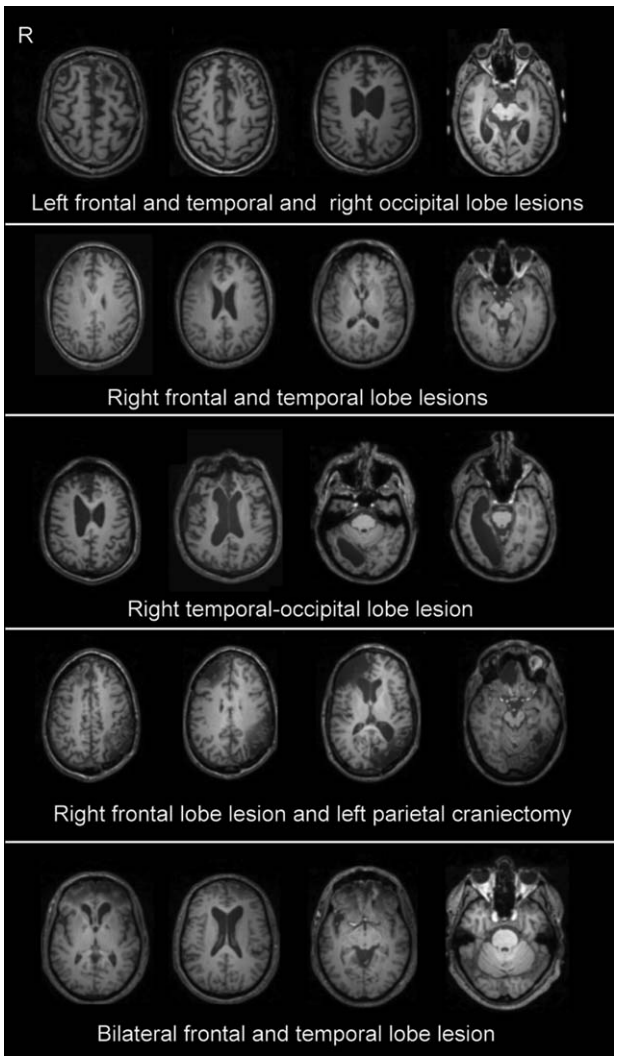

FIGURE 1: Transverse sections through T1-weighted magnetic resonance imaging in traumatic brain injury patients (n = 5) with focal brain lesions. R = right.

informed consent. The project was approved by Hammersmith and Queen Charlotte's and Chelsea Research Ethics Committee.

Control Groups

Two nonoverlapping groups of control subjects were used in this study. Seven age-matched controls underwent PK PET scanning and volumetric MRI scanning (mean age ± SD 46 ± 4.0 years, range 42–50 years). Fifteen age-matched subjects underwent the neuropsychological assessment (mean age ± SD 37.3 ± 11.3 years, range 19–60 years), and of those 10 age-matched control subjects had diffusion tensor imaging (mean age ± SD 40 ± 10.9 years, range 19–60 years).

Neuropsychological Assessment

A comprehensive neuropsychological assessment was performed on all TBI subjects and on 15 age-matched controls of similar premorbid intellectual ability. The test battery used was designed to be sensitive to cognitive impairments commonly observed following TBI (see Supplementary Methods).

Volumetric and Diffusion Tensor MRI

Standard protocols were used for high-resolution T1, gradient-echo (T2*), and diffusion tensor imaging (DTI) to assess the extent of focal brain injury and white matter disruption (see Supplementary Methods). Fractional anisotropy (FA) and mean diffusivity were calculated in 3 regions of interest within the corpus callosum, as well as the anterior and posterior internal capsule. These regions are frequently disrupted by diffuse axonal injury, and provide a representative measure of the degree of white matter tract damage.[19,20]

PET Image Acquisition and Analysis

A high-level overview of our methodology is provided in Figure 2. PET scanning was performed using standard protocols at the Cyclotron Building, Hammersmith Hospital, London, United Kingdom, using a Siemens ECAT 962 EXACT HR+ scanner (see Supplementary Methods). Thirty seconds after the start of emission scanning, a mean dose of 370.9MBq of PK was administered intravenously over 10 seconds into the antecubital vein. This was followed by a 60-minute dynamic emission PET scan acquired as 18 time frames. The ligand PK binds to TSPO expressed by activated microglial cells. The widespread expression of this protein makes it difficult to select a reference region representing nonspecific PK uptake. For this reason, we used a supervised clustering procedure to identify reference clusters of voxels in the gray matter having PK time activity curves mirroring those of controls.[21] These clusters could be widely distributed (see Supplementary Methods for more information).

Brain Segmentation and Region of Interest Definition

PK binding potentials were sampled from a number of anatomically defined regions of interests (ROIs). The MAPER (multi-atlas propagation with enhanced registration) procedure was used to generate anatomical ROIs in the subjects' native space. The procedure has previously been shown to yield accurate and robust segmentations in normal subjects and patients with dementia.[22,23] This approach minimizes the potential sampling error associated with misregistration and brain atrophy. ROIs containing focal brain injury were removed from the analysis (5 patients), as correct anatomical segmentation of the injured region was not always possible. The following regions were chosen to provide a representative sampling of cortical, subcortical, and white matter structures, and included a number of regions likely to be affected by TBI: the anterior and posterior cingulate cortices, inferior and superior frontal gyri, hippocampi, occipital lobes, cerebellum, caudate, putamen, brainstem and thalamic nuclei, corpus callosum, and anterior and posterior limbs of the internal capsule.

In the 5 patients with focal brain injury, we investigated PK binding within the lesion, the lesion penumbra, and the normal gray and white matter of the same hemisphere. We defined cylinder-shaped ROIs 10mm long with a 5mm radius in and around the most prominent lesion (Supplementary Fig 1). One ROI was placed centrally within the lesion, and a second within tissue adjacent to the lesion that returned abnormal T1 signal. Cylinders were orientated parallel to the long axis of

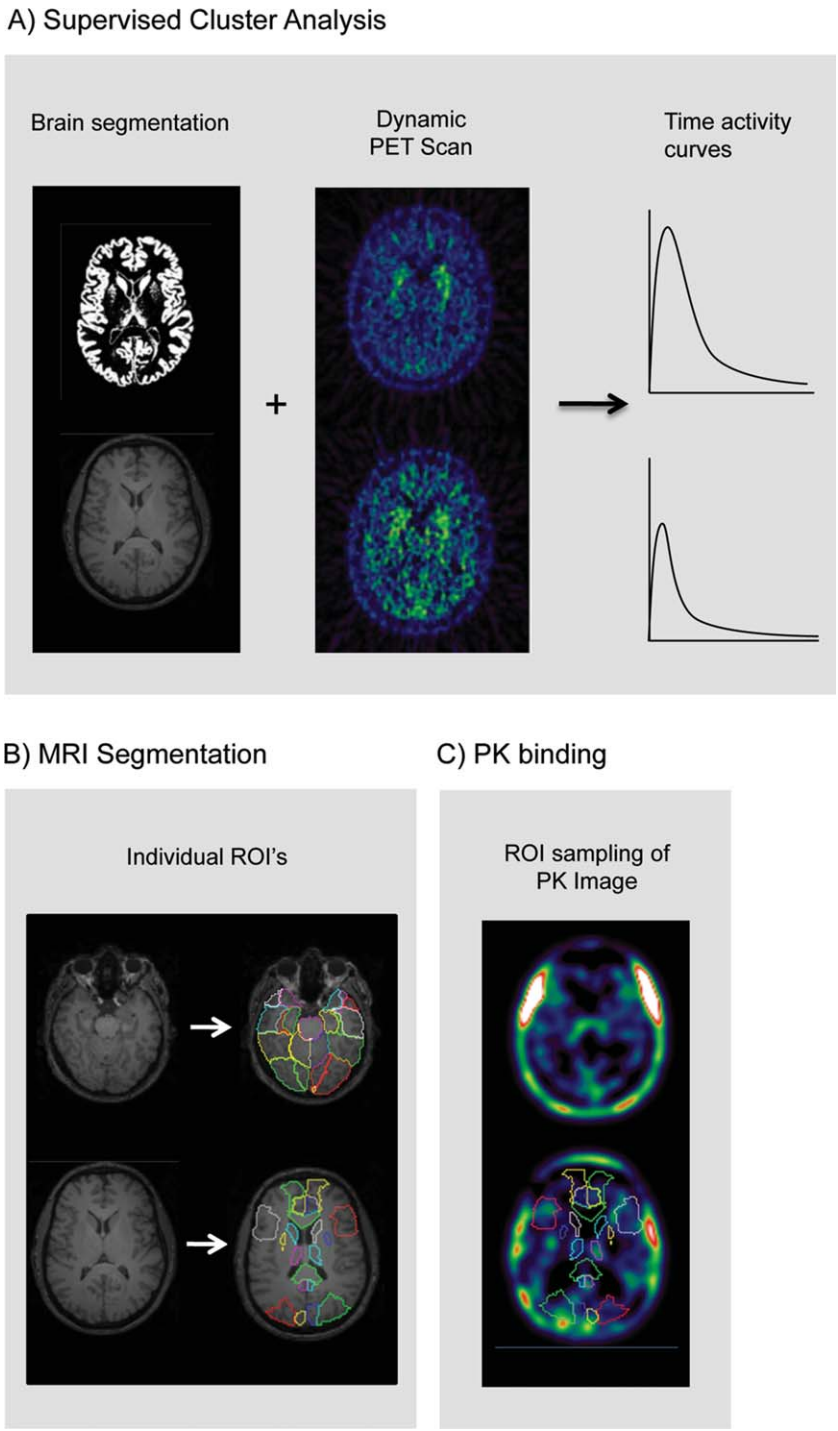

FIGURE 2: High-level overview of the methodology used for [11C](R)PK11195 (PK) region of interest (ROI) analysis. (A) PK binding potential images are first created using supervised cluster analysis. Time activity curves (TACs) are calculated for each voxel of the subject's dynamic positron emission tomography (PET) scan. TAC kinetics are used to classify pixels into tissue groups using tissue segmentation from the subjects' magnetic resonance imaging (MRI) scan. For example, the gray matter segmentation is used as a reference region in which TACs are calculated for normal and abnormal PK binding. (B) ROIs are generated using the automated MRI segmentation program MAPER (multi-atlas propagation with enhanced registration). (C) These individualized ROIs are then used to sample PK binding from the parametric PK binding potential imaged generated by supervised cluster analysis.

the lesion. A further 2 ROIs were placed in gray and white matter returning normal magnetic resonance signal in the same hemisphere as the lesion sampled.

Whole-Brain Voxel-Wise Analysis

An additional interrogation of the whole-brain analysis at a voxel level was performed using SPM5 (http://www.fil.ion.ucl.

ac.uk/spm/software/spm5/). Here group differences in PK binding potentials were tested across all voxels in the image (see Supplementary Methods).

Results

Neuropsychology

Our TBI patients showed a characteristically slowed speed of information processing.[24] Significantly slower responses were seen across a range of cognitive tasks of varying complexity (Table 2). In other ways the patients were well matched neuropsychologically with controls, and indeed they outperformed the control group on a measure of verbal reasoning. One patient could not be fully assessed because of upper limb disability and difficulty communicating verbally.

TBI Patients Show Persistent Increases in Microglial Activation Remote from Focal Damage

Patient PK binding potentials were significantly higher than those of controls in a number of brain regions distant from any focal damage (Fig 3). Initial analysis showed no significant hemispheric differences in binding potentials ($p > 0.3$ for all paired Student t test interhemispheric comparisons). Therefore, PK binding is reported as an average of binding in the 2 hemispheres where this is appropriate (Fig 4). Analysis of variance showed a significant group by region interaction ($F_{1,13} = 1.09$, $p = 0.033$), resulting from higher patient PK binding in the thalami ($t = 4.443$, $df = 15$, $p < 0.001$), putamen ($t = 3.63$, $df = 15$, $p = 0.002$), occipital lobes ($t = 2.75$, $df = 15$, $p = 0.015$), and posterior limb of the internal capsules ($t = 2.67$, $df = 15$, $p = 0.017$). Nonparametric testing with Mann-Whitney U tests confirmed these results (thalami $p = 0.005$, putamen $p = 0.006$, occipital lobes $p = 0.008$, anterior limb of internal capsule $p = 0.011$). Thalamic PK binding potentials remained significantly elevated compared to controls after Bonferroni correction for multiple comparisons. Whole-brain interrogation using SPM also localized bilateral increases in thalamic PK binding in the TBI patients (see Supplementary Results and Supplementary Fig 2).

There was no correlation between the time interval since head trauma and PK binding ($p > 0.2$). The highest PK binding was actually observed in the patient whose injury was most remote in time (see Fig 3). PK binding also did not correlate with structural measures of brain injury. In the 4 regions showing significantly raised PK binding, there was no correlation between tracer uptake and the volume of the regions ($p > 0.2$ for all analyses). Additionally, there was no correlation between PK binding and the measures of white matter damage provided by DTI. TBI often produces diffuse axonal injury, and this can be quantified as loss of white matter anisotropy (directionality of water diffusion) using DTI.[19,20] As expected, compared to a matched control group, our patients showed evidence of white matter disruption. Fractional anisotropy was significantly lower and mean diffusivity higher in all 3 white matter regions in the patient group, except for FA measured in the anterior limb of the internal capsule. However, there was no significant correlation between PK binding and either of these metrics ($p > 0.2$ for all analyses).

Microglial Activation Is Not Persistently Increased around the Site of Focal Brain Lesions

Visual inspection of individual TBI patient PK images showed no obviously increased uptake in the vicinity of focal lesions evident on MRI (see Fig 3). To confirm this quantitatively, we modeled PK binding in regions of interest placed in and around the most prominent focal lesion. PK binding was similar within the focal lesion and in the lesion penumbra (Fig 5). This was, however, significantly lower for both those regions than in the thalami (lesion $t = -20.1$, $df = 4$, $p < 0.005$, penumbra $t = -25.8$, $df = 4$, $p < 0.005$), and in normal-appearing white matter (lesion $t = -3.9$, $df = 4$, $p = 0.017$, penumbra $t = -7.1$, $df = 4$, $p = 0.002$) of the same hemisphere. PK binding in the lesion was also significantly lower than binding in normal-appearing gray matter of the same hemisphere (lesion $t = -3.9$, $df = -22.4$, $p < 0.005$). To assess regions connected by transcallosal fibers to areas of focal injury, we also examined PK binding in ROIs contralateral to focal brain injury within the frontal and temporal lobes. Binding potentials were within the normal range (mean $\pm$ 2 SD) in all of these regions (Supplementary Table 2).

Increased Thalamic Microglial Activation Is Correlated with the Degree of Cognitive Impairment

In distant regions showing increased microglial activation following TBI, we next investigated whether cognitive impairment (defined as impairment of the TBI group relative to controls) correlated with PK binding. This analysis should be regarded as preliminary, given our small sample size. Higher thalamic PK uptake correlated inversely with the speed of processing complex information, as indexed by time to complete the conflicting (Inhibition) trials on the Stroop (Fig 6), a test of executive function (Spearman $r = 0.828$, $p = 0.006$). This result remained significant after controlling for current intelligence quotient, and remained borderline significant after controlling for multiple comparisons using Bonferroni correction (α threshold of 0.004). The speed of complex information processing (Stroop Inhibition) and basic

TABLE 2: Neuropsychological Test Results: Traumatic Brain Injury and Control Patients

Cognitive Domain	Cognitive Variable	TBI, Mean ± SD[a]	Control, Mean ± SD[a]	TBI vs Control
Processing speed				
Visual search	TMT Trails A (s)	31.7 ± 15.0, n = 10	19.7 ± 4.5, n = 14	$t = 2.06$[b]
Complex	TMT Trails B (s)	57.3 ± 28.6, n = 10	43.0 ± 12.6, n = 14	$t = 1.16$[b]
Naming	Stroop Color Naming (s)	37.9 ± 12.0, n = 9)	33.2 ± .4.0, n = 14)	$t = 3.15$[c]
Reading	Stroop Word Reading (s)	26.3 ± 6.3, n = 9	28.9 ± 6.3, n = 15	$t = -0.53$[b]
Complex	Stroop Inhibition (s)	69.7 ± 30.7, n = 9	23.3 ± 4.4, n = 15	$t = 4.50$[c]
Choice RT	CRT median RT (ms)	456 ± 62, n = 9	408 ± 51, n = 15	$t = 2.16$[d]
Executive function				
Inhibition	Inhibition, naming (s)	31.8 ± 22.4, n = 9)	28.7 ± 17.6, n = 15)	$t = 0.23$[b]
Cognitive flexibility	Inhibition/Switching, naming + reading ÷ 2 (s)	46.7 ± 27.9, n = 9	32.2 ± 10.5, n = 14	$t = 1.39$[b]
Word generation fluency	Letter Fluency FAS Test, total	40.4 ± 4.8, n = 9	46.0 ± 12.0, n = 15	$t = 0.36$[b]
Set-shifting	Alternating-switch cost, TMT Trails B − A (s)	25.6 ± 17.8, n = 10	23.3 ± 9.8, n = 14	$t = 0.57$[b]
Memory				
Immediate/ working	Digit Span forward	10.5 ± 1.5, n = 10	11.5 ± 2.2, n = 15	$t = -1.28$[b]
	Digit Span backward	7.2 ± 1.4, n = 10	7.5 ± 2.0, n = 15	$t = -0.66$[b]
Logical	WMS-III LM I first recall total	28.4 ± 3.7, n = 9	26.4 ± 9.0, n = 15	$t = 0.02$[b]
	WMS-III LM I total	47.1 ± 5.4, n = 9	42.7 ± 13.7, n = 15	$t = 0.17$[b]
	WMS-III LM II delayed recall	31.9 ± 5.1, n = 9)	25.6 ± 9.2, n = 15)	$t = 0.99$[b]
Associative	PT immediate recall total	26.0 ± 5.7, n = 10	26.9 ± 7.1, n = 15	$t = -1.03$[b]
Intellectual ability				
Reading	WTAR age-scaled score	107 ± 10.1, n = 9	112 ± 9.8, n = 15	$t = -1.10$[b]
Verbal	WASI Similarities	39.4 ± 3.7, n = 9	34.5 ± 6.3, n = 15	$t = 2.45$[d]
Nonverbal	WASI Matrix Reasoning	28.1 ± 3.5, n = 10	26.8 ± 5.0, n = 15	$t = 0.71$[b]

Neuropsychological results for TBI patients and age-matched control group. Group contrasts were made controlling for individual differences in current intellectual ability. Color Naming, Word Reading, Inhibition, Inhibition/Switching, and Letter Fluency are subtests of the Delis-Kaplan Executive Function System.
[a]Following exploratory data analysis, control subjects identified as extreme outliers (≥3 × interquartile range) were excluded.
[b]Nonsignificant.
[c]$p \leq 0.01$.
[d]$p \leq 0.05$.CRT = Choice-Reaction Task; FAS Test = generating as many words as possible in one minute beginning with "F," "A," and "S"; PT = People Test; RT = reaction time; SD = standard deviation; TBI = traumatic brain injury; TMT = Trail Making Test; WASI = Wechsler Abbreviated Scale of Intelligence; WMS-III LM = Wechsler Memory Scale Logical Memory, 3rd ed.; WTAR = Wechsler Test of Adult Reading.

Stroop Color Naming was also correlated with thalamic volume (Spearman $r = -0.787$, $p = 0.12$ and $r = -0.733$, $p = 0.025$, respectively), such that smaller volumes were associated with poorer performance. The relationship between PK binding and complex processing speed approached significance after controlling for the influence of thalamic atrophy (Spearman $r = 0.670$, $p = 0.069$). The other 3 regions with increased PK binding

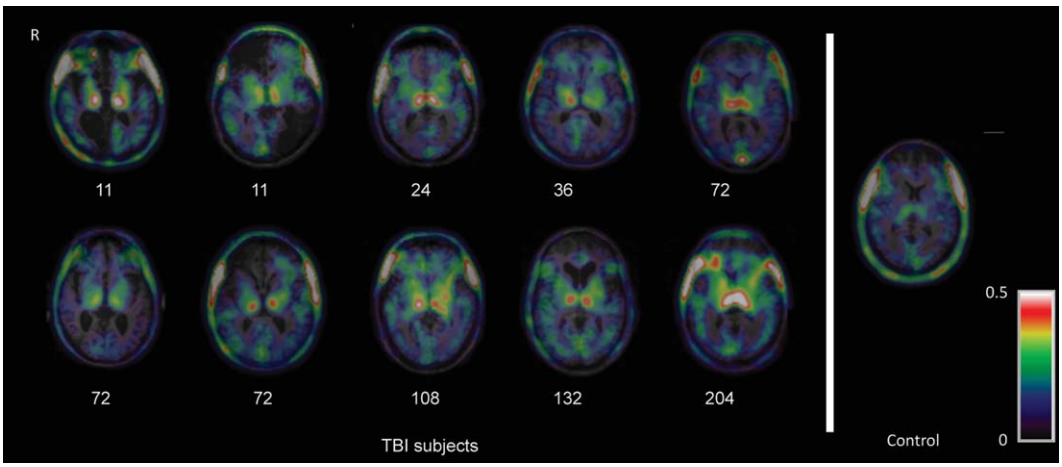

FIGURE 3: Chronic microglial activation is present following traumatic brain injury (TBI). Overlay images of the transverse T1 magnetic resonance imaging at the level of the thalamus superimposed with [11C](R)PK11195 (PK) images of all TBI subjects and a representative control subject. Numbers indicate time in months from the time of TBI to positron emission tomography scanning. Images illustrate the greater binding of PK in the thalami of all TBI subjects. R = right.

did not show significant correlations with the degree of cognitive impairment.

Discussion

TBI is often regarded as a single event causing static pathological damage. Using PK PET, we demonstrate in vivo that microglial activation persists many years after the initiating TBI. This result builds on findings in animal models and postmortem human studies, which also show that TBI triggers a long-term inflammatory response.[5,6,12] Surprisingly, persistent microglial activation is not found in areas of focal brain injury, but rather is most prominent within subcortical structures remote from the site of focal injury, particularly the thalami and putamen. This may reflect the dense connectivity of these structures. TBI often results in diffuse axonal injury that disconnects subcortical structures,[25] and microglia have been shown to

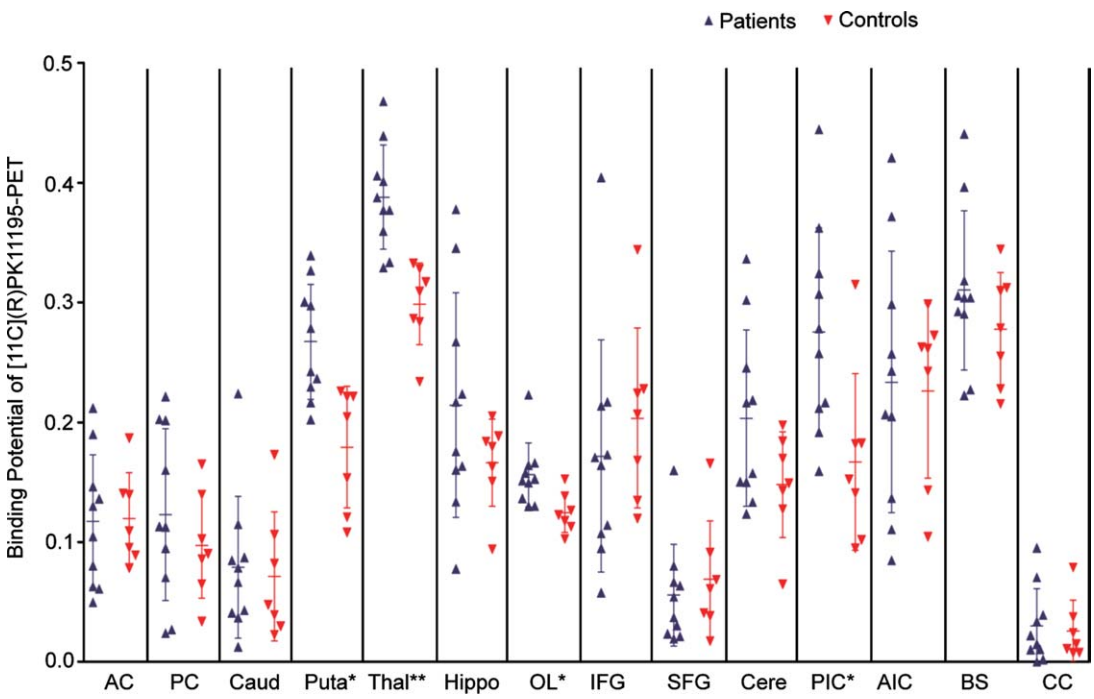

FIGURE 4: [11C](R)PK11195 binding in the regions of interests investigated. Individual subjects' binding potentials are plotted with patients in blue and control subjects in red. PET = positron emission tomography; AC = anterior cingulate; PC = posterior cingulate; Caud = caudate; Puta = putamen; Thal = thalami; Hippo = hippocampus; OL = occipital lobe; IFG = inferior frontal gyrus; SFG = superior frontal gyrus; Cere = cerebellum; PIC = posterior limb of internal capsule; AIC = anterior limb of internal capsule; BS = brainstem; CC = corpus callosum. *$p < 0.05$ significance; **survives Bonferroni multiple comparison correction.

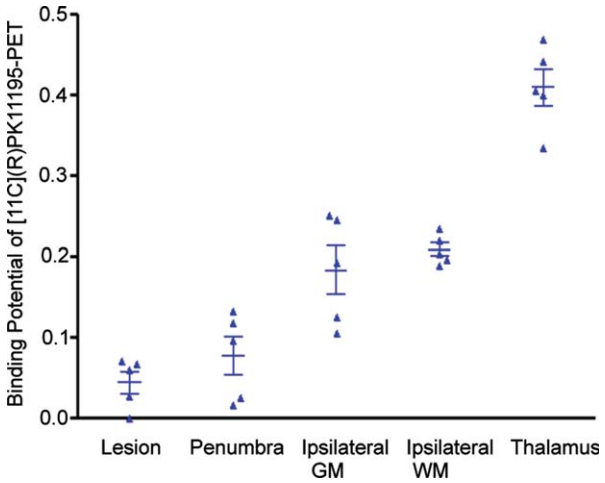

FIGURE 5: Microglia are not chronically activated around the site of focal brain damage following traumatic brain injury. [11C](R)PK11195 (PK) binding potentials (BPs) in representative regions drawn at the lesion site, in the penumbral region of the lesion, and within normal-appearing gray and white matter in the same hemisphere. Thalamic binding values correspond to the mean BP of the right and left thalami. Results demonstrate no abnormal increase in PK binding in or around the lesion site. PET = positron emission tomography; GM = gray matter; WM = white matter.

be persistently activated at sites of white matter abnormality.[5,6,14] Patients show a highly variable clinical outcome following TBI, for reasons that are poorly understood,[2] and we provide evidence that impaired information processing after TBI is associated with greater thalamic microglial activation. Our results emphasize that TBI should be viewed as a condition with a persistent inflammatory component, and this may provide a novel target for therapeutic intervention.

Microglial activation is observed within the first minutes of focal brain injury, and activated cells are seen in remote but connected structures as the inflammatory response develops.[8,9] For example, 2 weeks after a stroke affecting the corticospinal tract, high PK binding has developed at the infarct site. This is accompanied by increased binding in connected parts of the pyramidal tract and ipsilateral thalamus.[14] At 6 months, the remote microglial activation persists, whereas binding at the infarct site has normalized.[14] This suggests that microglia local to brain injury behave differently from those in remote connected structures, a distinction supported by distinct patterns of major histocompatibility complex expression.[11,26] Our work corroborates these chronic findings after stroke in TBI patients. First, low PK binding at the site of focal lesions provides evidence that microglial activation does not persist in these areas. This could be due to the astrocytic response to TBI enclosing and isolating the damaged area.[27] Alternatively, microglia may persist at the site of focal lesions but downregulate expression of TSPO over time. Second, persistent PK binding is seen after TBI, and is particularly prominent in the thalami. Importantly, the nature of this thalamic signal early after TBI has been confirmed by a combined PK autoradiography and immunohistochemistry study in rats, which demonstrated that high thalamic binding shortly after cortical injury is secondary to the presence of large numbers of activated microglia, with a minor contribution from small numbers of other cell types such as astrocytes.[17]

Animal models of TBI also demonstrate that ongoing neuronal damage is seen in the striatum and thalamus,[28] and that activated microglia are present in these regions up to 1 year after trauma.[5,11] In humans, postmortem studies also show that activated microglia are present in both thalami and the brainstem many years after TBI.[6,13] In the thalami, cells are mainly observed in white matter surrounding separate thalamic nuclei.[6] Following motor stroke, increased PK binding in parts of the pyramidal tract remote from the infarct has been shown to correlate with the extent of white matter damage,[14] and this could also be an important factor in triggering persistent microglial activation following TBI. As a group, our patients showed evidence of generalized white matter damage, consistent with the presence of diffuse axonal injury.[19,20] However, the location of increased PK binding did not correlate with the white matter structural change detected by DTI. This could reflect the high individual variability in the location of white matter damage, which depends on the nature of each injury, making correlations difficult to demonstrate at a group level.

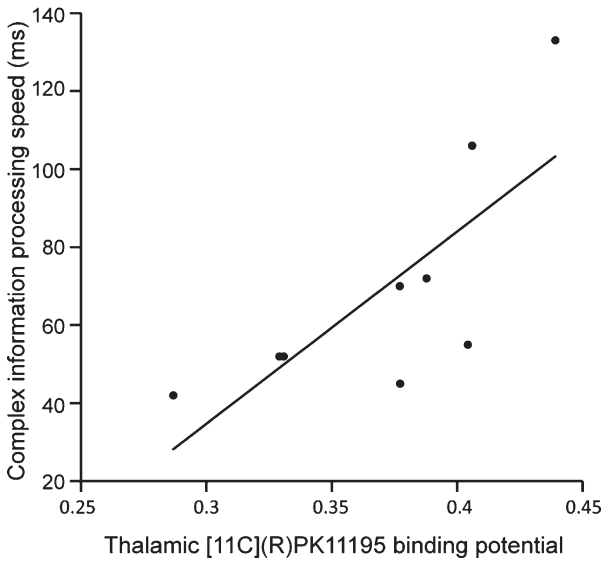

FIGURE 6: Thalamic microglial activation correlates with complex information-processing speed. [11C](R)PK11195 binding in bilateral thalamic regions is plotted against incongruent items on the Delis-Kaplan Executive Function System Color-Word Interference (Stroop) Inhibition subtest, providing a measure of speed of processing complex information.

The clinical significance of persistent microglial activation remains uncertain, and PK is likely to label subpopulations of activated microglia whose functions following TBI may be distinct and time dependent. Microglia play an important role in the immune response, releasing cytokines, acting as antigen-presenting cells, and clearing debris in the acute phase after brain injury.[9] However, these benefits may be countered by damaging effects when microglial activation is prolonged and accompanied by an excessive and poorly regulated inflammatory response.[12] Activated microglia can be cytotoxic,[29] and their persistent activation might predispose to the development of neurodegenerative conditions such as Alzheimer disease in susceptible individuals, or provide the context in which such diseases take a more aggressive course.[12,30] In contrast, recent work suggests that persistent microglial activation in regions remote from focal injury might promote brain repair.[5,11,14] For example, in humans, microglial activation in the pyramidal tract remote from a motor stroke was correlated with a positive clinical outcome.[14] In nonhuman primates, microglia continue to release brain-derived neurotrophic factor (BDNF) many months after an injury, when the production of other cytokines associated with the acute inflammatory reaction has stopped.[14] The release of BDNF is associated with local synaptogenesis, which suggests that activated microglia might play a role in regulating brain repair after TBI.[11]

Our results also provide evidence for a correlation between the amount of microglial activation in the thalamus and aspects of cognitive function, although this relationship was of borderline significance after controlling for multiple comparisons and should be regarded as preliminary. Patients with higher thalamic PK binding showed more impaired information-processing speed. This relationship is unlikely to simply be secondary to thalamic atrophy, as there was no significant correlation between PK binding and thalamic atrophy, despite the presence of a separate relationship between processing speed and thalamic volume. Cognitive impairment after TBI results in part from the disconnection of distributed brain networks, and damage within the thalamic nuclei particularly involved with cognitive functions is often observed,[6] which may explain the relationship. Persistent microglial activation in the thalamus could drive adaptive changes in synaptic plasticity, which are most prominent in patients with severe injury. Alternatively, microglial activation could simply reflect underlying thalamic damage or directly produce neuronal damage that evolves over time. A cross-sectional design, such as that we employed, does not help to decide between these possibilities. The results we report suggest the need for large longitudinal clinical studies using PK, which will be necessary to determine the functional significance of thalamic microglial activation.

The observation that microglia are persistently activated emphasizes that TBI should not be viewed as a static insult, but instead as a trigger for a complex cascade of events that includes a persistent inflammatory state. This suggests that the window of opportunity for therapeutic intervention following TBI may be much longer than is usually considered. In vivo PK imaging provides a biomarker to investigate this inflammatory state, and can be used to study the time course of inflammation after TBI and the effects of interventions aimed at manipulating the inflammatory cascade.

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Potential Conflicts of Interest

D.J.B.: consultancy, GE Healthcare.

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