

# Dopamine and Neuroinflammation in Schizophrenia – Interpreting the Findings from Translocator Protein (18kDa) PET Imaging

Sotiria Maria Iliopoulou <sup>1</sup>  
Stergios Tsartsalis<sup>2</sup>  
Stefan Kaiser<sup>1,2</sup>  
Philippe Millet<sup>1,2</sup>  
Benjamin B Tournier<sup>1,2</sup>

<sup>1</sup>Adult Psychiatry Division, Department of Psychiatry, Geneva University Hospitals (HUG), Geneva, 1225, Switzerland; <sup>2</sup>Faculty of Medicine, University of Geneva, Geneva, 1204, Switzerland

**Abstract:** Schizophrenia is a complex disease whose pathophysiology is not yet fully understood. In addition to the long prevailing dopaminergic hypothesis, the evidence suggests that neuroinflammation plays a role in the pathophysiology of the disease. Recent studies using positron emission tomography (PET) that target a 18kDa translocator protein (TSPO) in activated microglial cells in an attempt to measure neuroinflammation in patients have shown a decrease or a lack of an increase in TSPO binding. Many biological and methodological considerations have been formulated to explain these findings. Although dopamine has been described as an immunomodulatory molecule, its potential role in neuroinflammation has not been explored in the aforementioned studies. In this review, we discuss the interactions between dopamine and neuroinflammation in psychotic states. Dopamine may inhibit neuroinflammation in activated microglia. Proinflammatory molecules released from microglia may decrease dopaminergic transmission. This could potentially explain why the levels of neuroinflammation in the brain of patients with schizophrenia seem to be unchanged or decreased compared to those in healthy subjects. However, most data are indirect and are derived from animal studies or from studies performed outside the field of schizophrenia. Further studies are needed to combine TSPO and dopamine imaging to study the association between microglial activation and dopamine system function.

**Keywords:** microglia, inflammation, biomarker, neuroimaging, PET, translocator protein

## Introduction

Schizophrenia is a complex psychiatric disorder characterized by positive, negative and cognitive symptoms. The etiology of the disease is not clearly understood. Disturbances in several neurotransmitter pathways, various inflammatory mechanisms, environmental risk factors and genetic components have been suggested to be among the underlying mechanisms.<sup>1</sup>

The dopaminergic hypothesis has been the most prevailing theory about the pathophysiology of the illness. It associates symptoms of schizophrenia with frontal hypodopaminergia and striatal hyperdopaminergia.<sup>2</sup> In addition to its function as a neurotransmitter, dopamine also acts on dopamine receptors on human and rodent microglia, as well as on peripheral immune cells.<sup>3–5</sup> Interestingly, dopamine seems to modulate microglial activation state, their motility and their phagocytic activity, possibly exercising a recently reviewed immunomodulatory role in several affections.<sup>6,7</sup>

An increasing body of evidence suggests that inflammatory processes in the central nervous system (CNS) contribute to the development of schizophrenia,

Correspondence: Sotiria Maria Iliopoulou  
Rue de Lausanne 20bis, 1225 Chêne  
Bourg, Geneva, Switzerland  
Tel +41766897182  
Fax +41223054599  
Email soil@hcuge.ch



mainly via proinflammatory cytokines, glial and peripheral immune cells.<sup>8</sup> Firstly, elevated levels of proinflammatory cytokines have been found in the serum and cerebrospinal fluid of patients with schizophrenia.<sup>9,10</sup> Although penetration into the CNS of peripheral pro-inflammatory molecules is limited because of the blood-brain barrier, there is evidence of a certain level of permeability between the CNS and the periphery.<sup>11</sup> Secondly, postmortem studies have demonstrated elevated levels of pro-inflammatory markers and microglial density in the brains of patients with schizophrenia, but the results have been heterogeneous.<sup>12–14</sup> Supporting the hypothesis of glial activation, a transcriptional profiling study recently demonstrated the over-expression of genes linked to the inflammatory response in the cortex, hippocampus and striatum in schizophrenia.<sup>15</sup> Thirdly, a meta-analysis of clinical trials showed that anti-inflammatory drugs may alleviate psychotic symptoms and cognitive deficits, although the sample sizes in the original studies were small.<sup>16</sup>

In recent years, the study of neuroinflammation in schizophrenia has become possible with the use of positron emission tomography (PET) and the development of radiotracers that target the 18 kDa translocator protein (TSPO). TSPO is overexpressed in activated microglial cells and astrocytes, and it has been suggested that it reflects inflammation in the brain.<sup>17–19</sup> However, recent *in vivo* studies have shown decreased or similar levels of TSPO in patients with first-episode or chronic schizophrenia as compared to controls.<sup>19</sup>

In this review, we explore the role of dopamine on microglial activation and TSPO binding in schizophrenia, after reviewing the results of *in vivo* PET randomized controlled trials using second-generation TSPO radioligands as a biomarker of microglial activation. We thus examine whether a dopamine-induced microglial modulation could be a possible explanation for the decreased/unaltered TSPO levels shown in these studies, in addition to their methodological and biological limitations that have been discussed so far.

## Search Strategy

Concerning the review of the *in vivo* findings on TSPO binding in schizophrenia, the PubMed database was searched with the following keywords:

((Positron Emission Tomography OR PET) AND (schizophrenia OR schizophreniform OR psychosis)) AND

(microglia\* OR microglia\* activation OR TSPO OR Translocator protein OR peripheral benzodiazepine receptor)

up to 30 September 2021. The research yielded 112 results. We identified three meta-analysis and thirteen *in vivo* imaging studies which are discussed below.

Concerning the review of the interactions between neuroinflammation and the dopaminergic system, PubMed was searched using the following keywords: (dopamine[Text Word] OR “dopamine synthesis” OR BH4 OR tetrahydrobiopterin OR “dopamine transporter” OR VMAT OR “dopamine receptor”) AND (microglia [Text Word] OR cytokines[Text Word] OR pro inflammatory[Text Word] OR neuroinflammation OR TSPO) which yielded 2878 results (Microglia AND TSPO) with 464 results (Dopamine AND TSPO AND Microglia) with 12 results and (schizophrenia OR schizophreniform OR psychosis) AND (imaging OR PET OR SPECT) AND (dopamine OR receptor) with 2598 results. Sixty-four studies were included to represent the heterogeneous results of every query. Thirty-seven out of 64 were selected among the results of the search algorithms, and 27 out of 64 were used as support/evidence of the pathways or theories mentioned in this review. Given the scarcity of human *in vivo* studies in schizophrenia patients, we also mentioned representative findings from *in vitro* and animal studies as well as studies out of the field of schizophrenia research.

## TSPO Binding Alterations in Patients with Schizophrenia

### Overview of the Meta-Analytic Findings

The three recent meta-analysis of the literature identified thirteen *in vivo* imaging PET TSPO studies with approximately 200 subjects suffering from early or chronic schizophrenia-spectrum disorders.<sup>20–22</sup>

In the study of Marques et al, two separate meta-analysis were conducted depending on the measure used to quantify TSPO tracing in total grey matter.<sup>22</sup> All but one study used the first-generation radioligand [11C]-PK11195, which has a high nonspecific binding and lipophilicity, characteristics that limit the accuracy of its quantification.<sup>23</sup> Several parameters are used to measure the density of radiotracer receptors and quantify the tracer distribution, such as the binding potential (BP), distribution volume ratio (DVR) and total volume of distribution (VT). A significant elevation of TSPO binding potential (BP) in patients was found across all studies ( $g = 0.31$ ,

Confidence Intervals CI: 0.02–0.6) with moderate heterogeneity ( $I^2 = 58\%$ ).<sup>24–28</sup> A sensitivity analysis restricted to the five studies using PK11195 found a similar effect size of 0.35 (CI: 0.01–0.7). The only study using the second-generation ligand [11C]-DAA1106 found no difference in patients versus controls but was not identified as an outlier in the funnel plot.<sup>29</sup> No difference in results was observed when adjusting for publication bias.

The authors found no difference in TSPO VT between patients and controls.<sup>30–35</sup> The majority of the studies in this meta-analysis used second-generation radioligands, which presents considerably less nonspecific binding than [11C]-PK11195 and has an increased signal-to-noise ratio. This ligand thus has an increased potential to detect more subtle alterations in TSPO binding. Heterogeneity was found to be moderate to high ( $I^2 = 53\%$ ).

Plavén-Sigraý et al conducted an individual participant data meta-analysis of second-generation radioligand studies using VT in three regions of interest (frontal and temporal lobe and hippocampus) as the outcome measure.<sup>20</sup> These results were recently extended to include two additional datasets.<sup>21</sup> Using Bayesian model comparison, a reduction in VT in all three regions in patients versus controls was found (estimated standardized difference in VT in patients versus controls:  $-0.42$  (CI:  $-0.74, -0.08$ ) in the frontal cortex,  $-0.38$  (CI:  $-0.73, -0.04$ ) in the temporal cortex and  $-0.52$  (CI:  $-0.84, -0.21$ ) in the hippocampus). Heterogeneity was low with an  $I^2$  found less than 15% in all analyses.

Overall, both Plavén-Sigraý et al and Marques et al do not observe an increase in VT in patients with schizophrenia compared to controls. While Plavén-Sigraý et al found decreased levels of TSPO in patients versus controls, Marques et al did not observe a significant difference between groups. Some possible explanations for the different results between the two studies have been mentioned by Plavén-Sigraý et al: the authors included one more *in vivo* study showing lower levels in VT without regional specificity between 13 patients suffering from a first psychotic episode versus 15 controls.<sup>36</sup> They also excluded two patients out of fourteen in the study of Bloomfield et al, due to lack of controls with the same TSPO genotype, and they did not include the second-generation study by Takano et al that did not control for TSPO genotype for this very reason.<sup>20</sup> This study was included in the meta-analysis by Marques et al.<sup>22</sup> Finally, they identified an overlap of fourteen control subjects in Kenk et al and Hafizi et al, assigning these subjects to

Hafizi et al data set, as to best match the patient group.<sup>20</sup> Methodologically, Plavén-Sigraý et al estimated the effect sizes using individual patient data, which permitted them to control for potential confounding effects, such as age, sex, or medication, rather than using aggregate data as did Marques et al.<sup>37</sup>

## Limitations of TSPO Measurement Accuracy

Possible confounders such as age, gender and duration of illness have been recently discussed by De Picker et al.<sup>38</sup> Gender and duration of illness were not found to account for differences in TSPO in patients versus controls in the meta-analysis by Plavén-Sigraý et al as mentioned above. Most studies found no difference in TSPO levels in patients suffering from recent-onset or chronic schizophrenia versus those in healthy controls.<sup>29–33,35,39</sup> The meta-analysis of Plavén-Sigraý et al found no age-by-group interaction effect on VT in the examined regions.<sup>21</sup> However, a recent retrospective multicenter study found positive correlations between age and TSPO  $V_T$  in the frontal and temporal cortex of 140 healthy subjects with a positive correlation between  $V_T$  and age in all regions in male subjects.<sup>40</sup> The same study found a significant negative correlation of BMI with tracer binding but came with several limitations such as heterogeneity in demographic participants' data and the unknown smoking status of several subjects.<sup>40</sup>

As far as smoking is concerned, two trials controlled for smoking, and no correlation was found.<sup>28,32</sup> Given the scarcity of data directly examining the effect of smoking on neuroinflammation *in vivo*, further research is needed to make robust conclusions.

As far as antipsychotics are concerned, preclinical evidence suggests that antipsychotic medication may alter neuroinflammatory reactions by attenuating microglial activity.<sup>41–43</sup> The meta-analysis by Plavén-Sigraý et al showed no changes in radioligand binding in medicated subjects versus controls.<sup>20</sup> The inverse effects have been observed in an *in vivo* rodent study after chronic antipsychotic treatment with haloperidol and olanzapine at high doses.<sup>44</sup>

The parameters used to measure the density of radiotracer receptors have each their own strengths and weaknesses, and the selection of a specific measure may alter the results of TSPO studies. For example, the systematic review of Marques et al reported a significant elevation in tracer

binding in trials using BP as the outcome measure; this was not the case with VT.<sup>22</sup> The methodological differences of TSPO quantification have been explored in the literature, but their description is out of the scope of this study.<sup>45</sup>

As far as radioligands are concerned, Conen et al published a large dataset using PK11195, showing no difference in BP TSPO levels in the anterior cingulate gyrus between recent onset or chronic schizophrenia patients versus their age-matched controls, likely reflecting that this methodology is not sensitive to detect subtle differences in TSPO.<sup>46</sup> This lack of reduction may be dependent not only on the tracer properties but also on the poor reliability of the outcome measures used, as noted in the previous paragraph.<sup>47,48</sup> Second-generation radioligands are considered to display inter- and within-subject variability.<sup>49</sup> Interindividual variations in binding affinity have been found to be associated with a single nucleotide polymorphism (rs6971) in TSPO, resulting in the existence of apparent “low-affinity binders”, “high-affinity binders” and “mixed-affinity binders” when second-generation radioligand are used. Low-affinity binders present no measurable TSPO radiotracer binding and are currently routinely excluded from PET studies.<sup>50,51</sup> While the majority of trials account for this polymorphism, one out of the eight second-generation tracer trials did not, suggesting that the results may underestimate tracer binding if low-affinity binders are included in the study.<sup>29</sup> For this very reason, this study was not included in the meta-analysis of Plavén-Sigra et al; hence, this limitation does not apply for this meta-analysis. The effect of genotype rs6971 in the TSPO gene was studied in two separate sub-analysis of the five studies using the VT method that accounted for genotyping in the meta-analysis of Marques et al.<sup>22,31–35</sup> The authors showed significant group differences in mixed-affinity binders (effect size  $-0,56$ , CI  $-1,08$ ,  $-0,04$ ), but not in high-affinity binder group.

## Biological Explanations for Decreased TSPO Levels in Schizophrenia

It has been implied that alterations in TSPO binding may not be directly correlated with glial cell activation markers.<sup>52</sup> An infection-mediated schizophrenia mouse model study by Notter et al demonstrated reduced TSPO binding in the prefrontal cortex of symptomatic female mice and a lack of association between microglial morphology and TSPO expression.<sup>53</sup> Another in vitro animal study found that TSPO ligands inhibit toll-like receptor (TRL)-activated microglia

and astrocytes.<sup>54</sup> Furthermore, studies concerning TSPO expression in M1 microglia have been inconclusive. In in vitro rodent microglia, mRNA TSPO expression was increased after pro-inflammatory stimulation, but only a slight increase on protein levels was observed.<sup>55</sup> Similar findings stem from a recent study.<sup>56</sup> On the other hand, an in vitro study showed that TSPO expression did not increase in primary human microglia upon pro-inflammatory activation contrary to rodent microglia.<sup>57</sup> TSPO expression decreased during anti-inflammatory M2 microglial polarization in a mice model of brain hypoxia.<sup>58</sup>

Moreover, reduced TSPO levels in schizophrenia patients could reflect mitochondrial dysfunction in this patient group, including a decrease in the number of mitochondria or the alternation of the number of TSPO binding sites.<sup>59–61</sup>

Indirect data outside the field of schizophrenia research have shown that systemic proinflammatory signals may reduce TSPO levels in the brain, suggesting the existence of compensatory mechanisms to attenuate neuroinflammation or processes unrelated to the activation of glial cells.<sup>62</sup> Increased levels of peripheral proinflammatory cytokines have been shown to exist along with the downregulation of TSPO in the prefrontal cortex in a schizophrenia mouse model, and this occurred without an elevation in local cytokine expression, which might be explained by the anti-inflammatory role of TSPO.<sup>53,63,64</sup> Animal and human models have suggested that TSPO immunoreactivity is also found in vascular endothelial cells, which may play a role in modifying TSPO levels in the brain, as proposed in a schizophrenia animal model.<sup>53,65</sup>

Recent studies on Alzheimer’s disease suggest that not every microglial subtype expresses TSPO.<sup>66–68</sup> Some studies failed to show the upregulation in TSPO mRNA in human activated microglia ex vivo, but the results were heterogeneous and not specific to schizophrenia.<sup>69,70</sup>

The aforementioned considerations strengthen the hypothesis that the conceptualization of TSPO alterations as indicators of neuroinflammatory status is not straightforward.

## Reciprocal Interactions Between Neuroinflammation and the Dopaminergic System Overview

In terms of the biological interpretation of the findings on PET-TSPO binding, the complex interaction between dopamine and neuroinflammation has received little attention so far. In vitro, microglia can express five dopamine

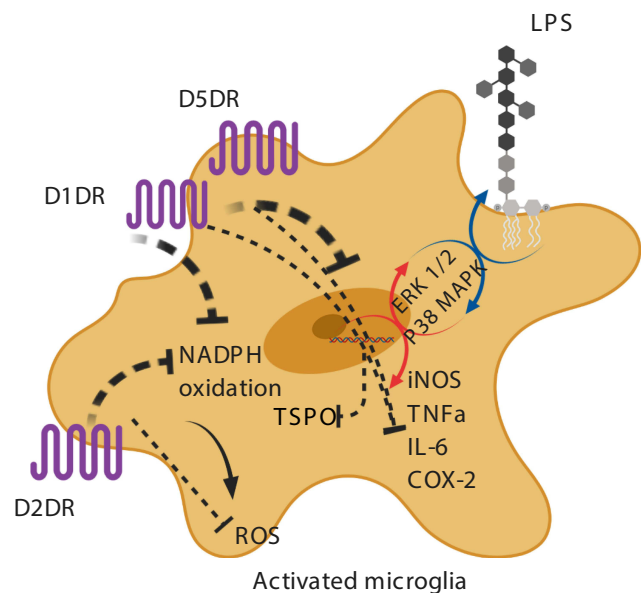


receptors (D1 to D5) depending on the species.<sup>4,71</sup> Different microglia populations may express different dopamine receptors and exhibit different responses to dopamine according to their activation phenotype.<sup>72,73</sup> For example, M1 or pro-inflammatory microglia produce proinflammatory cytokines (such as tumor necrosis factor alpha TNF- $\alpha$ , interleukin (IL)-1 $\beta$  and IL-12) and high levels of inducible nitric oxide (iNOS) in response to dopamine. On the other hand, M2 or anti-inflammatory microglia express anti-inflammatory cytokines (such as IL-10 and Transforming growth factor beta TGF $\beta$ ).<sup>74</sup>

## Influence of Dopamine on Neuroinflammation

In vitro evidence suggests that dopamine decreases lipopolysaccharide (LPS)-induced nitric oxide (NO) release, but not TNF-alpha and IL-6, via D1-like (D1DR) and D2-like dopamine receptors (D2DR).<sup>71,75,76</sup> It has been shown that in LPS-treated microglia, the stimulation of D1DR and D2DR inhibits the activity of the local renin-angiotensin system in the brain, leading to the suppression of the pro-inflammatory AT1/NADPH-oxidase/superoxide axis, a major intermediate in oxidative stress pathways.<sup>77</sup> A possible mechanism proposed is the downregulation of the extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (p38MAPK) (Figure 1).<sup>73,78,79</sup> It has also been reported that D1/2DR in microglial cells inhibits the NLRP3 inflammasome and interleukin-1 beta in an in vitro mouse model of intracerebral hemorrhage.<sup>76</sup> Indirectly, astrocytic D2DR has also been shown to inhibit microglial pro-inflammatory activation through the production of  $\alpha$ B-crystallin in astrocytes.<sup>80</sup>

Findings outside of the field of schizophrenia research are in line with the aforementioned data. In Parkinson's disease, animal studies have shown that acetyl-L-carnitine-induced upregulation of D1 receptors, attenuating microglial activation in the prefrontal cortex and hippocampus.<sup>81</sup> Genetic deficiency of the D3 receptor has been found to inhibit neuroinflammatory pathways in a murine model of Parkinson's disease (PD).<sup>82,83</sup> De novo synthesized D2 receptors on microglia inhibit astrogliosis and neuroinflammation after ischemic stroke.<sup>84</sup> Conversely, an increase of dopamine release in the striatum after cocaine injections in mice temporarily increased TNF- $\alpha$  mRNA and protein levels in microglia by acting on their D2 receptors in an in vivo study about addiction.<sup>85</sup>



**Figure 1** Activation of dopamine receptors on microglia and microglial inhibition. **Notes:** In LPS-treated microglia, it has been shown that dopamine inhibits the AT1/NADPHoxidase/superoxide axis and the synthesis of NO and pro-inflammatory cytokines. Dopamine-induced downregulation of ERK 1/2 and p38MAPK activity has been suggested as a potential mechanism. Created with BioRender.com.

**Abbreviations:** LPS, lipopolysaccharide; D1DR, D1 dopamine receptor; D2DR, D2 dopamine receptor; D5DR, D5 dopamine receptor NADPH, nicotinamide adenine dinucleotide phosphate; ERK, extracellular signal-regulated kinase; p38 MAPK, p38 mitogen-activated protein kinase; iNOS, inducible nitric oxide synthase; TNF $\alpha$ , tumor necrosis factor alpha; IL-6, interleukin-6; COX-2, cyclooxygenase-2; ROS, reactive oxygen species; TSPO, translocator protein; dotted line, inhibition; circular arrow, uninhibited pathway; colorful arrow, uninhibited pathway. Image created with biorender.com.

Overall, high levels of dopamine may inhibit microglial activation by acting on their D1 and D2 dopaminergic receptors.

## Microglial Modulation by Dopamine and PET-TSPO Findings

Dopamine synthesis and release has been shown to be increased in the striatum of patients with schizophrenia. Therefore, the dopamine-mediated attenuation of pro-inflammatory microglial activity could account at least in part for the absence of statistically significant differences in TSPO binding in the striatum of patients versus controls.<sup>29,33,86</sup> The lack of increase in TSPO binding in the thalamus of patients, where an excess innervation of dopaminergic terminals was initially suspected in post-mortem findings, could also be in line with dopamine-induced microglial inhibition.<sup>29,35,46,87</sup>

In contrast, in the prefrontal cortex and other extra-striatal areas decreased dopamine release has been suggested.<sup>88</sup> Concerning the frontal cortex, Kenk et al did not show an increase in TSPO binding, while Plaven-Sigra et al found decreased TSPO binding.<sup>88,89</sup> As far as

other extra-striatal regions are concerned, the meta-analysis of Plaven-Sigray showed a decrease in TSPO binding in temporal cortex and hippocampus where dopamine synthesis and release has been shown to be decreased.<sup>89</sup> Controversially, preliminary findings of a recent cross-sectional *in vivo* study found a TSPO over-expression in the hippocampus in a subset of participants, which included antipsychotic-free schizophrenia patients and subjects at clinical high risk of psychosis.<sup>90</sup> However, authors did not provide data about dopamine release or D1/2DR in the hippocampus *per se* but suggest another potential mechanism explaining the potential neuroinflammation in this region.<sup>90</sup>

Outside of the field of schizophrenia research, the reduction of microglial activation by dopamine has been explored in PD and Alzheimer's disease (AD). Firstly, *in vivo* imaging data in PD have shown that TSPO binding may be increased or unchanged in nigrostriatal and cortical regions of patients where lower levels of dopamine have been found.<sup>91,92</sup> Secondly, in rodent models of Alzheimer's disease (AD), the dopaminergic degeneration of the ventral tegmental area (VTA) was associated with reduced dopamine levels in the hippocampus where microglial TSPO binding has been found to be increased.<sup>93,94</sup> However, we did not find any *in vivo* trials in patients measuring regionally both TSPO and dopamine levels, and the evidence for an association is only indirect so far.

On a receptor level, increased or unaltered levels in striatal D2/3DR radioligand binding in drug-free and drug-naïve patients, respectively, has been observed, whereas findings about extrastriatal binding of D2/3DR have been mixed.<sup>95,96</sup> However, associating existent data concerning D2/D3 receptors in schizophrenia and regional specific microglial modulation by these receptors is not feasible. Firstly, it has not been specified if and up to which extent alternations in dopamine receptor-binding concern microglia. Furthermore, DRD2 exists in an active and inactive state and the increase of the first is not necessarily associated with an increase in total receptor binding in patients.<sup>97</sup> Finally, it has been suggested that antipsychotics may increase active DRD2 in the striatum.<sup>98</sup> In sum, we cannot exclude that possible alterations on DR levels in several brain regions in schizophrenia may concern microglia, but if and how these changes interfere with dopamine-induced microglial inhibition is unclear.

Whether or not the dopamine-induced microglial inhibition is followed by a decrease or a lack of an increase in

TSPO binding in patients suffering from schizophrenia versus controls remains to be established. Rodent studies have shown that inhibiting microglial activation with minocycline decreases gliosis and TSPO binding.<sup>99</sup> Decreased microglial activation seemed to be the case after 12 weeks of administration of oral minocycline in patients suffering from brain injury.<sup>100</sup> A recent study showed unaltered TSPO binding in patients suffering from chronic major depressive disorder after administration of oral minocycline, which may be a disease-specific effect according to the authors.<sup>101</sup>

In sum, further studies are warranted to measure both TSPO and dopamine release and specify whether a causal and regionally specific link exists between them in schizophrenia.

### Influence of TSPO on Microglial Activation in Animal and Human Studies

While trying to elucidate dopamine and microglial interactions, it should be taken into consideration that TSPO itself may modulate microglial activation.

Interestingly, *in vivo* and *in vitro* findings in animal models of neurodegenerating diseases showed that TSPO ligands significantly reduced microgliosis and dopamine depletion with neuroprotecting effects.<sup>102–104</sup> Contradictory *in vitro* data on rodent microglia exist about the action of TSPO ligands on microglial activation concerning both their pro – and their anti-inflammatory polarization. TSPO ligands may reduce M1 polarization or increase the production of reactive oxygen species and pro-inflammatory cytokines from microglia or contribute to M2 polarization.<sup>58,103,105–107</sup> Those differences may be associated with the different ligands and mitochondrial inflammatory induction methods that have been used. In a human microglial *in vitro* study, two TSPO ligands stimulated the release of anti-inflammatory cytokines, and TSPO knock-down microglia released more pro-inflammatory cytokines in comparison with wildtype microglia after mitochondrial activation.<sup>55</sup> It is currently unknown if TSPO further inhibits pro-inflammatory microglial activation along with dopamine in schizophrenia.

### Influence of (Neuro)inflammation and TSPO on Dopamine

It would be simplistic to consider that dopamine-mediated microglial modulation is unidirectional. Interestingly, the role of inflammation on mesolimbic dopamine modulation and motivational drive has been recently reviewed.<sup>108</sup>

However, no study, to our knowledge, has examined the association – if any – between inflammatory cytokines and regional dopamine alterations and symptoms in schizophrenia. Three potential mechanisms by which pro-inflammatory cytokines interfere with dopaminergic pathways are discussed below.

### Altered Dopamine Synthesis

To our knowledge, little is known of the effects of TSPO ligands on dopamine. In a PD mouse model, a TSPO agonist decreased dopamine turnover rates in MPTP-treated animals and dopamine levels became comparable with those measured in control animals.<sup>104</sup>

Besides TSPO, pro-inflammatory cytokines have been shown to activate the biosynthesis and the oxidative use of 5,6,7,8-tetrahydrobiopterin (BH4), a cofactor involved in the synthesis of dopamine, serotonin and nitric oxide.<sup>109</sup> Furthermore, increased glutamate release under the influence of pro-inflammatory cytokines may increase the effects of oxidative stress on BH4 and dopamine synthesis according to in vitro studies.<sup>110–112</sup>

In patients with schizophrenia, a significant decrease in plasma BH4 was observed and was correlated with CSF levels.<sup>113</sup> The hypothesis of a dopaminergic hypofunction due to deficiency of BH4 has thus been tested in animal studies. Yang and colleagues developed a strain of genetically modified mice that produced approximately 60% less BH4 in the brain compared to wildtype that had a significant reduction (over 90%) in the levels of dopamine in the caudate putamen and cortex and presented symptoms similar to those observed in phencyclidine or amphetamine-induced animal models of schizophrenia.<sup>114,115</sup>

### Impaired Packaging and Release

The cytoplasmic dopamine concentration is mainly regulated by two transporters: the membranous dopamine transporter (DAT), which translocates dopamine from extracellular spaces into the extravesicular cytoplasmic compartment of neurons, and the vesicular monoamine transporter 2 (VMAT2) on synaptic vesicles, which mediates the packaging of dopamine into cytoplasmic vesicles.<sup>116,117</sup>

In rat enterochromaffin-like cells, IL-1 and TNF have been associated with decreased expression of VMAT2.<sup>118</sup> In an animal study, the anti-inflammatory pituitary adenylate cyclase-activating polypeptide 38 was shown to increase VMAT2 expression and thus lead to reduced

dopamine release from and/or increased reuptake into vesicles after METH administration, potentially resulting in elevated cytoplasmic dopamine levels, auto-oxidation and generation of reactive oxygen species.<sup>119,120</sup> Reduced dopamine release in the striatum of rhesus monkeys after four weeks of peripheral interferon- $\alpha$  (INF- $\alpha$ ) has been observed and associated with anhedonia-like symptoms.<sup>121</sup>

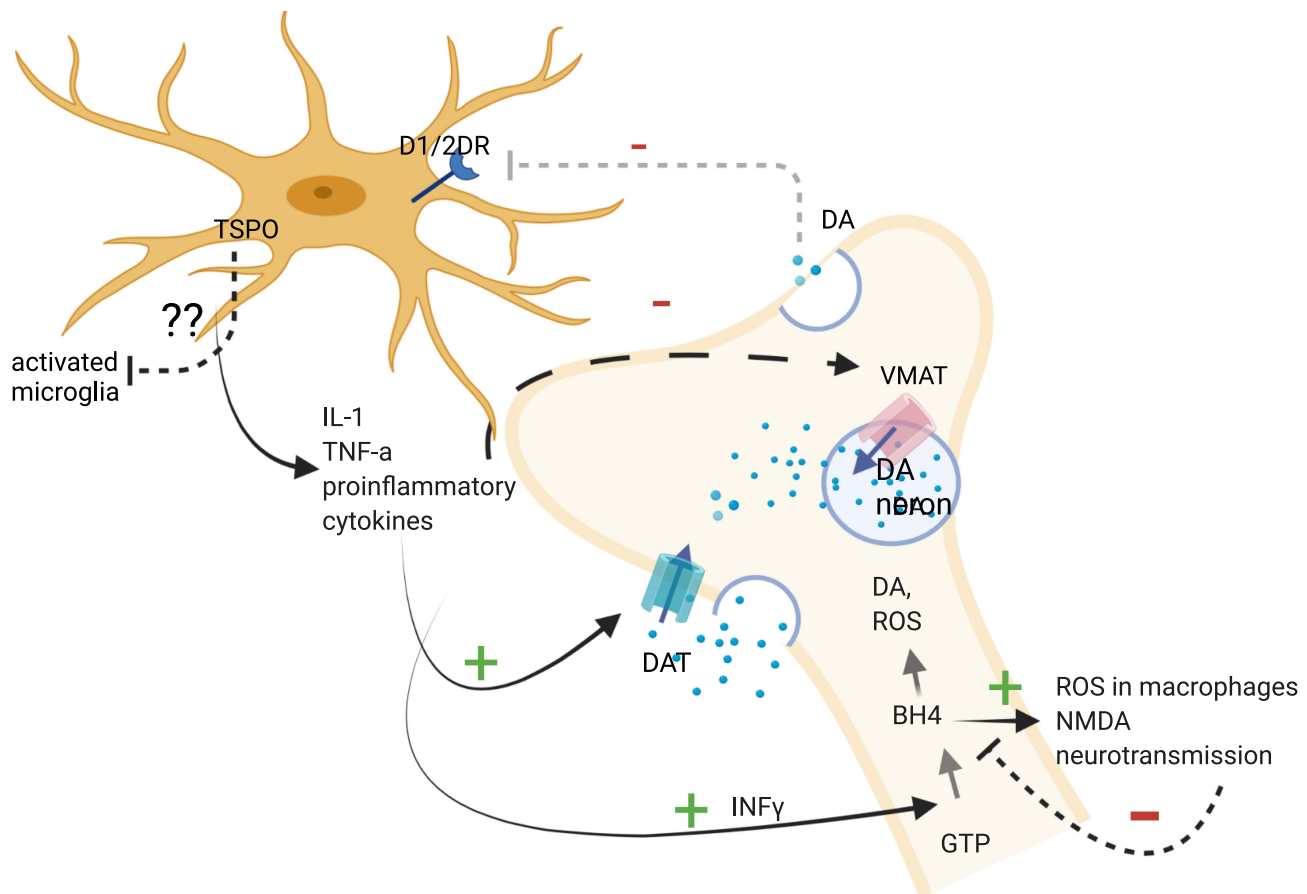
In patients with hepatitis C, peripheral administration of INF- $\alpha$  for four to six weeks was followed by increased dopamine uptake and decreased turnover in ventral striatum during winning trials when a gambling task was performed.<sup>122</sup> A decreased activity in those regions was also demonstrated and associated to anhedonia, similarly to findings in schizophrenia suggesting a negative association between ventral striatal activation and apathy.<sup>122,123</sup>

However, no direct evidence concerning the interactions of neuro-inflammatory mechanisms and DAT/VMAT dysregulation or dopamine release in schizophrenia has been published to our knowledge.

### Impaired Dopamine Receptor Signaling

Less is known about the effects of inflammation on dopamine receptor signaling. Decreased D2 receptor binding (but not DAT binding) was observed in the striatum of rhesus monkeys in the study of Felger et al.<sup>121</sup> A recent study showed that interactions between the microglial complement C3 receptor and complement C3 protein are associated with immune activation and downregulation of D1 receptors in the nucleus accumbens in adolescent male rats.<sup>124</sup>

In sum, the in vitro and indirect data suggest that pro-inflammatory cytokines and the modulation of TSPO activity may alter dopamine synthesis, trigger oxidative stress in neurons by increasing intracellular dopamine levels and impair dopamine receptor function. However, these functions in schizophrenia have yet to be demonstrated, and it is not known up to which extent specific brain regions are concerned, whether the alterations in dopamine receptors number or activation status are concerned and how or if the dopamine receptors on microglia are influenced in order to conclude in an association between TSPO levels and neuro-inflammation based on imaging trials (Figure 2). For example, while a cytokine-induced decrease in dopamine release was confirmed in brain regions where reduced dopamine levels have been demonstrated, it is not known if an increase in microglial activation and in TSPO levels is present, and the latter has not been found increased in the frontal cortex in schizophrenia patients in in vivo PET-TSPO trials. Further



**Figure 2** Pathways between proinflammatory cytokines, dopaminergic neurons and microglia.

**Notes:** Proinflammatory cytokines have been shown to activate the biosynthesis of BH4, which is involved in the synthesis of dopamine and stimulates the production of reactive oxygen species in macrophages and NMDA neurotransmission. IL-1 and TNF have been associated with decreased expression of VMAT2. Pro-inflammatory cytokines have been associated with increased expression of DAT, which results in the elevation of cytoplasmic DA levels in neurons. Decreases in dopamine release may result in decreased dopamine-induced microglial inhibition. The role of TSP0 on activated microglia where it is expressed remains to be established, but some studies suggested that it promotes anti-inflammatory microglial polarization. Created with BioRender.com.

**Abbreviations:** GTP, guanosine triphosphate; INF $\gamma$ , interferon gamma; BH4, tetrahydrobiopterin; DA, dopamine; VMAT, vesicular monoamine transporter; DAT, dopamine transporter; ROS, reactive oxygen species; IL-1, interleukin-1; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; DRD1,2, dopamine receptor 1,2; dotted line/arrow, inhibition; arrows, activated pathway; +, activation; -, inhibition; ??, unknown. Image created with biorender.com.

research is warranted in order to measure dopamine receptors number and activation status in microglia which can be done with already described techniques, along with cytokine levels in specific brain regions in patients.<sup>125</sup>

## Non-Dopaminergic Neurotransmitter Receptors on Microglia

Microglial cells also express glutamate receptors (recently reviewed by Spampinato et al), as well as other neurotransmitter receptors.<sup>126,127</sup> In vitro, metabotropic glutamate receptor 5 (mGluR5) inhibits microglial activation with a reduction in nitric oxide, reactive oxygen species, and TNF $\alpha$  production, whereas mGluR2 but not mGluR3 receptors induce TNF $\alpha$  release and microglial activation.<sup>128–132</sup> In

rodent models of schizophrenia, mGlu2 and mGlu3 mRNA and protein levels have been found to be decreased in the frontal cortex, but this decrease was not necessarily microglial-specific.<sup>133</sup> Post-mortem findings showed a reduction in mGlu5 receptor signaling in the dorsolateral prefrontal cortex of individuals with schizophrenia.<sup>134</sup> However, this does not seem to be in line with the lack of increase in TSP0 binding observed in this region of interest.<sup>33</sup> Although glutamate and glutamine levels have been measured in several brain regions in patients, imaging limitations with glutamate proton magnetic resonance spectroscopy need to be taken into account as this method does not differentiate between intra- and extracellular compartments.<sup>135</sup> Further research is warranted in order to specify how and where glutamate transmission modulates microglial activation as reflected by TSP0 imaging, taking into consideration the methodological limitations of



glutamate imaging and its interactions with N-methyl-D-aspartate receptors and dopaminergic neurons. The overview of the role of neurotransmitters other than dopamine on microglia is out of the scope of this study.

## Conclusion and Future Directions

The goal of this review was to explore the role of dopamine in the modulation of microglial activity, as reflected by TSPO levels in schizophrenia, according to the two most recent meta-analysis of in vivo human trials. Previously investigated confounding factors in these trials, biological and methodological interpretations seem unlikely to fully account for the decreased/unaltered TSPO findings in schizophrenia. We have proposed a new theoretical framework in which dopamine may inhibit microglial activation leaving TSPO levels unaltered or decreased in patients compared to controls. However, the interactions between dopamine and neuroinflammation are not uni-directional and the TSPO itself may exercise possible immunomodulatory effects as presented above. Furthermore, it remains to be elucidated which extent TSPO expression reflects a pro- or anti-inflammatory microglial activation, given the conflicting evidence discussed above and the fact that the spectrum of microglial phenotypes is actually thought to be wider and more complex than the simplified M1/2 classification.<sup>74</sup>

It is known that the dopamine levels and D2 availability differ across different brain regions of patients, but a regionally specific alteration of TSPO levels due to dopamine-induced microglial inhibition does not seem to be the case for the most part according to existing data.<sup>89,136–139</sup> A possible explanation could be that PET TSPO studies have not tested for the receptor's density in the same brain regions as PET DA studies.<sup>22</sup> Dopamine release in schizophrenia is not fully mapped, and the dopamine receptor density measured in patients is not specific for microglia to our knowledge. Future research is needed to test our hypothesis, combining TSPO and dopamine imaging to explore the association between microglial activation and dopamine levels brain region by brain region, ideally quantifying microglial dopamine receptors at the same time. Shedding light on these mechanisms will both ameliorate our understanding of how the microglia respond to altered dopamine levels and if they are affected by dopamine receptors' dysregulation in schizophrenia.

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## Disclosure

The authors report no conflicts of interest in this work.

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