Role of Translocator Protein Density, a Marker of Neuroinflammation, in the Brain During Major Depressive Episodes

Elaine Setiawan, PhD; Alan A. Wilson, PhD; Romina Mizrahi, MD, PhD; Pablo M. Rusjan, PhD; Laura Miller, HBSc; Grazyna Rajkowska, PhD; Ivonne Suridjan, HBSc; James L. Kennedy, MD; P. Vivien Rekkas, PhD; Sylvain Houle, MD, PhD; Jeffrey H. Meyer, MD, PhD, FRCP

IMPORTANCE The neuroinflammatory hypothesis of major depressive disorder is supported by several main findings. First, in humans and animals, activation of the immune system causes sickness behaviors that present during a major depressive episode (MDE), such as low mood, anhedonia, anorexia, and weight loss. Second, peripheral markers of inflammation are frequently reported in major depressive disorder. Third, neuroinflammatory illnesses are associated with high rates of MDEs. However, a fundamental limitation of the neuroinflammatory hypothesis is a paucity of evidence of brain inflammation during MDE. Translocator protein density measured by distribution volume (TSPO V) is increased in activated microglia, an important aspect of neuroinflammation.

OBJECTIVE To determine whether TSPO V is elevated in the prefrontal cortex, anterior cingulate cortex (ACC), and insula in patients with MDE secondary to major depressive disorder.

DESIGN, SETTING, AND PARTICIPANTS Case-control study in a tertiary care psychiatric hospital from May 1, 2010, through February 1, 2014. Twenty patients with MDE secondary to major depressive disorder and 20 healthy control participants underwent positron emission tomography with fluorine F-18-labeled N-(2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl)acetamide ([18F]FEPPA). Patients with MDE were medication free for at least 6 weeks. All participants were otherwise healthy and nonsmokers.

MAIN OUTCOMES AND MEASURES Values of TSPO V in the prefrontal cortex, ACC, and insula.

RESULTS In MDE, TSPO V was significantly elevated in all brain regions examined (multivariate analysis of variance, $F_{15,23} = 4.5$ ($P = .001$)). The magnitude of TSPO V elevation was 26% in the prefrontal cortex (mean [SD] TSPO V, 12.5 [3.6] in patients with MDE and 10.0 [2.4] in controls), 32% in the ACC (mean [SD] TSPO V, 12.3 [3.5] in patients with MDE and 9.3 [2.2] in controls), and 33% in the insula (mean [SD] TSPO V, 12.9 [3.7] in patients with MDE and 9.7 [2.3] in controls). In MDE, greater TSPO V in the ACC correlated with greater depression severity ($r = 0.63$ ($P = .005$)).

CONCLUSIONS AND RELEVANCE This finding provides the most compelling evidence to date of brain inflammation, and more specifically microglial activation, in MDE. This finding is important for improving treatment because it implies that therapeutics that reduce microglial activation should be promising for MDE. The correlation between higher ACC TSPO V and the severity of MDE is consistent with the concept that neuroinflammation in specific regions may contribute to sickness behaviors that overlap with the symptoms of MDE.
Major depressive disorder (MDD) is highly prevalent and has an important impact, with active symptoms present in 4% of the adult population. Although MDD exhibits multiple molecular phenotypes, accumulating evidence suggests a role of inflammation in generating the symptoms of a major depressive episode (MDE). For example, induction of inflammation is associated with sad mood in humans, and direct induction of the central immune system in rodents is associated with the sickness syndrome of anhedonia, weight loss, and anorexia, which overlap with the diagnostic criteria for MDE. Also in MDD, several markers of peripheral inflammation, including levels of C-reactive protein, interleukin 6 (IL-6), and tumor necrosis factor (TNF), are frequently increased. Conditions that create markers of peripheral inflammation, including levels of TNF, interleukin 1β (IL-1β) in Brodmann area 10, and IL-1β in the dorsolateral prefrontal cortex (PFC), did not identify this result. Among investigations in suicide completers, 1 study reported greater HLA-DR staining, a marker of microglial activation, in the ACC of 7 patients with MDD. Microarray studies have had mixed results, with a positive finding by Shelton et al of increased proinflammatory and anti-inflammatory cytokine messenger RNA in Brodmann area 10 in 14 patients with MDD. In contrast, several other microarray studies, most of which sampled adjacent regions of the PFC, did not identify this result. Among investigations in suicide completers, a study reported greater HLA-DR staining, a marker of microglial activation, in the ACC and PFC, and a second study reported greater levels of IL-6, TNF, and IL-1β in Brodmann area 10. Neither study of suicide found a relationship to MDD (or MDE), but fewer than 10 patients with MDD were included in each study. The mixed results among postmortem investigations in MDD have been attributed to issues of variation in brain regions sampled, inclusion of patients with early- and late-onset MDD, comorbidity of other psychiatric disorders and addiction, and, with the exception of the microarray studies, small sample size, although lack of focus on sampling the state of MDE may be important for investigations of neuroinflammation.

Methods

All participants provided written informed consent after all procedures were fully explained. The protocol and informed consent forms were approved by the Research Ethics Board of the Center for Addiction and Mental Health, Toronto, Ontario, Canada.

Participants

Twenty patients with a current MDE secondary to MDD (hereinafter termed patients with MDE) and 20 age-matched healthy controls completed the study. Participants were recruited from the Toronto-area community and a tertiary care psychiatric hospital (Centre for Addiction and Mental Health) from May 1, 2010.
Translocator Protein Density in MDE

Each participant underwent 1-[18F]FEPPA PET scan conducted at the Research Imaging Centre at the Centre for Addiction and Mental Health. For this scan, intravenous [18F]FEPPA was administered as a bolus (mean [SD], 180.5 [14.5] MBq [to convert to millicuries, multiply by 0.02703]). The [18F]FEPPA was of high radiochemical purity (>96%) and high specific activity (mean [SD], 119 [125] TBq/mmol). Manual and automatic arterial blood sampling (programmable blood sampler PBS-101; Veenstra Instruments) was performed to determine the ratio of radioactivity in whole blood to radioactivity in plasma and the unmetabolized radioligand in plasma needed to create the input function for the kinetic analysis. The scan duration was 125 minutes after the injection of [18F]FEPPA. The PET images were obtained using a 3-dimensional brain scanner (HRRT; CPS/Siemens). All PET images were corrected for attenuation using a single photon point source, cesium 137 (half-life, 30.2 years; energy, 662 keV) and were reconstructed using a filtered back-projection algorithm, with a Hann filter at Nyquist cutoff frequency.

Each participant underwent 2-dimensional axial proton-density magnetic resonance imaging acquired with a 1.5-T scanner (Siemens) (section thickness, 2 mm; repetition time, >3500 milliseconds; echo time, 13 milliseconds; flip angle, 90°; number of excitations, 2; acquisition matrix, 256 × 256; and field of view, 22 cm). Regions of interest were automatically generated using the in-house software (ROMI) as previously described. Time activity curves were used to estimate TSPO VT using a 2-tissue compartment model that has been shown previously to be an optimal model to quantitate TSPO VT with [18F]FEPPA PET.

DNA Extraction and Polymorphism Genotyping

The binding affinity of the second generation of radiotracers for TSPO, including [18F]FEPPA, is known to be affected by a codominantly expressed single-nucleotide polymorphism (rs6971; C→T) in exon 4 of the TSPO gene (NCBI Entrez Gene 706). Individuals with high-affinity binding (Ala147/Ala147) and mixed-affinity binding (Ala147/Thr147) account for more than 90% of the population in North America. The polymorphism rs6971 was genotyped as described previously. One patient with MDE had low-affinity binding (Ala147/Thr147) and was not included in the analysis.

Statistical Analysis

For the primary hypothesis, we analyzed PET data by multivariate analysis of variance (MANOVA), with TSPO VT in the PFC, ACC, and insula as the dependent variables and diagnosis and genotype as the fixed factors. Main effects were considered significant at the conventional $P \leq .05$. Effects in each region, analyzed by univariate ANOVA, were considered significant after Bonferroni correction ($P \leq .017$).

As a secondary analysis, we performed a MANOVA that included every brain region sampled (eg, all cortical and subcortical regions) to assess the effect of diagnosis on TSPO VT. A partial correlation controlling for the rs6971 genotype was used in a secondary analysis to quantify the relationship between TSPO VT in the primary regions of interest and the severity of symptoms of MDE measured by the total 17-item HDRS score. The HDRS score was missing in 1 patient with MDE who

### Table 1. Demographic Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With MDE (n = 20)</th>
<th>Healthy Controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, No. (%)</td>
<td>12 (60)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>34.0 (11.3)</td>
<td>33.6 (12.8)</td>
</tr>
<tr>
<td>TSPO genotype, No. of participants(^a)</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>MAB</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>23.4 (5.4)</td>
<td>24.8 (2.9)</td>
</tr>
<tr>
<td>17-Item HDRS score, mean (SD)(^b)</td>
<td>20.0 (3.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Age at first MDE, mean (SD), y</td>
<td>15.7 (5.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Previous MDE, No. (%)</td>
<td>6 (3)</td>
<td>NA</td>
</tr>
<tr>
<td>Previous antidepressant trial, No. (%)</td>
<td>9 (45)</td>
<td>NA</td>
</tr>
<tr>
<td>No previous antidepressant trial, No. (%)</td>
<td>11 (55)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HAB, high-affinity binding; HDRS, Hamilton Depression Rating Scale; MAB, mixed-affinity binding; MDE, major depressive episode; NA, not applicable; TSPO, translocator protein.

\(^a\) Indicates single-nucleotide polymorphism rs6971 of the TSPO gene known to influence fluoro F 18-labeled N-(2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl)acetamide binding.

\(^b\) Scores were derived on the day of scanning, with data missing for 1 patient with MDE.
was not included in this analysis. Partial correlations were considered significant at the Bonferroni-corrected threshold of \( P \leq .008 \).

**Results**

We observed a global effect of diagnosis on TSPO \( V_T \) (Figure 1 and Table 2). A MANOVA including all subregions of the PFC and several other cortical and subcortical regions indicated a global brain effect of diagnosis with elevated TSPO \( V_T \) in the patients with MDE compared with the controls (main effect of diagnosis, \( F_{13,23} = 4.5 \) \( P = .001 \)). We also evaluated the regions selected in our hypothesis. Using the effect of diagnosis in the ANOVA by region, patients with MDE had significantly greater TSPO \( V_T \) in the PFC (\( F_{13,23} = 8.1 \) \( P = .007 \)), anterior cingulate cortex, \( F_{13,23} = 12.2 \) \( P = .001 \)), insula, \( F_{13,23} = 12.3 \) \( P = .001 \), and dorsal putamen, \( F_{13,23} = 14.1 \) \( P = .001 \). Ventral striatum, \( F_{13,23} = 6.9 \) \( P = .01 \), thalamus, \( F_{13,23} = 13.6 \) \( P = .001 \), and hippocampus, \( F_{13,23} = 7.5 \) \( P = .009 \). All second-generation TSPO radioligands, such as fluorine \( ^{18} \) F-labeled (N-(2-(2-fluoroethoxy)benzyl)-(4-phenoxypyridin-3-yl)acetamide, [(18F)FEPPA], show differential binding according to the single-nucleotide polymorphism rs6971 of the TSPO gene, resulting in HAB and MAB. Horizontal bars indicate means in each group.

The total 17-item HDRS score was positively correlated with TSPO \( V_T \) in the ACC after correcting for the rs6971 genotype (\( r = .63 \) \( P = .005 \)) (Figure 2). Similar correlations were found in the insula and PFC, but these did not survive Bonferroni correction (insula, \( r = 0.57 \) \( P = .01 \); PFC, \( r = 0.46 \) \( P = .06 \)).

In the patients with MDE but not in the healthy controls (eAppendix in the Supplement), BMI was significantly and negatively correlated with TSPO \( V_T \) in the insula after correcting for rs6971 genotype (\( r = -0.61 \) \( P = .006 \)). The relationship between BMI and TSPO \( V_T \) was also present in the ACC (\( r = -0.55 \) \( P = .02 \)) and the PFC (\( r = -0.49 \) \( P = .03 \)), but neither survived Bonferroni correction (for further details on the relationship to clinical characteristics, see the eTable in the Supplement). In the patients with MDE, none of the serum markers of inflammation had a significant positive correlation with TSPO \( V_T \) in the primary regions of interest (Table 3).

**Discussion**

This study is the first, to our knowledge, to detect microglial activation, as indicated by increased TSPO \( V_T \), in a substantial sample of patients with MDE. Although the finding was prominent in the primary regions of the PFC, ACC, and insula, it was also present throughout all the regions assayed. The highest levels of TSPO \( V_T \) occurred in patients with MDE with the

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**Figure 1. Elevated Translocator Protein Density Measured by Distribution Volume (TSPO VT) During a Major Depressive Episode (MDE) Secondary to Major Depressive Disorder (MDD)**

TSPO \( V_T \) was significantly greater in the 20 patients with MDE (15 with high-affinity binding [HAB] and 5 with mixed-affinity binding [MAB]) compared with the 20 healthy control participants (14 with HAB and 6 with MAB). Calculation of analysis of variance resulted in the following effects of diagnosis by region: prefrontal cortex, \( F_{13,23} = 8.1 \) \( P = .007 \); anterior cingulate cortex, \( F_{13,23} = 12.2 \) \( P = .001 \); insula, \( F_{13,23} = 12.3 \) \( P = .001 \); dorsal putamen, \( F_{13,23} = 14.1 \) \( P = .001 \); ventral striatum, \( F_{13,23} = 6.9 \) \( P = .01 \); thalamus, \( F_{13,23} = 13.6 \) \( P = .001 \); and hippocampus, \( F_{13,23} = 7.5 \) \( P = .009 \). All second-generation TSPO radioligands, such as fluorine \( ^{18} \) F-labeled (N-(2-(2-fluoroethoxy)benzyl)-(4-phenoxypyridin-3-yl)acetamide, [(18F)FEPPA], show differential binding according to the single-nucleotide polymorphism rs6971 of the TSPO gene, resulting in HAB and MAB. Horizontal bars indicate means in each group.
TSPO VT in the anterior cingulate cortex was positively related to scores on the 17-item Hamilton Depression Rating Scale (17-item HDRS) after correcting for the rs6971 genotype (0-7 indicates no depression; 8-15, mild symptom level; 16-20, substantial level of symptoms; and >20, moderate to severe depression). All second-generation TSPO radioligands, such as fluorine F18–labeled N-(2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl)acetamide ([18F]FEPPA), show differential binding according to the single-nucleotide polymorphism rs6971 of the TSPO gene, resulting in high-affinity binding (HAB) and mixed-affinity binding (MAB).

However, reducing microglial activation itself might also have therapeutic utility. Consistent with this viewpoint, minocycline hydrochloride, a second-generation tetracycline antibiotic known to reduce microglial activation may be monitored by techniques such as stimulating microglial targets like CX3CR1 to promote a more quiescent state, suppressing the effects of cytokines in the central nervous system, or promoting a shift in microglial activity toward repair-oriented functions by activating purinergic receptors, may hold promise.35 Reducing microglial activity toward repair-oriented functions by activating purinergic receptors, may hold promise.35 Reducing microglial activation may also be monitored by techniques such as [18F]FEPPA PET.

We found MDE to be associated with elevated TSPO VT across all brain regions examined, and regional TSPO VT was intercorrelated, although the relationships between TSPO VT and the severity of MDE were most pronounced in the ACC. We propose that although global mechanisms may account for elevated TSPO VT in multiple brain regions in MDD, greater TSPO VT in specific regions and/or their associated circuitry...
Table 3. Correlation Between Regional TSPO VT and Peripheral Inflammatory Markers in Major Depressive Episodes

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Region, r Value (P Value)*</th>
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<tbody>
<tr>
<td></td>
<td>Prefrontal</td>
</tr>
<tr>
<td><strong>Marker Only</strong></td>
<td></td>
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<tr>
<td>IL-1β</td>
<td>-0.35 (.13)*</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.20 (.39)</td>
</tr>
<tr>
<td>TNF</td>
<td>-0.29 (.21)</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.27 (.25)</td>
</tr>
<tr>
<td><strong>Controlled for rs6971 Genotype</strong></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>-0.39 (.10)</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.29 (.24)</td>
</tr>
<tr>
<td>TNF</td>
<td>-0.33 (.16)</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.52 (.02)</td>
</tr>
<tr>
<td><strong>Controlled for BMI</strong></td>
<td></td>
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<tr>
<td>IL-1β</td>
<td>-0.18 (.46)</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.12 (.62)</td>
</tr>
<tr>
<td>TNF</td>
<td>0.18 (.46)</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.15 (.54)</td>
</tr>
<tr>
<td><strong>Controlled for rs6971 Genotype and BMI</strong></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>-0.25 (.31)</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.22 (.39)</td>
</tr>
<tr>
<td>TNF</td>
<td>0.05 (.84)</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.42 (.08)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IL-1β, interleukin (IL) 1β; TNF, tumor necrosis factor; TSPO VT, translocator protein density measured by distribution volume.

*The r values represent the correlation coefficient (or partial correlation coefficient) followed by the 2-tailed, uncorrected P value. Positive r values reflect greater TSPO VT when a higher serum level of the peripheral marker is present.

The lack of correlation between the central and peripheral inflammatory markers is consistent with previous reports. Bromander et al. found no correlation between serum and cerebrospinal fluid TNF in patients undergoing knee surgery. Similarly, dissociation between central and peripheral cytokines in preclinical data has been reported after peripheral or central inflammatory stimuli. Peripheral cytokines have been proposed to cross the blood-brain barrier in severe medical illness to induce neuroinflammation and symptoms of depression. However, our results suggest that central inflammation may be present during MDE even when peripheral inflammation is absent.

This study has several limitations, most of which are related to the interpretation of TSPO VT and the use of PET imaging. To the best of our knowledge, the most supported explanation for greater TSPO binding with PET is microglial activation, although TSPO has other roles, such as translocating cholesterol from the outer to the inner mitochondrial membranes for steroid hormone synthesis and participating in the mitochondrial permeability transition pore hetero-

Conclusions

To our knowledge, this study is the first to find evidence of a significant elevation of brain TSPO density, a marker of mi-
Microglial activation and neuroinflammation, during MDE. Although MDD often has been associated with increased peripheral inflammatory markers, the present study provides the first important compelling evidence of a neuroinflammatory process of microglial activation during MDE in a substantial group of patients unbiased by other psychiatric illnesses or recent medication. Correlations found between greater regional TSPO $V_T$ in the ACC and insula with severity of MDE and BMI, respectively, may be explained by microglial activation leading to abnormal function in these regions contributing to symptoms. Given the magnitude of difference in TSPO $V_T$ between the patients with MDE and healthy controls, replication should be possible in future studies, particularly if the MDE sample is focused on those with higher overall severity. Finally, the current results support further investigation of brain-penetrant therapeutics that reduce microglial activation to treat MDE.

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Author Affiliations: Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Setiawan, Wilson, Mizrahi, Rusjan, Miller, Suridjan, Kennedy, Rekkas, Houle, Meyer); Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (Setiawan, Wilson, Mizrahi, Rusjan, Miller, Suridjan, Kennedy, Rekkas, Houle, Meyer); Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada (Wilson, Mizrahi, Kennedy, Houle, Meyer); Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada (Mizrahi, Suridjan, Kennedy, Meyer); Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson (Rajkowska).

Author Contributions: Dr Meyer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Setiawan, Wilson, Houle, Meyer.

Acquisition, analysis, or interpretation of data: Setiawan, Mizrahi, Rusjan, Miller, Rajkowska, Suridjan, Kennedy, Rekkas, Houle, Meyer.

Drafting of the manuscript: Setiawan, Meyer.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Setiawan, Rekkas, Meyer.

Obtained funding: Setiawan, Houle, Meyer.

Administrative, technical, or material support: Wilson, Mizrahi, Rusjan, Miller, Suridjan, Kennedy, Houle, Meyer.

Study supervision: Meyer.

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Correction: This article was corrected on March 9, 2015, to fix Table 2.

REFERENCES
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