**Neuropsychopharmacology (2017) 42,** 2472–2473

**www.neuropsychopharmacology.org**

**Commentary**

# Microglia Activation in Subjects at Risk for Psychosis: Fact or Fiction?

**Patricio O'Donnell**[*,1]

[1]*Translational Research and Early Clinical, Takeda Pharmaceuticals, Cambridge, MA, USA*

*Neuropsychopharmacology* (2017) **42,** 2472–2473; doi:10.1038/npp.2017.179; published online 13 September 2017

The notion that inflammation and immune signals may play a role in the pathophysiology of psychiatric conditions has been gaining considerable support. In no small part, this support was driven by imaging studies assessing neuroinflammation-related markers. In particular, microglia activation has been reported in several psychiatric conditions, including schizophrenia and clinical high risk (CHR) subjects, using PET ligands that bind to the 18 kDa translocator protein (TSPO) (Bloomfield *et al*, 2016). Despite the excitement the initial findings generated, studies have not been consistent. In the current issue, Hafizi *et al* (2017) report lack of differences in CHR subjects compared to controls. This is the largest study assessing neuroinflammation in this population so far, and the authors controlled carefully for genotype and other factors. The authors have also used a validated outcome measure, a two-tissue compartment model that provides total volume of distribution (VT). This contrasts with previous studies that used ligand distribution volume ratio (DVR), a measure considered unacceptable by most PET imagers (Innis *et al*, 2007). So, yet another negative finding with TSPO binding in a psychiatric condition raises a number of questions for the field.

One conclusion could be that there simply is no microglia activation in CHR subjects. But to make sense of the data (both presented in this issue and reported previously), we need to solve a few outstanding issues. First, we need to understand better what exactly TSPO ligands are binding to. TSPO is a mitochondrial protein that was reported elevated in the brain, initially in hepatic encephalopathy. Soon after, reports emerged of elevated TSPO binding in several neurodegenerative conditions, and more recently psychiatric conditions. It was assumed for quite some time that increased TSPO activity selectively reflects activation of microglia, the resident brain macrophages. However, it is now evident that TSPO is expressed in mitochondria of many brain cell types beyond microglia, including astrocytes (Lavisse *et al*, 2012) and neurons (Notter *et al*, 2017). Thus, increased TSPO binding may reflect the functional state of mitochondria in several cell types and not necessarily inflammatory processes. It could well be that conditions of strongly active microglia and immune activation, such as neurodegenerative disorders, show large and reliably measurable TSPO binding. If microglia were indeed activated in psychiatric conditions, this activation would likely be moderate and perhaps not easy to distinguish from the natural variability TSPO ligands. Unfortunately, it is becoming clear that the question of whether there is immune activation or neuroinflammation in psychiatric conditions cannot be answered with TSPO binding studies.

A second issue relates to the heterogeneity of subjects with psychiatric conditions, which may be even more pronounced in subjects at risk. Therefore, subjects enrolled in these studies may not be completely uniform in their underlying pathophysiology. It is possible that some, but not all patients exhibit brain inflammation or immune activation. The fact that despite the overall negative data, this study identified a correlation between one domain (apathy) and FEPPA VT in the hippocampus may reflect the possibility that whatever TSPO binding is measuring, it could be present in a specific domain within the CHR population.

Third, an important caveat in this type of studies is lack of statistical power. The authors recognized this issue and determined the sample size needed based on the known variability of other TSPO ligands. It cannot be ignored that despite this being the largest study in CHR subjects, it is still underpowered. However, the data showed a trend towards reduced TSPO binding in CHR subjects, suggesting it is unlikely that an elevation would be observed.

What do TSPO binding studies really tell us? Could this mitochondria-linked marker be expression of mitochondria health in different cell types? If so, more than neuroinflammation, TSPO binding could be reflection of redox state or metabolic activity in different brain cells. As neurodegenerative disorders and to some extent psychiatric disorders may show oxidative stress in the brain (Steullet *et al*, 2016), it is possible that the positive studies are picking up a mild signal driven by oxidative stress and altered mitochondria activity. Indeed, neurodegeneration in the brain will be accompanied by cell damage and diseased mitochondria. A

*Correspondence: Dr P O'Donnell, Takeda Pharmaceuticals, 350 Massachusetts Avenue, Cambridge, MA 02139, USA, Tel: +1 617 761 6829, E-mail: patricio.odonnell@takeda.com
Received 9 June 2017; revised 3 August 2017; accepted 4 August 2017; accepted article preview online 17 August 2017

more subdued process, perhaps driven by genetic or environmental changes in immune signals in the brain, which are essential for synaptic remodeling and function, could also yield changes in mitochondria activity (and even oxidative stress). As those changes are subtle and perhaps present in just a subset of patients, TSPO binding may not be the ideal tool to assess them. If redox state and cell metabolic activity is what TSPO binding captures, finding correlations with symptoms and disease domains will not be straightforward. Of note, blood redox state correlates with a functional measure of sensory processing, mismatch negativity (MMN), but only in controls. The correlation is lost in schizophrenia patients (Ballesteros *et al*, 2013). If TSPO binding reflects mitochondria activity, it could be correlated with functional domains in healthy brains but the correlation may be lost in a diseased brain, making it difficult to obtain a conclusive measure. The better we are at parsing out specific domains and making a priori hypotheses about linking immune and redox processes to these domains, the sooner we will have clear answers about the role of these processes in psychiatric disorders.

## FUNDING AND DISCLOSURE

The author was employee and shareholder at Pfizer, Inc until May 2017. The author is currently an employee at Takeda Pharmaceuticals.

## REFERENCES

Ballesteros A, Summerfelt A, Du X, Jiang P, Chiappelli J, Tagamets M *et al* (2013). Electrophysiological intermediate biomarkers for oxidative stress in schizophrenia. *Clin Neurophysiol* **124**: 2209–2215.

Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo A, Owen DR *et al* (2016). Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C]PBR28 PET brain imaging study. *Am J Psychiatry* **173**: 44–52.

Hafizi S, Da Silva T, Gerritsen C, Kiang M, Bagby RM, Prce I *et al.* Imaging microglial activation in individuals at clinical high risk for psychosis: an *in vivo* PET study with [18F]FEPPA. *Neuropsychopharmacology* (this issue).

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN *et al* (2007). Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* **27**: 1533–1539.

Lavisse S, Guillermier M, Herard AS, Petit F, Delahaye M, Van Camp N *et al* (2012). Reactive astrocytes overexpress TSPO and are detected by TSPO positron emission tomography imaging. *J Neurosci* **32**: 10809–10818.

Notter T, Coughlin JM, Gschwind T, Weber-Stadlbauer U, Wang Y, Kassiou M *et al* (2017). Translational evaluation of translocator protein as a marker of neuroinflammation in schizophrenia. *Mol Psychiatry*. doi:10.1038/mp.2016.248 (in press).

Steullet P, Cabungcal JH, Monin A, Dwir D, O'Donnell P, Cuenod M *et al* (2016). Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A 'central hub' in schizophrenia pathophysiology? *Schizophr Res* **176**: 41–51.