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# Evaluation of P-glycoprotein function at the blood–brain barrier using [<sup>18</sup>F]MC225-PET

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P-glycoprotein (P-gp) is an ATP-dependent efflux transporter located at the blood–brain barrier (BBB), involved in the transport of a variety of neurotoxic substances out of the brain. Alterations in P-gp function play an essential role in the pathophysiological mechanisms underlying neurodegenerative disorders. The most widely used tracer to measure BBB P-gp function in vivo is (*R*)-[<sup>11</sup>C]verapamil [1]. However, (*R*)-[<sup>11</sup>C]verapamil is an avid P-gp substrate, and its low uptake hampers the measurement of increases in P-gp function. In order to overcome this limitation, [<sup>18</sup>F]MC225 was developed as a novel PET tracer to measure P-gp function in vivo. [<sup>18</sup>F]MC225 is a weaker P-gp substrate and has shown higher brain uptake than (*R*)-[<sup>11</sup>C]verapamil at baseline in preclinical studies [2]. This may facilitate the evaluation of both increases and decreases in P-gp function.

In addition, the longer half-life of fluorine-18 enables the use of [<sup>18</sup>F]MC225 in centers without an onsite cyclotron.

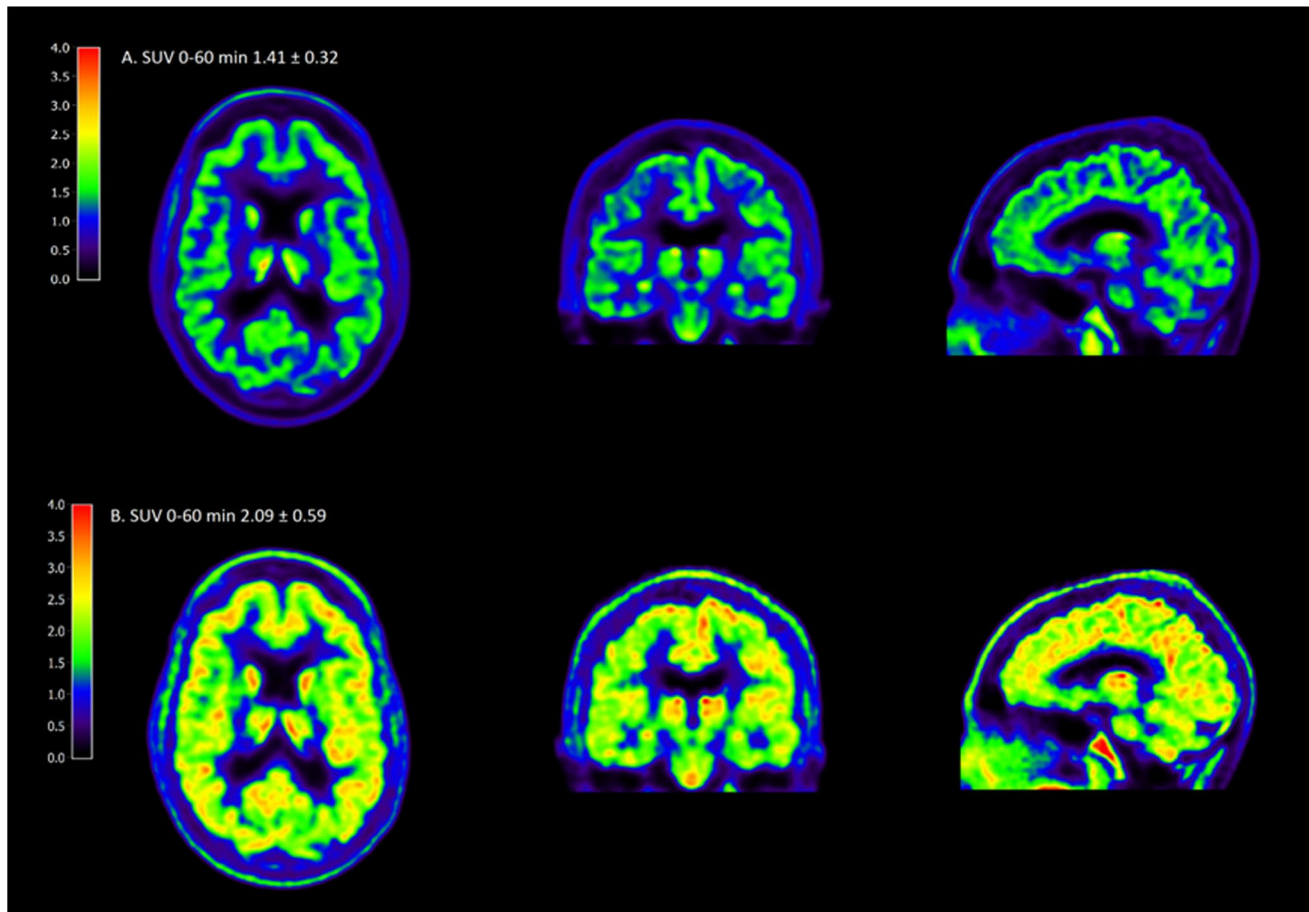
These standardized uptake value (SUV) images show one of the first [<sup>18</sup>F]MC225 PET brain scans in a healthy human subject in both unblocked (A) and blocked (B) P-gp state. Blocking was achieved by continuous intravenous administration of the specific P-gp inhibitor cyclosporin (2.5 mg/kg/h), starting 30 min prior to the scan. Quantitatively, the whole brain grey matter volume of distribution  $V_T$  changed from  $V_T = 4.38$  at baseline to  $V_T = 5.48$  after cyclosporin administration, showing higher uptake at baseline levels compared with previously described data of [<sup>11</sup>C]verapamil ( $V_T = 1.28$  at baseline,  $V_T = 2.00$  after P-gp inhibition) [3], illustrating [<sup>18</sup>F]MC225 as a promising tracer to measure BBB P-gp function in humans.

This article is part of the Topical Collection on Image of the month.

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## Declarations

**Ethics approval and informed consent** All procedures performed involving the human participant were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient.

**Competing interests** GL received a research grant from Siemens Healthineers for appointing a PhD candidate. The other authors declare no competing interests.

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## References

1. Lubberink M, Luurtsema G, van Berckel BN, Boellaard R, Toornvliet R, Windhorst AD, et al. Evaluation of tracer kinetic models for quantification of P-glycoprotein function using (*R*)-[<sup>11</sup>C]verapamil and PET. *J Cereb Blood Flow Metab.* 2007. <https://doi.org/10.1038/sj.jcbfm.9600349>.
2. García-Varela L, Arif WM, Vázquez García D, Kakiuchi T, Ohba H, Harada N, et al. Pharmacokinetic modeling of [18F]MC225 for quantification of the P-glycoprotein function at the blood-brain barrier in non-human primates with PET. *Mol. Pharm.* 2020 <https://doi.org/10.1021/acs.molpharmaceut.0c00514>
3. Muzi M, Mankoff DA, Link JM, Shoner S, Collier AC, Sasongko L, et al. Imaging of cyclosporine inhibition of P-glycoprotein activity using <sup>11</sup>C-verapamil in the brain: studies of healthy humans. *J Nucl Med.* 2009. <https://doi.org/10.2967/jnumed.108.059162>.

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