Inflammation in the Neurocircuitry of Obsessive-Compulsive Disorder

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**IMPORTANCE** For a small percentage of obsessive-compulsive disorder (OCD) cases exhibiting additional neuropsychiatric symptoms, it was proposed that neuroinflammation occurs in the basal ganglia as an autoimmune response to infections. However, it is possible that elevated neuroinflammation, inducible by a diverse range of mechanisms, is important throughout the cortico-striato-thalamo-cortical circuit of OCD. Identifying brain inflammation is possible with the recent advance in positron emission tomography (PET) radioligands that bind to the translocator protein (TSPO). Translocator protein density increases when microglia are activated during neuroinflammation and the TSPO distribution volume ($V_T$) is an index of TSPO density.

**OBJECTIVE** To determine whether TSPO $V_T$ is elevated in the dorsal caudate, orbitofrontal cortex, thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex in OCD.

**DESIGN, SETTING, AND PARTICIPANTS** This case-control study was conducted at a tertiary care psychiatric hospital from May 1, 2010, to November 30, 2016. Participants with OCD (n = 20) and age-matched healthy control individuals (n = 20) underwent a fluorine F 18-labeled $N$-(2-(2-fluoroethoxy)benzyl)-$N$-(4-phenoxypyridin-3-y)acetamide PET scan. It is a high-quality second-generation TSPO-binding PET radiotracer. All participants were drug and medication free, nonsmoking, and otherwise healthy.

**MAIN OUTCOMES AND MEASURES** The TSPO $V_T$ was measured in the dorsal caudate, orbitofrontal cortex, thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex. Compulsions were assessed with the Yale-Brown Obsessive Compulsive Scale.

**RESULTS** In the OCD and healthy groups, the mean (SD) ages were 27.4 (7.1) years and 27.6 (6.6) years, respectively, and 11 (55%) and 8 (40%) were women, respectively. In OCD, TSPO $V_T$ was significantly elevated in these brain regions (mean, 32%; range, 31%-36% except anterior cingulate cortex, 24%; analysis of variance, effect of diagnosis: $P < .001$ to $P = .004$). Slightly lower elevations in TSPO $V_T$ (22%-29%) were present in other gray matter regions. The Yale-Brown Obsessive Compulsive Scale measure of distress associated with preventing compulsive behaviors significantly correlated with TSPO $V_T$ in the orbitofrontal cortex (uncorrected Pearson correlation $r = 0.62, P = .005$).

**CONCLUSIONS AND RELEVANCE** To our knowledge, this is the first study demonstrating inflammation within the neurocircuitry of OCD. This regional distribution of elevated TSPO $V_T$ argues that the autoimmune/neuroinflammatory theories of OCD should extend beyond the basal ganglia to include the cortico-striato-thalamo-cortical circuit. Immunomodulatory therapies should be investigated in adult OCD, rather than solely childhood OCD, particularly in cases with prominent distress when preventing compulsions.
obsessive-compulsive disorder (OCD) is a debilitating neuropsychiatric disorder, significantly affecting the function of 1% to 2% of adolescents and adults. A third of OCD cases inadequately respond to pharmacotherapies with good evidence for this condition, such as serotonin reuptake inhibitors and clomipramine. Some directions, based on models of striatal dopaminergic hyperactivity with stereotypy and abnormal glutamate uptake/regulation in the cortico-striato-thalamo-cortical (CSTC) circuit, have led to more positive clinical trials of augmentation with antipsychotics and N-methyl-D-aspartate receptor antagonists, respectively. Although such findings are being incorporated in treatment algorithms, more consistently impactful treatment approaches are needed and the major barrier in therapeutic development is the paucity of novel pathological targets identified in the brain of OCD.

An autoimmune pathophysiology has been proposed for several case series of OCD characterized by prepubertal acute onset, episodic course, and concurrent neurological abnormalities such as choreiform movements occurring or exacerbating after exposure to infection. This syndrome has been termed pediatric autoimmune neuropsychiatric disorder associated with group A beta-hemolytic streptococcus (GABHS) (PANDAS) or pediatric acute neuropsychiatric syndrome (PANS). Cross reactivity between gangliosides in basal ganglia neurons with the GABHS cell wall is mechanistically implicated in Sydenham chorea, a series of rapid and uncoordinated jerky movements affecting the face, feet, and hands, which may occur within 6 months of the acute GABHS infection, and there are some reports of antibasal ganglia antibodies in the serum of PANDAS cases.

Although PANDAS and PANS are relevant for only a minority of OCD cases, it is possible that the broader state of neuroinflammation and/or autoimmunity, inducible by a more diverse range of mechanisms, is important in OCD. Prevalence of anxiety disorder is strongly elevated, with rates of 30% to 40% in medical conditions such as systemic lupus erythematosus and multiple sclerosis, for which autoimmunity is an important component of the medical disease. Also, specific prevalence rates of OCD in systemic lupus erythematosus and multiple sclerosis are typically several fold higher. In addition, OCD specifically is associated with developmental disorders such as Tourette syndrome and tic disorder for which excessive autoimmunity is also implicated. Moreover, induction of neuroinflammation in rodents with lipopolysaccharide administration is associated with anxiety behaviors, such as reduced exploration in the open field test, even when accounting for changes in motor activity.

Microglial activation, an important component of neuroinflammation, can be measured with translocator protein (TSPO) positron emission tomography (PET) imaging because microglia increase expression of TSPO when they are activated. In a [1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isouquolinine carboxamide ([11C]PK11195) PET study of 17 children with PANDAS and 15 healthy control adults, Kumar et al. using a reference tissue approach, found elevated TSPO binding in the basal ganglia but not thalamic regions. These findings cannot be extrapolated as being applicable to OCD because this study investigated PANDAS rather than OCD. Also, this study restricted its regional analyses to the striatum and thalamus and did not investigate any other region implicated in the neurocircuitry of OCD. Given that with the exception of this neuroimaging study in PANDAS, which represents a small percentage of cases, there are no postmortem or neuroimaging studies of neuroinflammation in OCD, hence, it is not known as to whether neuroinflammation occurs in OCD.

While [11C]PK11195 was the first TSPO PET radiotracer, recent advances in PET radioligands for TSPO have resulted in a second generation of radiotracers for which the specific binding signal is at least several-fold higher, such as fluorine F18-labeled 2-(2-fluoroethoxy)benzyl-N-(4-phenoxy)pyridin-3-ylacetamide ([18F]FEPPA) PET. Moreover, [18F]FEPPA is an excellent radioligand for TSPO, having high and selective affinity, considerable brain uptake, and good reversibility. Moreover, radioactivemetabolitesarenotdetectedinbrain and the binding of [18F]FEPPA is increased during induced inflammation in animals as well as the positive control condition of Alzheimer disease in humans, which is associated with microglial activation in response to amyloid deposition.

The primary aim of this study is to compare TSPO distribution volume (Vp) in the CSTC circuit of OCD with healthy control individuals. It is hypothesized that TSPO Vp, being elevated in neuroinflammatory states, is greater in OCD. Because the strongest regional convergence across investigations of neurochemical abnormalities in OCD, such as 5-HT₂A, 5-HTT, 5-HT₁B, and mGluR5 receptor binding and fluorodeoxyglucose uptake, are in the dorsal caudate and the orbitofrontal cortex, these regions are given the highest priority. However, the neuropathology of OCD also implicates a broader group of structures in the CSTC circuit, such as the thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex, so these regions were given the next highest priority. Also, given that neuroinflammatory pathologies of the CSTC circuit, including vascular disease, tumors, Huntington disease, Tourette disorder, and Sydenham chorea, are associated with disturbances of complex motor behavior, the third

<table>
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<th>Key Points</th>
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| **Question** Is translocator protein distribution volume, a marker of the microglial component of neuroinflammation, elevated in the cortico-striato-thalamo-cortical (CSTC) circuit of obsessive-compulsive disorder (OCD)?

**Findings** In this case-control study, translocator protein distribution volume was significantly elevated in the CSTC of participants with OCD compared with healthy control individuals. The Yale-Brown Obsessive Compulsive Scale measure of distress associated with preventing compulsive behaviors was positively correlated with translocator protein distribution volume in the orbitofrontal cortex.

**Meaning** The presence of neuroinflammation in the CSTC of OCD argues for extending investigations of serum autoantibodies to the entire CSTC and that immunomodulatory therapies should be investigated in adult OCD.
aim, which was exploratory, is to assess the association between TSPO V_{1} in the dorsal caudate and orbitofrontal cortex with severity of compulsions in OCD.

**Methods**

**Participants**

Twenty participants with OCD and 20 age-matched healthy control individuals (within 4 years) completed the study. Participants were recruited from the Toronto, Ontario, Canada, area at a tertiary care psychiatric hospital (Centre for Addiction and Mental Health) from May 1, 2010, to November 30, 2016. All were aged 19 to 48 years, nonsmoking, and in good physical health (see demographic characteristics in Table 1). None of the participants had a history of autoimmune disease, and all were free of medical illnesses for at least 4 weeks. Fourteen healthy control individuals (70%), reported in a previous study, were also included in the present study. No other healthy or OCD cases in this study were included in any other study. The remaining control individuals have not been included in other studies. Eleven participants (55%) had OCD prior to age 12 years and 18 participants (90%) had OCD onset prior to age 20 years. The presence or absence of psychiatric disorders and OCD specifically were confirmed using the Structured Clinical Interview of DSM-IV. Two OCD cases had a history of a major depressive episode, a single episode occurring 4 and 5 years prior to their scan date. The severity of OCD was measured with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Clinical symptoms of OCD varied and severity of the obsessive-compulsive symptoms was moderate to severe on average (eTable 1 in the Supplement). None of the OCD cases met criteria for PANDAS or PANS.

Participant diagnosis was verified by a psychiatrist (J.H.M. or L.R.). Exclusion criteria for all participants were pregnancy; herbal, drug, or medication (including psychotropic) use within the past 6 weeks, except for oral contraceptives; substance abuse (including cigarette smoking); and any history of neurologic illness or injury. Other exclusion criteria consisted of concurrent active Axis I disorders, current or past alcohol or substance dependence, bipolar I or II disorder, and borderline or antisocial personality disorder, the latter ruled out with the Structured Clinical Interview for DSM-IV Axis I disorders. All participants underwent urine drug screening, and women received a urine pregnancy test on the screening and PET scanning days. 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 Centre for Addiction and Mental Health, Toronto, Ontario, Canada.

**Image Acquisition and Analysis**

Each participant underwent a single $^{[18F]}$FEPPA PET scan conducted at the Research Imaging Centre at the Centre for Addiction and Mental Health. Intravenous $^{[18F]}$FEPPA was administered as a bolus (mean [SD], 183.5 [10.5] MBq or 4.9 [0.3] mCi). The $^{[18F]}$FEPPA was of high radiochemical purity (98.0%) and high specific activity (mean [SD], 133.6 [118.7] TBq/mmol). The PET scan duration was 125 minutes after the injection of $^{[18F]}$FEPPA. Positron emission tomographic scans were acquired using a 3-dimensional brain scanner (HRRT; CPS/Siemens). Positron emission tomographic scans were acquired and reconstructed as described previously.

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 cut-off frequency. Manual and automatic blood sampling (ABSS, Model PBS-101; Veenstra Instruments) was conducted to determine the input function of parent compound in plasma for the kinetic analysis, based on the ratio of radioactivity in whole blood to radioactivity in plasma, and the percentage of parent compound in plasma. A biexponential function was used to fit the blood-to-plasma ratios and a Hill function was used to fit the percentage of unmetabolized tracer as previously described. A 2-tissue compartment model was applied to generate time activity curves from each region of interest (ROI) to quantitate TSPO V_{1} with $^{[18F]}$FEPPA PET, as this was previously demonstrated to be the optimal model for $^{[18F]}$FEPPA PET.

Regions of interest were automatically generated using the semiautomated software (ROMI; Research Imaging Centre, Centre for Addiction and Mental Health). ROMI is based on the individualization of a set of standard ROIs using magnetic resonance imaging (MRI) coregistered with the PET image, followed by a step of gray matter voxel selection, which incorporates the probability of gray matter based on the segmentation of the individual MRI as previously described. For the anatomical delineation of ROIs, the first 13 participants (OCD: n = 8; healthy: n = 5) underwent 2-dimensional axial proton density MRI acquired with a General Electric Signa 1.5-T MRI scanner (section thickness, 2 mm; repetition time, >5300 milliseconds; echo time, 13 milliseconds; flip angle, 90°; number of excitations, 2; acquisition matrix, 256 × 256; and field of view, 22 mm). The remaining 27 participants (OCD: n = 12; healthy: n = 15) underwent 2-dimensional axial proton density MRI with a 1.5-T Siemens MRI scanner (section thickness, 2 mm; repetition time, >5300 milliseconds; echo time, 13 milliseconds; flip angle, 90°; number of excitations, 2; acquisition matrix, 256 × 256; and field of view, 22 mm). The remaining 27 participants (OCD: n = 12; healthy: n = 15) underwent 2-dimensional axial

### Table 1. Demographic Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OCD (n = 20)</th>
<th>Healthy (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSPO genotype, No.</td>
<td>HAB</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MAB</td>
<td>7</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>27.4 (7.1)</td>
<td>27.6 (6.6)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>22.8 (2.9)</td>
<td>24.4 (2.2)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>23.0 (6.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Y-BOCS score, mean (SD)</td>
<td>13.7 (7.1)</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; MAB, mixed-affinity binding; NA, not applicable; OCD, obsessive-compulsive disorder; TSPO, translocator protein; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

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Translocator protein distribution volume was significantly greater across brain regions assessed in participants with obsessive-compulsive disorder (n = 20) compared with healthy control individuals (n = 20). The single-nucleotide polymorphism rs6971 of the TSPO gene, which influences binding of second-generation translocator protein positron emission tomography radioligands, was included as a nuisance factor in the analyses of variance. Translocator protein distribution volume values represent raw values unadjusted for genotype. For this polymorphism, high-affinity homozygotes are denoted as HAB (high-affinity binding) and heterozygotes are denoted as MAB (mixed-affinity binding). The dark horizontal bars indicate the mean for each group.

Figure 1. Elevated Translocator Protein Distribution Volume in Obsessive-Compulsive Disorder

Translocator protein distribution volume was significantly greater across brain regions assessed in participants with obsessive-compulsive disorder (n = 20) compared with healthy control individuals (n = 20). The single-nucleotide polymorphism rs6971 of the TSPO gene, which influences binding of second-generation translocator protein positron emission tomography radioligands, was included as a nuisance factor in the analyses of variance. Translocator protein distribution volume values represent raw values unadjusted for genotype. For this polymorphism, high-affinity homozygotes are denoted as HAB (high-affinity binding) and heterozygotes are denoted as MAB (mixed-affinity binding). The dark horizontal bars indicate the mean for each group.

To assess whether there was a global difference in TSPO $V_T$ between participants with OCD and healthy control individuals, a MANOVA was also applied with TSPO $V_T$ from all regions sampled included as the dependent variables, with diagnosis and genotype as independent predictor factors. The association of TSPO $V_T$ in the dorsal caudate and orbitofrontal cortex with time occupied, interference, distress, resistance, and control over obsessions and compulsions was assessed applying a partial correlation coefficient controlling for genotype. This was treated as a posthoc analysis. Statistical analyses were performed using IBM SPSS version 22.0.46

To investigate whether there was evidence for a pattern of TSPO $V_T$ elevation in OCD that differs as compared with the elevations found in major depressive disorder, a post hoc analysis was done comparing the relative TSPO $V_T$ values in the dorsal caudate and orbitofrontal cortex, regions most implicated in OCD, in relation to TSPO $V_T$ in the anterior cingulate cortex, a region implicated in major depressive disorder (eAppendix in the Supplement).

Results

Translocator protein $V_T$ was significantly greater in the OCD cases within the dorsal caudate, orbitofrontal cortex, thalamus, ventral striatum, dorsal putamen, and anterior cingulate cortex (MANOVA; main effect of diagnosis: $F_{6,32} = 2.8$, $P = .03$; main effect of genotype: $F_{6,32} = 6.2$, $P < .001$) (Figure 1). Differences in individual regions were robust (ANOVA:s: dorsal caudate: $F_{1,37} = 15.5$, $P < .001$; orbitofrontal cortex: $F_{1,37} = 13.5$, $P = .001$; thalamus: $F_{1,37} = 13.2$, $P = .001$; ventral striatum: $F_{1,37} = 14.4$, $P = .001$; dorsal putamen: $F_{1,37} = 12.8$, $P = .001$; and anterior cingulate cortex: $F_{1,37} = 9.5$, $P < .001$).
Table 2. TSPO Density Measured By VT Across Multiple Brain Regions in Obsessive-Compulsive Disorder

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>TSPO VT, Mean (SD)</th>
<th>Healthy</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HAB (n = 13)</td>
<td>MAB (n = 7)</td>
<td>Total (n = 20)</td>
</tr>
<tr>
<td>Dorsal caudate</td>
<td>10.7 (2.3)</td>
<td>6.9 (1.4)</td>
<td>9.4 (2.7)</td>
</tr>
<tr>
<td>OFC</td>
<td>13.4 (2.8)</td>
<td>9.3 (2.1)</td>
<td>12.0 (3.2)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>16.2 (3.2)</td>
<td>8.9 (2.4)</td>
<td>13.7 (4.6)</td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>12.1 (2.2)</td>
<td>6.8 (1.3)</td>
<td>10.2 (3.2)</td>
</tr>
<tr>
<td>Dorsal putamen</td>
<td>11.8 (2.4)</td>
<td>6.6 (1.7)</td>
<td>10.0 (3.3)</td>
</tr>
<tr>
<td>ACC</td>
<td>12.4 (2.3)</td>
<td>6.9 (1.7)</td>
<td>10.5 (3.4)</td>
</tr>
<tr>
<td>MPFC</td>
<td>12.8 (2.4)</td>
<td>7.1 (1.7)</td>
<td>10.8 (3.5)</td>
</tr>
<tr>
<td>DLPPC</td>
<td>13.0 (2.1)</td>
<td>7.3 (1.9)</td>
<td>11.0 (3.4)</td>
</tr>
<tr>
<td>VLPFC</td>
<td>13.9 (2.6)</td>
<td>8.2 (1.8)</td>
<td>11.9 (3.6)</td>
</tr>
<tr>
<td>Insula</td>
<td>13.3 (2.6)</td>
<td>7.5 (1.8)</td>
<td>11.8 (3.6)</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>13.5 (2.5)</td>
<td>7.8 (2.1)</td>
<td>11.5 (3.6)</td>
</tr>
<tr>
<td>Inferior parietal cortex</td>
<td>14.1 (3.1)</td>
<td>8.1 (1.8)</td>
<td>12.0 (4.0)</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>13.9 (2.6)</td>
<td>7.8 (2.1)</td>
<td>11.8 (3.8)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>12.2 (2.3)</td>
<td>6.9 (2.0)</td>
<td>10.3 (3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; DLPPC, dorsolateral prefrontal cortex; HAB, high-affinity binding; MAB, mixed-affinity binding; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; TSPO, translocator protein; VLPFC, ventrolateral prefrontal cortex; VT, distribution volume.

P = .004, with elevations of 35.6%, 30.9%, 33.5%, 33.8%, 32.6%, and 23.5% magnitudes, respectively (Figure 1 and Table 2). In addition, generally lesser but significant elevations of TSPO VT were observed in all gray matter regions sampled (Table 2). There was no effect of age or sex on TSPO VT in any region (MANOVA; main effect of age: F6,31 = 0.69, P = .66; main effect of sex: F6,31 = 0.85, P = .54).

Greater TSPO VT in the orbitofrontal cortex was significantly correlated with greater distress associated with preventing compulsive behaviors as reported on the Y-BOCS (uncorrected Pearson partial correlation coefficient controlling for genotype; r = 0.62; P = .005) (Figure 2 and Table 3).

Reanalysis of the data set omitting the 2 patients who had a history of a major depressive episode demonstrated the results were similarly significant (MANOVA; main effect of diagnosis: F6,30 = 2.5, P = .04; main effect of genotype: F6,30 = 5.5, P = .001). Differences in individual regions were robust (ANOVA; dorsal caudate: F1,35 = 13.3, P = .001; orbitofrontal cortex: F1,35 = 13.8, P = .001; thalamus: F1,35 = 13.8, P = .001; ventral striatum: F1,35 = 14.0, P = .001; dorsal putamen: F1,35 = 13.8, P = .001; and anterior cingulate cortex: F1,35 = 9.3, P = .004). The eFigure and etable2 in the Supplement show further results comparing the relative TSPO VT values across the dorsal caudate and anterior cingulate cortex between those with OCD and those with major depressive episode, as well as an itemized list of Hamilton Depression Rating Scale score results in these samples.

Discussion

To our knowledge, this is the first study to investigate inflammation in the brain of OCD. The most prominent finding is

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The widespread distribution of elevations in TSPO levels are highly correlated with markers consistently demonstrated that the temporal course of toxin exposure, and lipopolysaccharide administration, it is interesting that TSPO VT was elevated by more than 30% within the orbitofrontal cortex, dorsal caudate, thalamus, dorsal putamen, ventral striatum, and, albeit to a slightly lesser extent, the anterior cingulate cortex. This finding was also present in the other gray matter regions of brain at a slightly lower level of magnitude and this regional distribution is consistent with a neuroinflammatory phenotype. These results have important implications for the pathophysiology of OCD and novel therapeutic treatment directions.

The best explanation for elevated TSPO VT is that it reflects neuroinflammation consequent to microglial activation. Across diverse models of cerebral artery occlusion, toxin exposure, and lipopolysaccharide administration, it is consistently demonstrated that the temporal course of elevations in TSPO levels are highly correlated with markers of microglial activation. The widespread distribution of elevated TSPO VT throughout gray matter is consistent with investigations of TSPO VT with more sensitive radioligands in diseases with microglial activation and more focal pathologies such as Alzheimer disease and stroke, which tend to find that no gray matter region is fully spared from an elevation of TSPO VT.26,27,50 This could be accounted for by diffuseness of initiating disease pathology; spread of microglial activating disease–associated molecular patterns and/or pathogen-associated molecular patterns; and/or paracrine effects of activated microglia.51 Even so, it is interesting that TSPO VT was elevated by more than 30% within the orbitofrontal cortex, dorsal caudate, thalamus, dorsal putamen, and ventral striatum. The involvement of the CSTC has important implications for the autoimmune etiology of OCD. Traditionally, investigations of autoantibodies in serum of OCD cases mostly focus on striatum, presumably because GABHS is associated with Sydenham chorea and the PANDAS mechanism is based on the epitope cross reactivity of the striatum with GABHS.6,7 Some investigators are beginning to evaluate serum autoantibodies to other parts of the CSTC circuit such as the thalamus,52 but our study argues that it is critical that such studies consistently pursue autoantibodies for the dorsal caudate and orbitofrontal cortex as well as the remainder of the CSTC circuit.

This study demonstrates that microglial activation occurs well beyond the initial, frequently childhood, onset of OCD, and the presence of activated microglia provides a useful opportunity to modulate their function as a therapeutic strategy. Although pharmaceutical development does not traditionally prioritize OCD, neuromodulatory treatments under development for other diseases associated with microglial activation, such as Alzheimer disease,53,54 might be repurposed toward OCD. Microglial activation may include components harmful to neurons and glia (termed M1 responses), such as creating reactive oxygen and nitrogen species and producing proinflammatory cytokines, but also include helpful components (termed M2 responses) such as clearing cellular debris, inducing angiogenesis, and promoting tissue repair.55 More specifically, the current study would suggest that medications under investigation for shifting activated microglia from an M1 to M2 state, such as azithromycin, minocycline, and bexarotene,56 should be investigated in OCD, particularly in samples in which the severity of distress associated with preventing compulsive behaviors is highly prevalent. Consistent with consideration of an immunomodulatory approach, minocycline, an antibiotic that, among its effects, inhibits major histocompatibility complex II expression and reduces M1 type markers,57 significantly reduced Y-BOCS scores in a recent randomized, double-blind, placebo-controlled study of add-on to fluvoxamine in 102 patients with OCD.58

**Table 3. Positive Correlation Between Regional Translocator Protein Distribution Volume in Dorsal Caudate and Orbitofrontal Cortex and Distress Associated With Compulsive Behaviors**

<table>
<thead>
<tr>
<th>Y-BOCS Subscale Correlations Controlling for rs6971 Genotypea</th>
<th>Dorsal Caudate</th>
<th>Orbitofrontal Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time spent performing compulsions</td>
<td>0.30, .17</td>
<td>0.38, .11</td>
</tr>
<tr>
<td>Interference due to compulsions</td>
<td>0.21, .38</td>
<td>0.32, .18</td>
</tr>
<tr>
<td>Distress associated with compulsions</td>
<td>0.48, .04</td>
<td>0.62, .005</td>
</tr>
<tr>
<td>Resistance against compulsions</td>
<td>0.06, .80</td>
<td>0.03, .90</td>
</tr>
<tr>
<td>Degree of control over compulsions</td>
<td>−0.04, .88</td>
<td>−0.09, .71</td>
</tr>
<tr>
<td>Total compulsion severity</td>
<td>0.28, .25</td>
<td>0.33, .17</td>
</tr>
<tr>
<td>Total obsession severity</td>
<td>0.20, .41</td>
<td>0.23, .35</td>
</tr>
<tr>
<td>Overall severity</td>
<td>0.25, .30</td>
<td>0.29, .23</td>
</tr>
</tbody>
</table>

Abbreviation: Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

a Indicates binding to the single-nucleotide polymorphism rs6971 of the TSPO gene known to influence binding of second-generation TSPO radioligands, including fluorine F 18–labeled N-(2-(2-fluoroethoxy) benzyl)-N-(4-phenoxypyridin-3-yl) acetamide.

b P value derived from uncorrected Pearson partial correlation coefficient controlling for rs6971 genotype.

**Limitations**

This study has several limitations, most of which are attributable to the interpretation of TSPO VT and the application of PET imaging. Elevated TSPO VT is well-established as a marker of microglial activation; however, given that TSPO has roles in translocating cholesterol from outer to inner cell membranes and may form an oligomer with the mitochondrial permeability transition pore,59 it is theoretically possible that as knowledge regarding TSPO increases, other factors will be identified that may influence TSPO binding in the brain. Also, binding of the PET radiotracer can be affected by changes in density and affinity of the target. In addition, the association between elevated TSPO and OCD, as well as greater distress associated with preventing compulsive behaviors, indicates significant associations among these phenomena but does not establish a causal one as this issue will require future study through a combination of longitudinal studies and assessment of immunomodulatory interventions.
Conclusions

In summary, to our knowledge, this study is the strongest evidence to date for inflammation in the brain in OCD. The demonstration of elevated TSPO V$_T$ in the CSTC circuit addresses a critical gap in the autoimmune/neuroinflammatory theory of OCD. The regional distribution of greater TSPO V$_T$ throughout the CSTC circuit argues for consideration of autoimmune mechanisms beyond the basal ganglia and suggests a new opportunity for repurposing immunomodulatory therapies to treat OCD.

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Study concept and design: Meyer.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Attwell, Setiawan, Rusjan, Mizrahi, Meyer.

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Study supervision: Wilson, Mizrahi, Houle, Meyer.

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