Multimodal imaging evaluation of the inflammatory response following experimental subarachnoid haemorrhage

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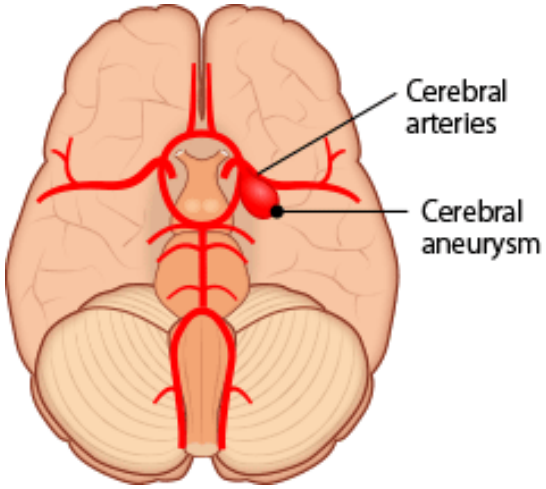
Background: **Subarachnoid haemorrhage (SAH)**

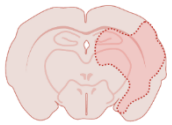


%80 cases: intracranial aneurysm (aSAH)

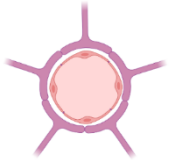
Early brain injury (EBI)

Delayed Cerebral Ischemia (DCI)

Neuronal and endothelial cell apoptosis



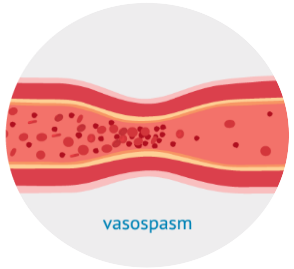
Cerebral oedema
Acute ischemia



Blood-brain barrier (BBB) disruption

Inflammation

Oxidative stress



Cerebral vasospasm
Microconstriction

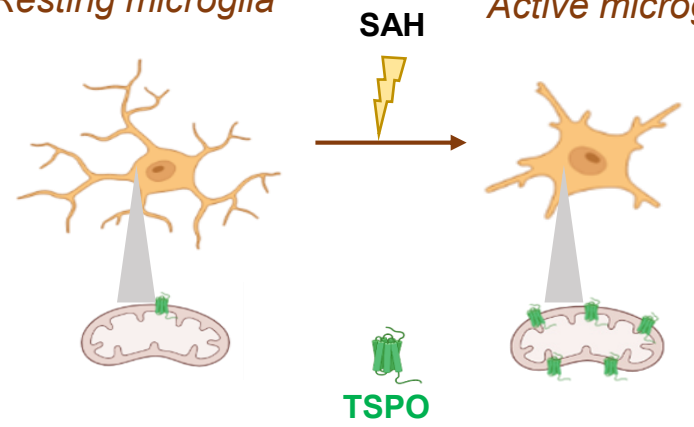
Microthrombosis

Background: **Subarachnoid haemorrhage (SAH)**

Inflammation

[^{18}F]DPA-714 → **Translocator protein (TSPO)**

Resting microglia *Active microglia*



Research Article

Molecular Imaging
Volume 15 : 1-8
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DOI: 10.1177/1536012116639189
mix.sagepub.com
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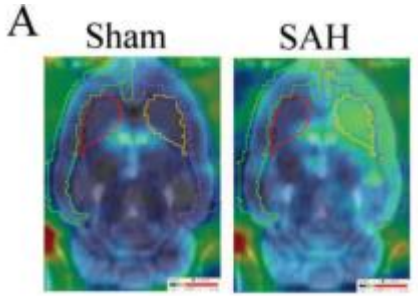
Detection of Neuroinflammation in a Rat Model of Subarachnoid Hemorrhage Using [^{18}F]DPA-714 PET Imaging

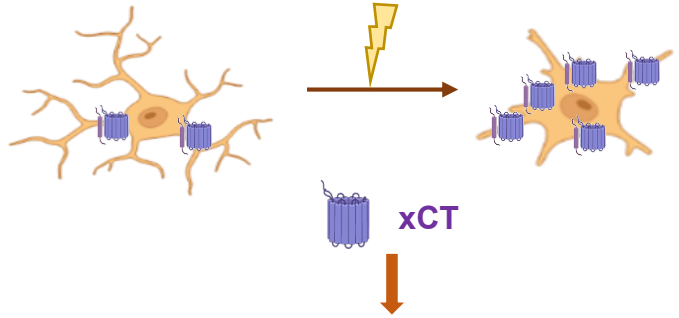
Clément Thomas, MD[1,2], Johnny Vercouillie, PhD[1], Aurélie Doméné[1], Clovis Tauber, PhD[1], Michael Kassiou, PhD[3], Denis Guilloteau, PhD[1,2], Christophe Destrieux, MD, PhD[1,2], Sophie Sérrière, PhD[1], and Sylvie Chalon, PhD[1]



Oxidative stress

[^{18}F]FSPG → **xCT**

Resting microglia *Active microglia*



Cystine-glutamate antiporter (system x_c^-)

Theranostics 2016, Vol. 6, Issue 11 1753

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

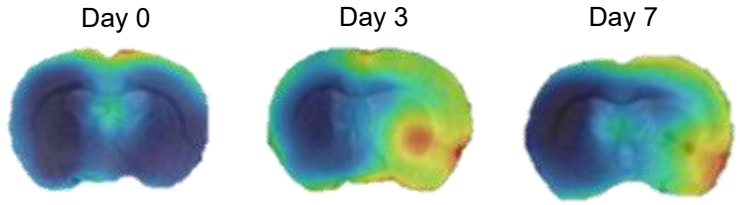
2016; 6(11): 1753-1767. doi: 10.7150/thno.15616

Research Paper

PET Imaging with [^{18}F]FSPG Evidences the Role of System xc$^-$ on Brain Inflammation Following Cerebral Ischemia in Rats

Maria Domercq[1], Boguslaw Szczupak[2], Jon Gejo[1], Vanessa Gómez-Vallejo[2,3], Daniel Padro[2,4], Kiran Babu Gona[2,3], Frédéric Dollé[5], Makoto Higuchi[6], Carlos Matute[1], Jordi Llop[2,3], Abraham Martín[2]✉

[^{18}F]FSPG-PET + MRI T_2W



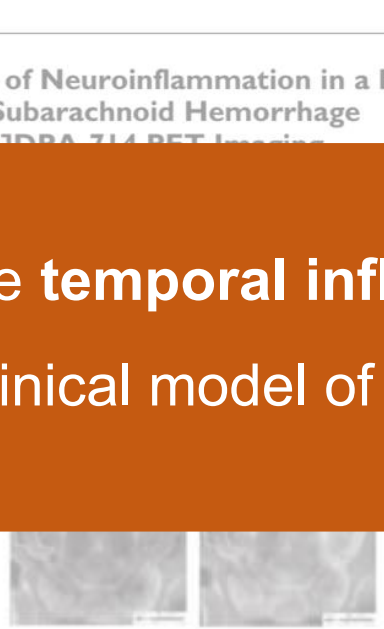
Hypothesis and objective

Hypothesis

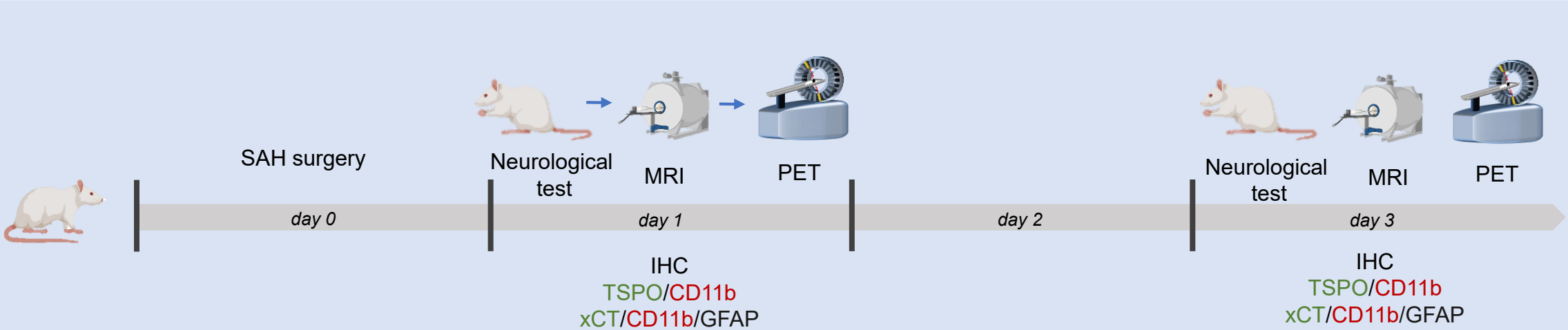
SAH onset produces an **inflammatory response** and increases **oxidative stress** levels. These changes can be observed by ***in vivo*** **imaging modalities.**

Objective

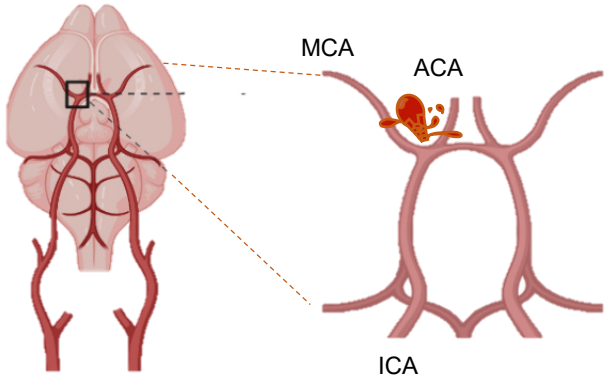
Evaluation of the **temporal inflammatory response** and the **role of oxidative stress** on a preclinical model of SAH using *in vivo* and *ex vivo* imaging modalities



Methods: **Experimental set-up**



SAH surgery
(perforation of the anterior cerebral artery, ACA)

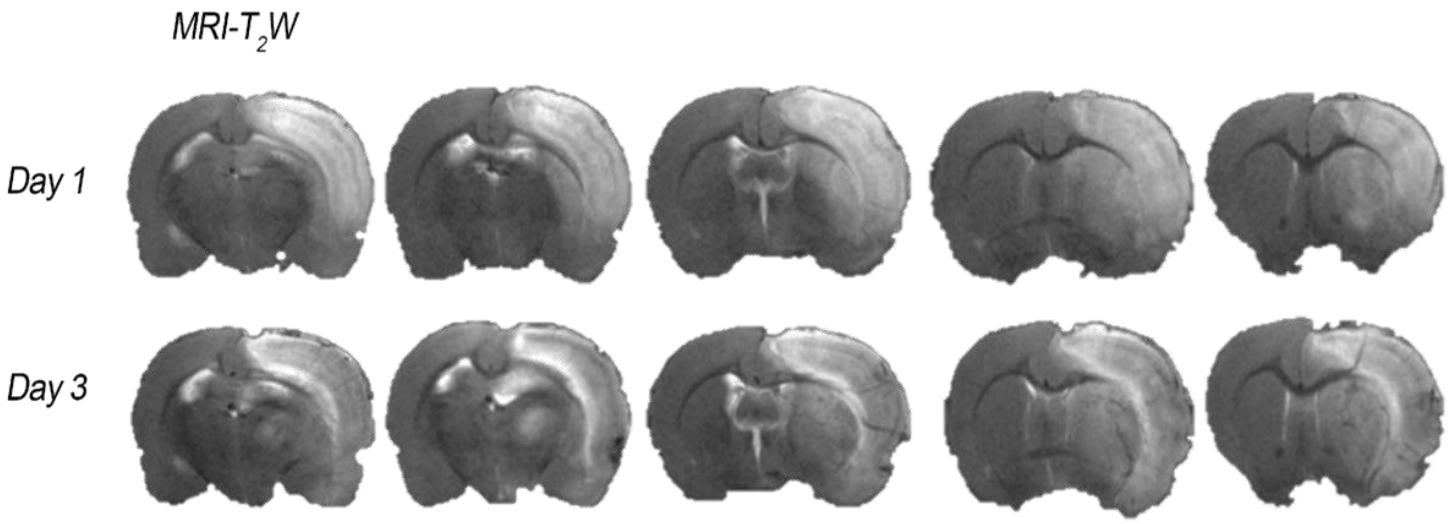


PET:

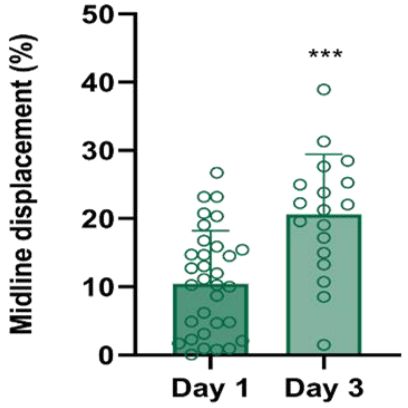
[^{18}F]DPA-714 → Glial activation

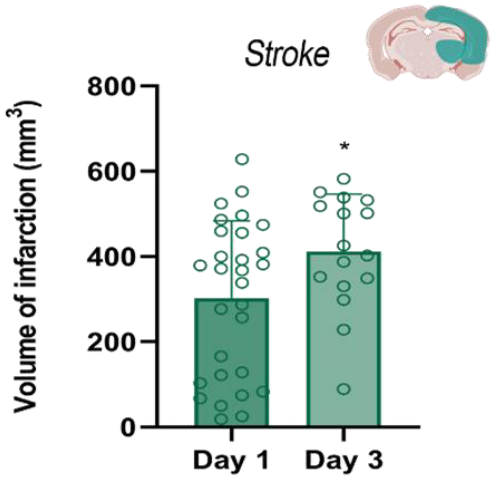
[^{18}F]FSPG → Oxidative stress

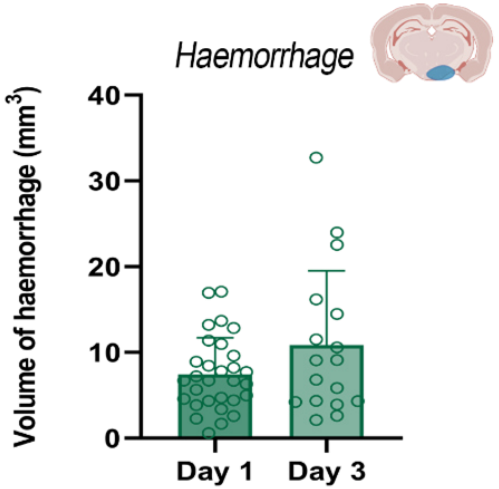
Results: **Description of the infarction**

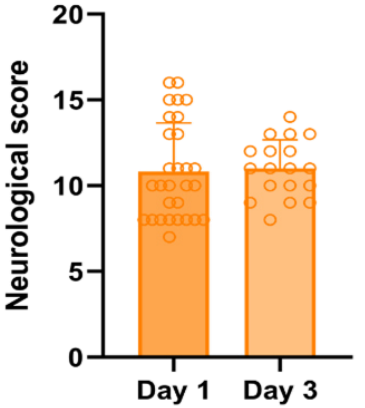


Both the **midline displacement** and the **volume of infarction** increased at **day 3** after SAH, confirming **the progressive ischemic damage** caused by this pathological condition.

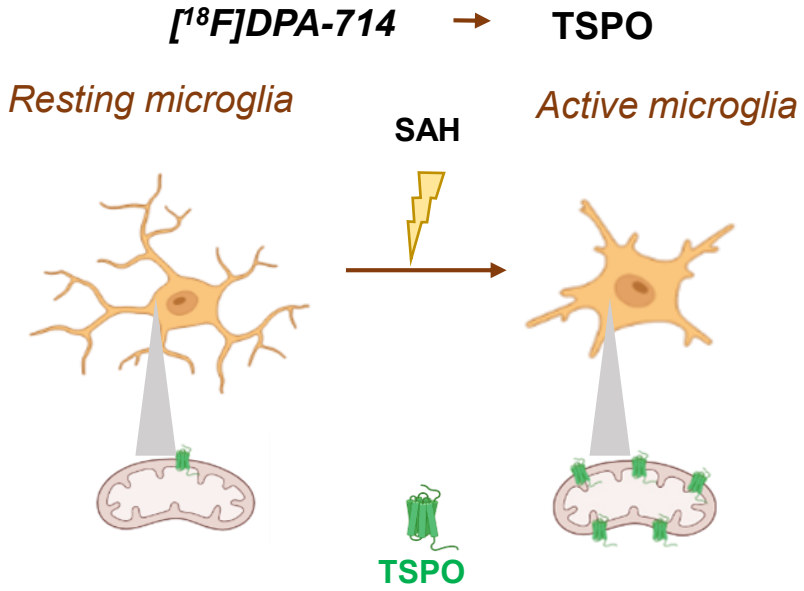


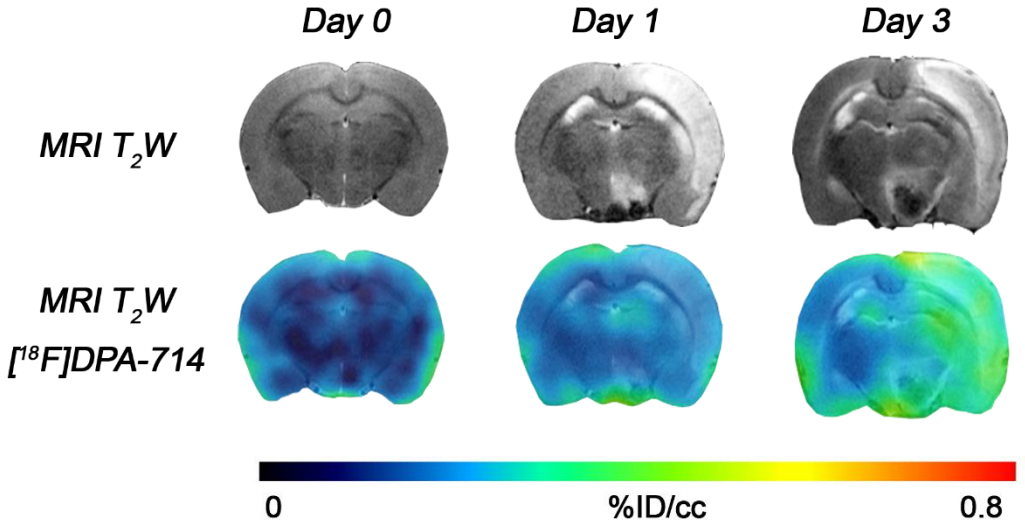




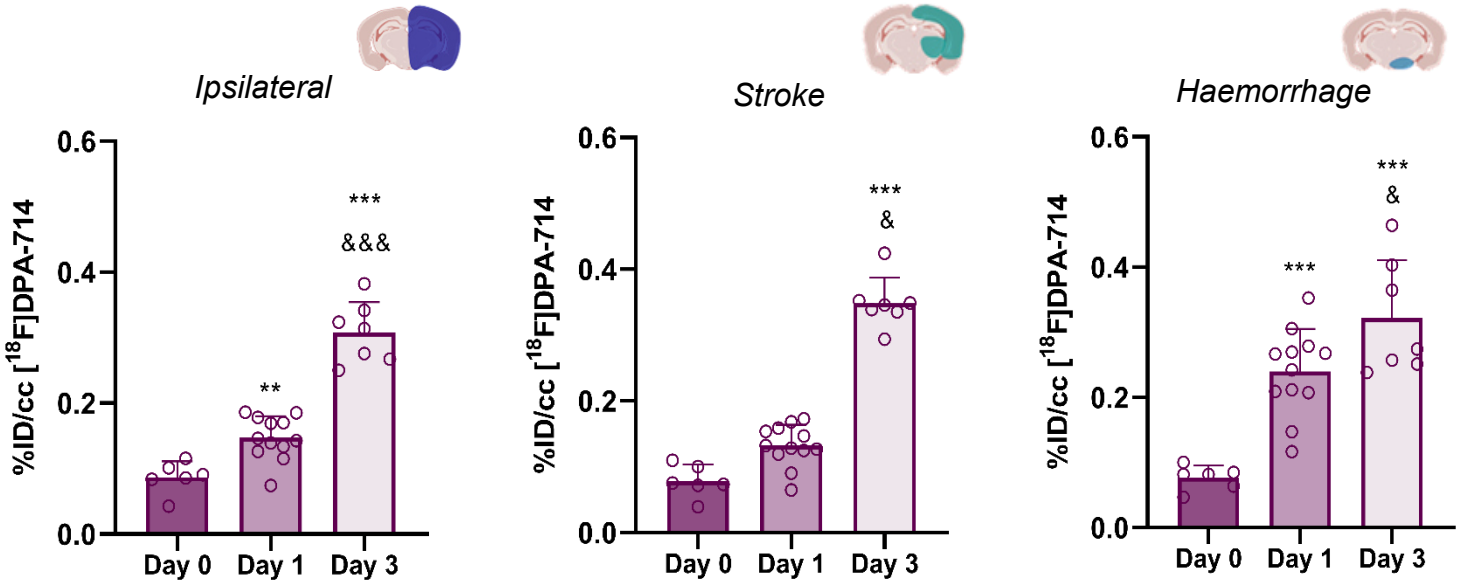


Results: **SAH and glial activation**

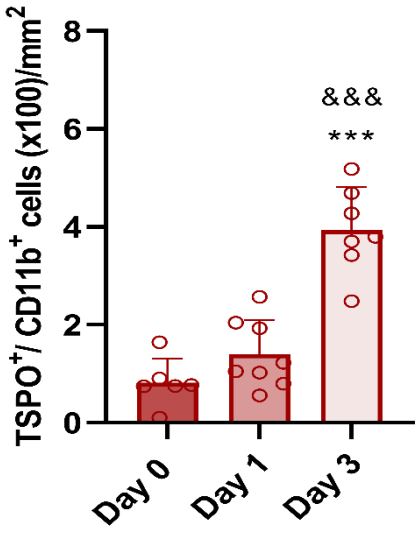




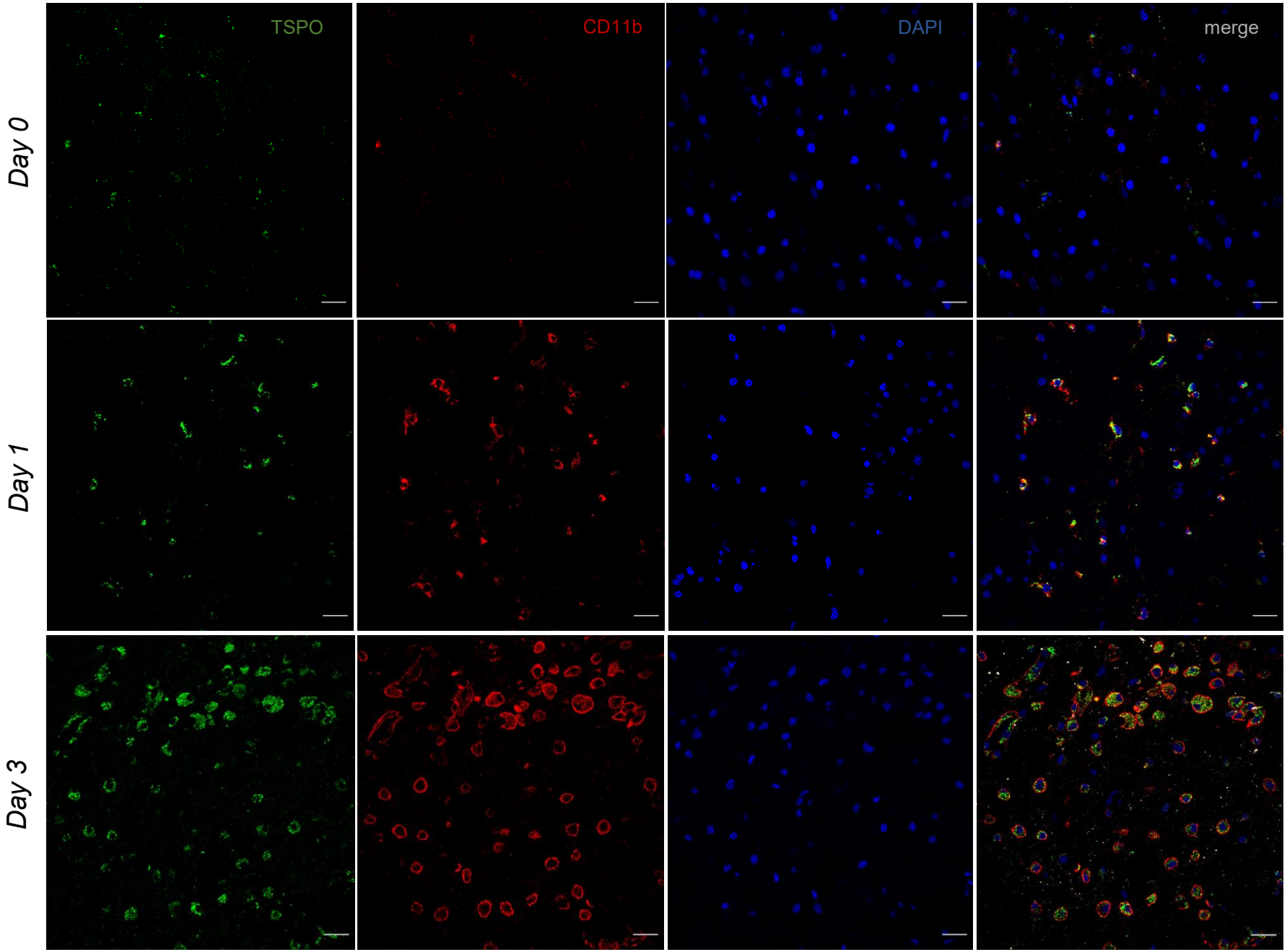
PET studies with [18F]DPA-714 showed a **progressive increase** of the PET signal, with **higher expression at day 3** in comparison with day 1 after the surgery.



Results: **SAH and glial activation**



There was a significant increase of **microglia/macrophages** (CD11b) expressing TSPO at day 3. This tendency was also observed at day 1.



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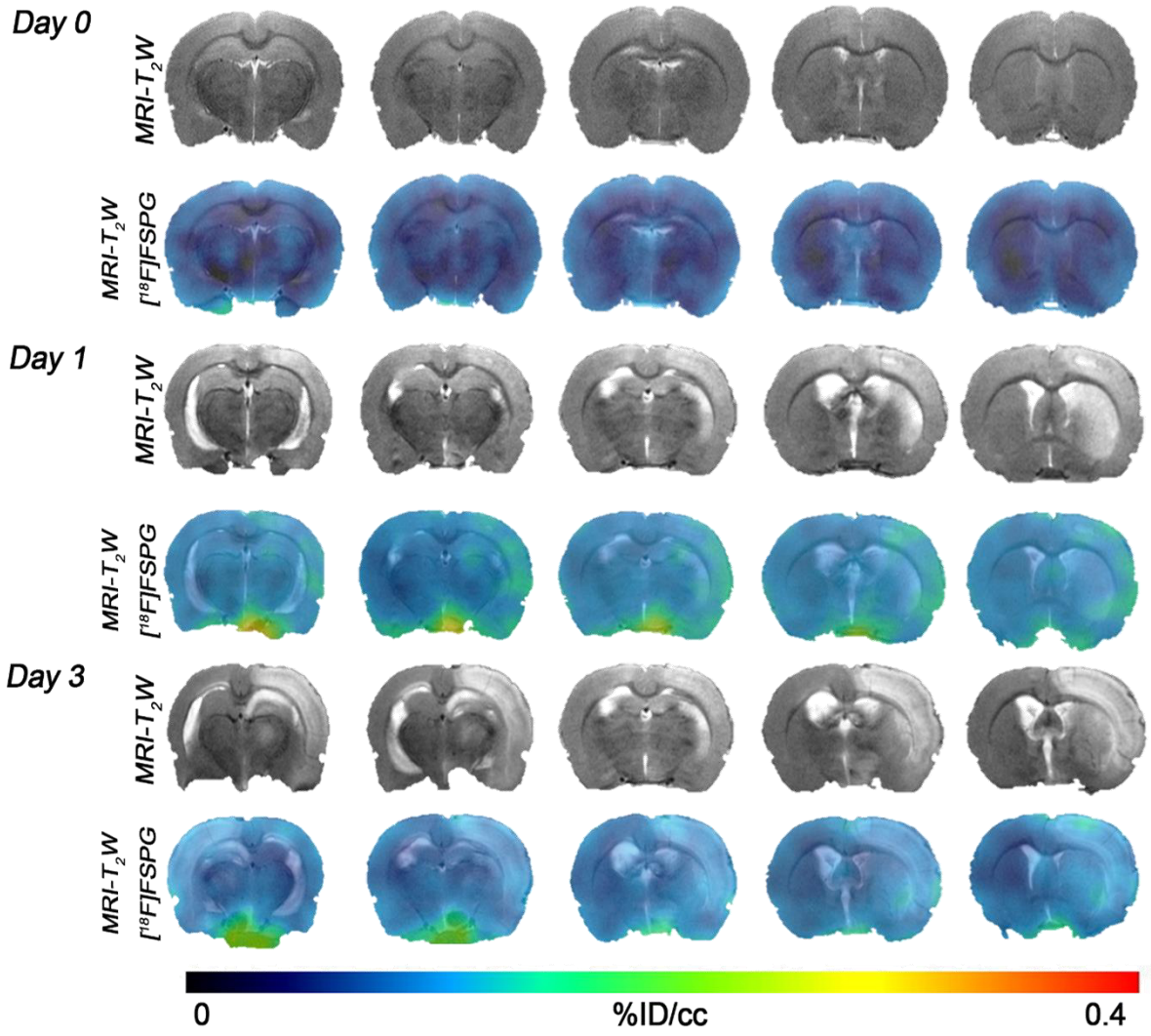
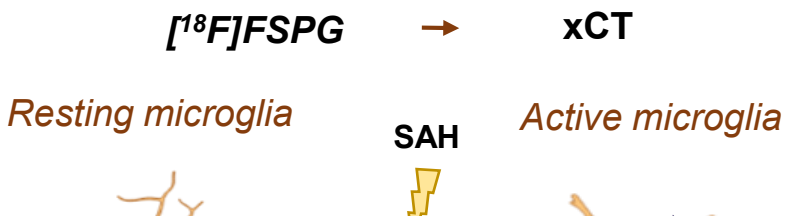
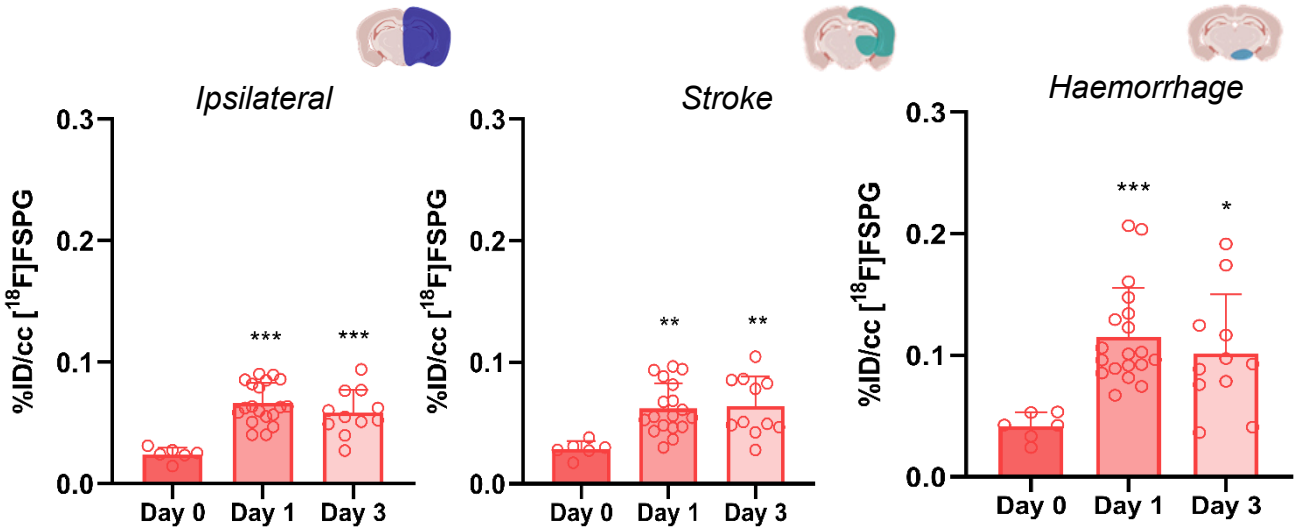
Results: **SAH and oxidative stress**

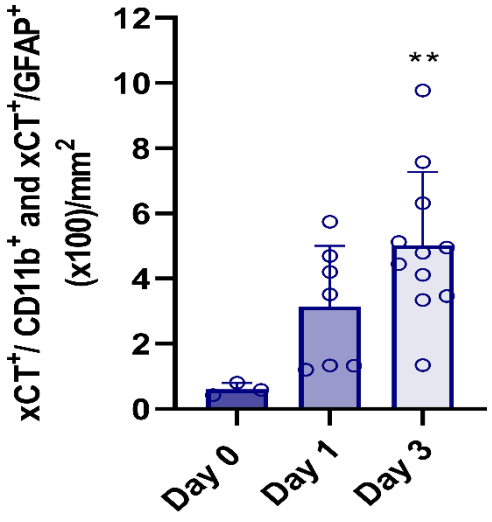




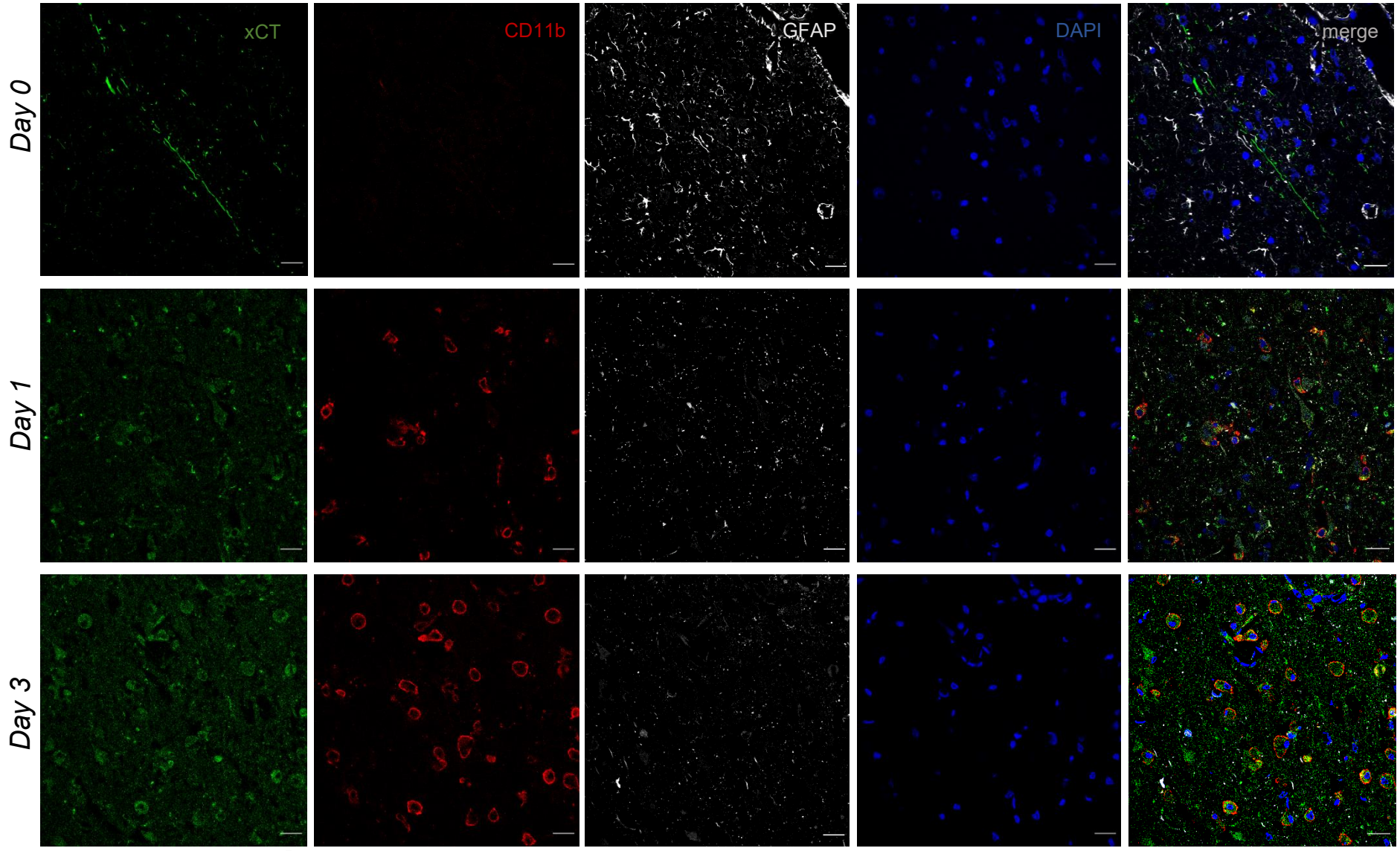


There was **an increase of [18F]FSPG-PET signal** at day 1, which was maintained until day 3.

Results: **SAH and oxidative stress**



There was an increase of **microglia/macrophages** (CD11b) and **astrocytes** (GFAP) expressing xCT at day 3.



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Conclusions

- 1. There is a higher expression of TSPO at **day 3**. This expression is related to **microglia/macrophages**, suggesting a progressive increase of inflammation.

- 2. The progressive **microglial activation** ($TSPO^+/CDb11^+$) observed at day 3 is related to an increase of **oxidative stress** ($xCT^+/CD11b^+$ and $xCT^+/GFAP^+$). This microglial activation contributes to **the increased oedema** and **volume of infarction** observed with MRI at day 3 in relation to day 1.

- 3. The **immediate oxidative stress** response observed by PET with [^{18}F]FSPG is mediated by both **microglia/macrophages** ($xCT^+/CD11b^+$) and **astrocytes** ($xCT^+/GFAP^+$).

- 4. ***In vivo* imaging modalities** are useful techniques to analyse the **inflammatory and oxidative stress response**.

Acknowledgements

Neuroimaging and biomarkers of Inflammation- Achucarro

Radiochemistry and Nuclear Imaging group- CIC biomaGUNE

Institut d'Investigacions Biomèdiques de Barcelona- CSIC
Carles Justicia Mercader
Anna Planas
Comprehensive Stroke Center, Hospital Clinic Barcelona
Sergio Amaro
Ramón Turné
Magnetic Resonance Imaging IDIBAPS Core Facility
Carlos Laredo

Molecular Imaging facility- CIC biomaGUNE
Sandra Plaza García
Ane Ruiz de Angulo
Aitor Lekuona
Vanessa Gómez
Víctor Salinas
Unai Cossío
Pedro Ramos-Cabrer
Daniel Padró

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ikerbasque Basque Foundation for Science
EUSKO JAURLARITZA GOBIERNO VASCO
neuron Network of European Funding for Neuroscience Research
Fundació La Marató de TV3
eitb MARATOIA
bioef
ERA-NET NEURON
GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMIA Y COMPETITIVIDAD
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Results: **SAH and metalloproteinases**