# Imaging of neuroinflammation: TSPO and beyond

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# Imaging of neuroinflammation: TSPO and beyond

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Neuroinflammation is a pathological phenomenon common to many disorders of the central nervous system (CNS). The process includes activation of microglia, the resident immune cells of the CNS, production of both pro- and anti-inflammatory mediators, tissue damage and tissue repair, and activation of astrocytes. This entire spectrum of phenomena represents the way in which the CNS reacts to any kind of insult, either acute or chronic. Since neuroinflammation can have both detrimental and beneficial effects, knowledge of the relative contributions of these two actions of the immune cells of the CNS could provide a means to selectively intervene in specific inflammatory processes and thus modify the detrimental outcome that can lead to tissue damage or neurodegeneration.

The chemical and cellular mediators of inflammation (cytokines, microglia, astrocytes, myeloid cells, T-cells) [1], the phenotypic characterization of pro- and anti-inflammatory microglia and other specific receptors and targets of inflammation (for instance toll-like receptors, purinergic receptors, fractalkine receptors) are known and well-studied, both *in vitro* and using animal models of neuroinflammation. However, at present, most of the inflammatory processes occurring *in vivo* cannot be studied in the living brain.

Positron emission tomography (PET) has made it possible to examine *in vivo* the 18-kDa translocator protein (TSPO) as a marker of microglia activation and neuroinflammation in a variety of CNS disorders, such as stroke, multiple sclerosis, Parkinson´s disease, Multiple System Atrophy, Progressive Supranuclear Palsy, Alzheimer´s disease and other dementias. For several reasons, however, TSPO imaging is not the "Holy Grail" for studying neuroinflammation *in vivo*. First, quantification of TSPO availability using the reference tracer *R*-[$^{11}$C]PK11195 is complex and requires advanced methods with several assumptions regarding the physiological behavior of the radioligand. Second, the development of second-generation TSPO radioligands only in part has provided improved imaging tools, as the presence of low-, mixed- and high-affinity binders contributes to large variability in the data. Third, it is well known that TSPO is not a specific marker for activated microglia, since it also is expressed on astrocytes. Finally, TSPO does not permit a distinction between pro- and anti-inflammatory microglia, which is a serious limitation when considering possible therapeutical strategies.

The knowhow acquired over the last 15-20 years on advantages and limitations of TSPO imaging as a marker of neuroinflammation underscores the need for new alternative neuroinflammation imaging markers. A tool complementary to TSPO imaging is the measurement of monoamino oxidase B (MAO-B) activity using L-[$^{11}$C]Deprenyl-D2 PET. There clearly is an inbalance between the large number of studies performed using TSPO radioligands and the limited number of studies using MAO-B radioligands as imaging tools of neuroinflammation. Therefore, at present, the complementary value of MAO-B imaging can still not be assessed adequately using available data. In addition, to the best of our knowledge, there is no human study that has compared TSPO and MAO-B imaging in any CNS disorders, so it still is difficult to make any comments on the relative value of the two markers for imaging neuroinflammation.

The European Union Concerted Action "Imaging of Neuroinflammation in Neurodegeneration" (INMiND) was established and funded by the 7th Framewotrk Programme in order to examine different aspects of neuroinflammation in neurodegenerative and other CNS disorders, using a transaltional approach ranging from target identification, through rodent models of CNS disorders to neuroinflammation in human subjects [2]. One of the goals of the Consortium is to develop new radioligands for imaging other targets of neuroinflammation, such as P2X7 receptors, metalloproitenases, and CB1 receptors that could be useful complementary targets to the well-established TSPO and MAO-B. The awareness of this need for additional tools to image neuroinflammation motivated the choice of the present monothematic issue that is focused on imaging of neuroinflammation primarily based on established literature on TSPO, but also extending beyond it.

Is there a need for a third generation of TSPO radioligands? Our view is that the third generation of radioligands for neuroinflammation will probably include targets other than TSPO. The examination of new targets specific for either pro-inflammatory or anti-inflammatory phenotypes of microglia will most likely provide additional knowledge on the role of these immune cells in the regulation of neuroinflammation. This knowledge will be pivotal in the design of new therapeutical strategies that modify the neuroinflammatory cascade [3] in order to reduce detrimental effects and promote anti-inflammatory processes that lead to tissue repair. In the future we hope to see studies that will combine imaging of TSPO with third generation radioligands to understand how microglia are involved in detrimental and beneficial effects in CNS disorders.

**Compliance with Ethics Guidelines**

**Research involving human participants and/or animals**. This article does not contain any studies with human participants performed by any of the authors.

**Conflict of interest.** Andrea Varrone and Adriaan A. Lammertsma declare no conflicts of interest.

**Author's contribution**. Andrea Varrone and Adriaan A. Lammertsma: Literature Search and Review, Content Planning Manuscript Writing and Editing

**References**


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3. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. Nat Rev Immunol. 2014 Jul;14(7):463-77. doi: 10.1038/nri3705.

Dear Editor,

Thanks for the reviewer´s comment.

The sentences “In this issue, the role of TSPO imaging as marker of neuroinflammation is reviewed from different perspectives, including its biology, required methodology for PET quantification, the numerous studies conducted in several CNS disorders with *R*-[$^{11}$C]PK11195 and second-generation TSPO radioligands. Since magnetic resonance imaging also has an important role in the study of neuroinflammation, additional attention is given to the use of this modality in CNS disorders associated with neuroinflammation.” Have been removed from the text as suggested by the reviewer