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CO-EXPOSURE TO LOW-DOSE GAMMA IRRADIATION WITH A CHEMICAL STRESSOR CAUSES DIFFERENTIAL OUTCOMES ON BRAIN TOXICITY PARAMETERS IN RAT

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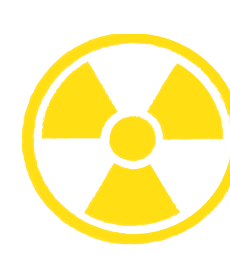
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Scientific Context

Occupational low dose γ irradiation

Cerebral effects of LDI

- **Epidemiology:** increased risks of cerebrovascular and neurodegenerative diseases (Lopes *et al.*, 2022; Richardson *et al.*, 2023; Dauer *et al.*, 2024)
- **Neuroinflammation and microglial activation** (Casciati *et al.*, 2016; Narasimhamurthy *et al.*, 2022)
- **Behavioral and neurocognitive disorders** (Kempf *et al.*, 2014)
- **Dose-dependent neuroprotective or adaptive effects** (Betlazar *et al.*, 2016)



Nuclear worker



Exposome and combined effects
Wild (2005) & Barouki (2022)

Chemical stressor : particulate aerosols

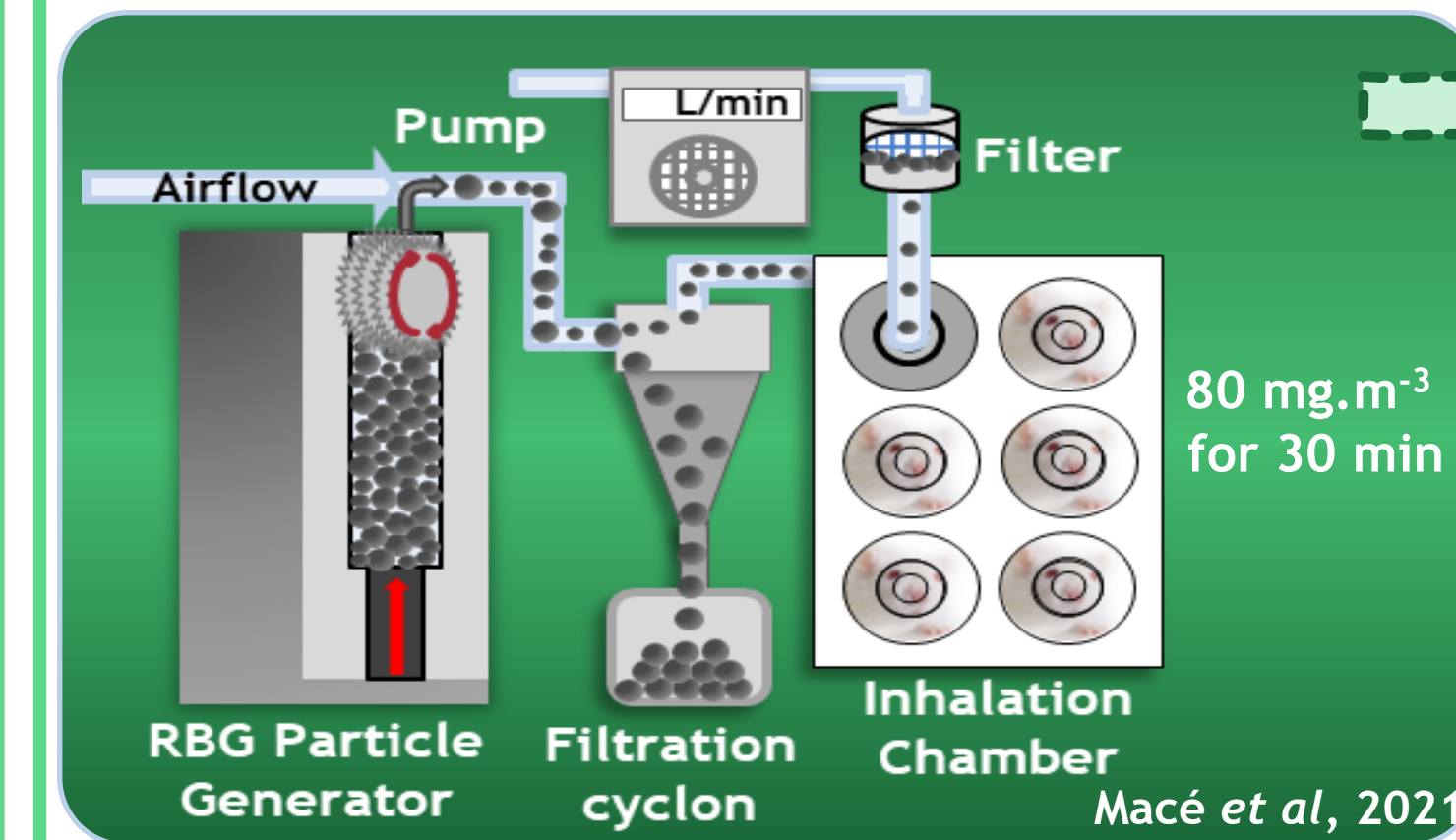
Cerebral effects of tungsten (W)

- **Emergent contaminant :** The shielding of fusion reactors is made of W and is eroded by the plasma
- From Macé *et al.*, 2024:
- W concentration increases in cerebral structures
- Increase of a neuronal suffering phenotypes in relation with oxidative stress in the frontal cortex
- Increase of microglial apoptosis in the olfactory bulb

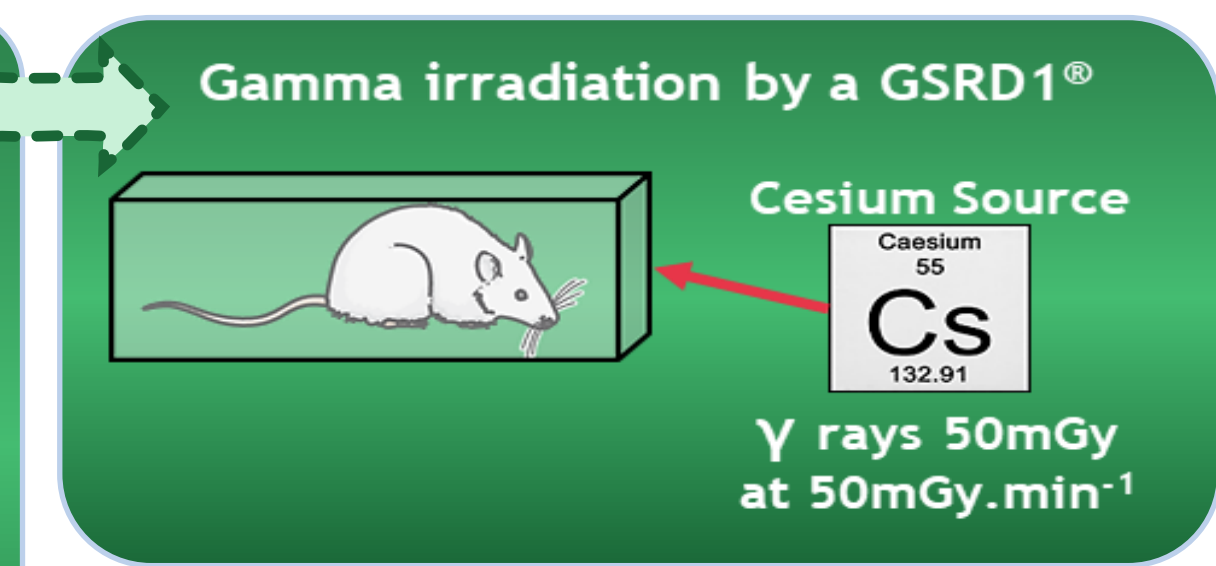
Low dose irradiations raise a scientific challenge due to uncertainties regarding their biological effects. The challenge is even higher if we consider co-exposure patterns, especially when combining a low-dose radiological exposure and a chemical stressor.

Experimental Protocol

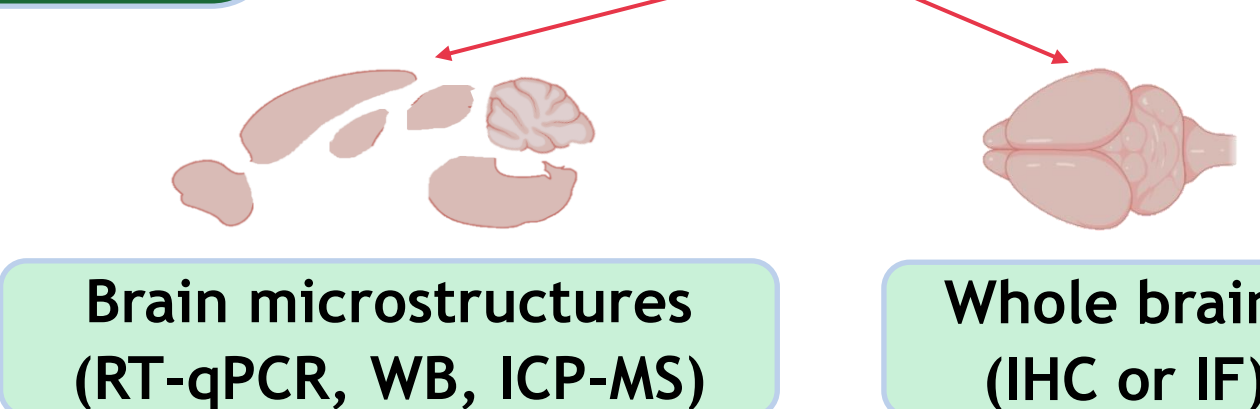
Nose-only inhalation set-up



Whole body irradiation



Sampling 24 hours or 28 days post-exposure

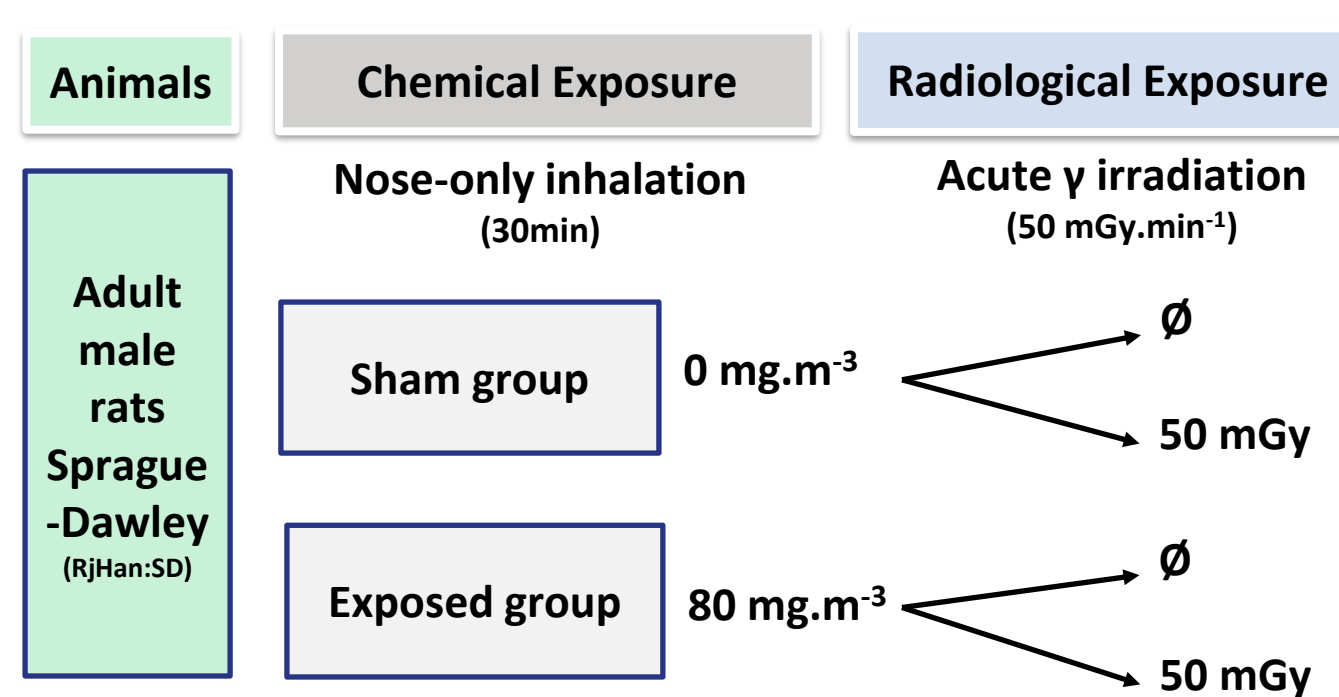


Rats RjHan:SD Experimental model:
Adult Male Sprague-Dawley

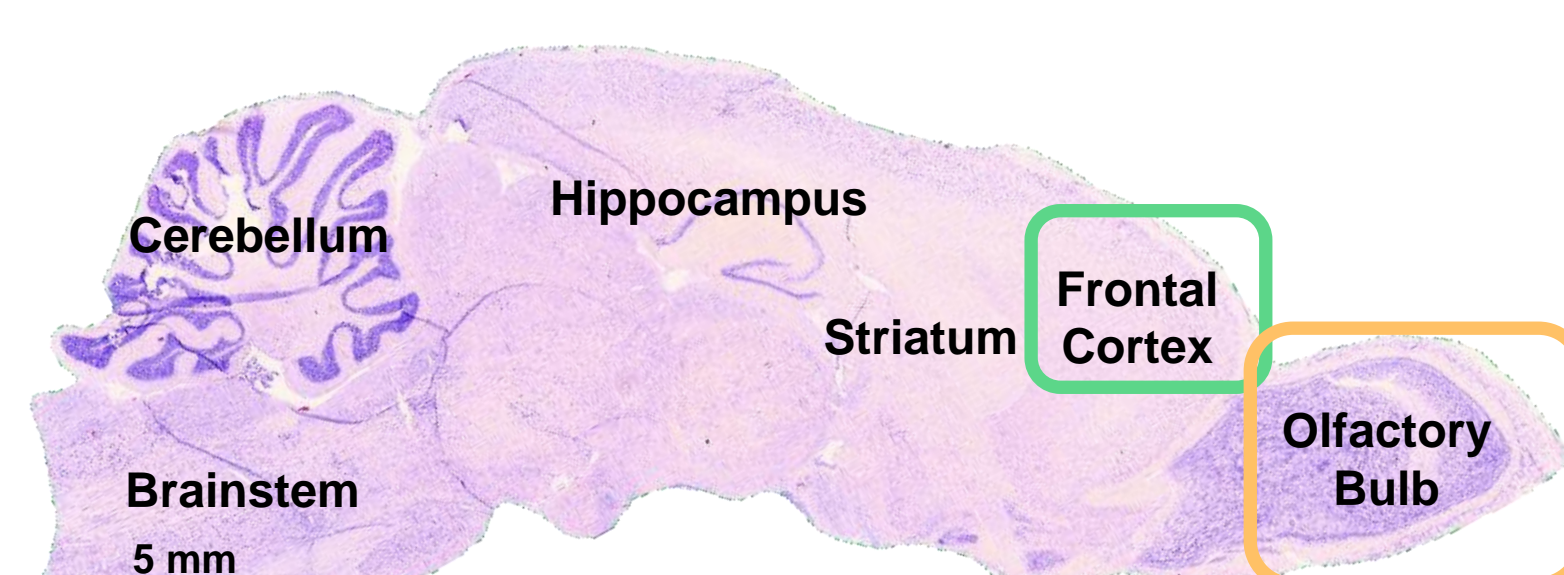
Can low dose gamma irradiation exposure cause differential effects if combined with tungsten particle inhalation? Do these effects persist?

Results

Experimental groups



Cerebral areas of interest

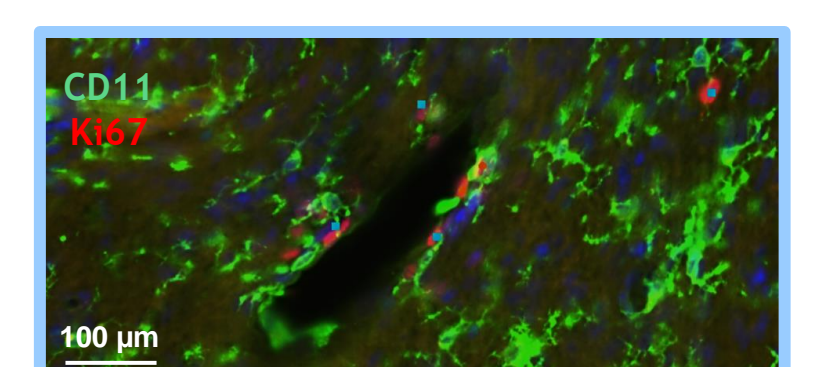
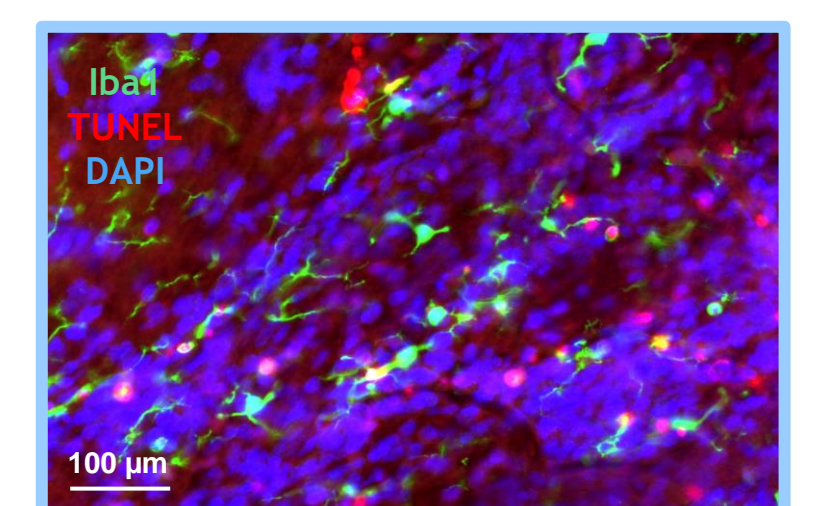


Longitudinal cut of a rat brain stained with Cresyl Violet

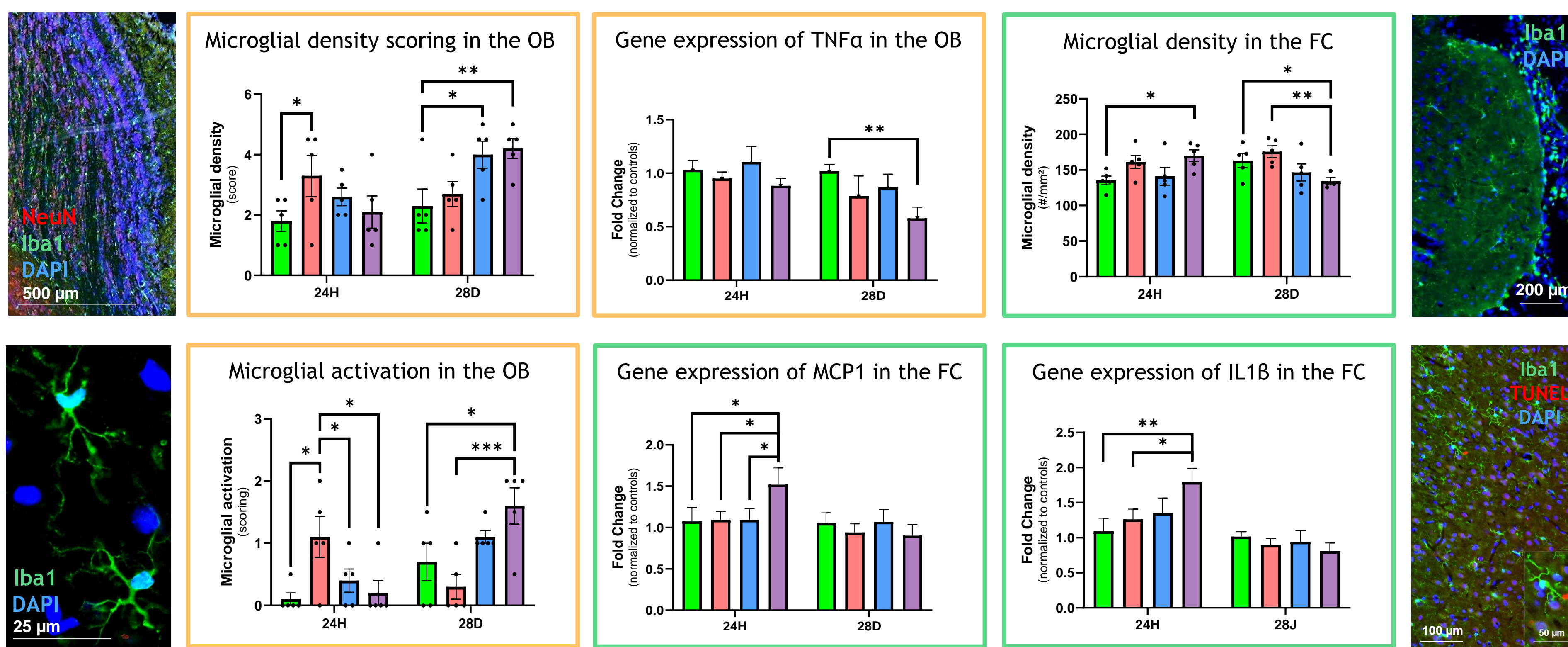
Common observations in the frontal cortex (FC) and the olfactory bulb (OB)

- No statistical difference at both time points for cleaved caspase 3 or TUNEL stainings
- No signs of cell or microglial proliferation at both time points using Ki67 staining

The olfactory bulb and frontal cortex could be overexposed due to particle nose-to-brain pathway



Effects on microglial cells and the role of inflammation in mediating interactions between the OB and the FC



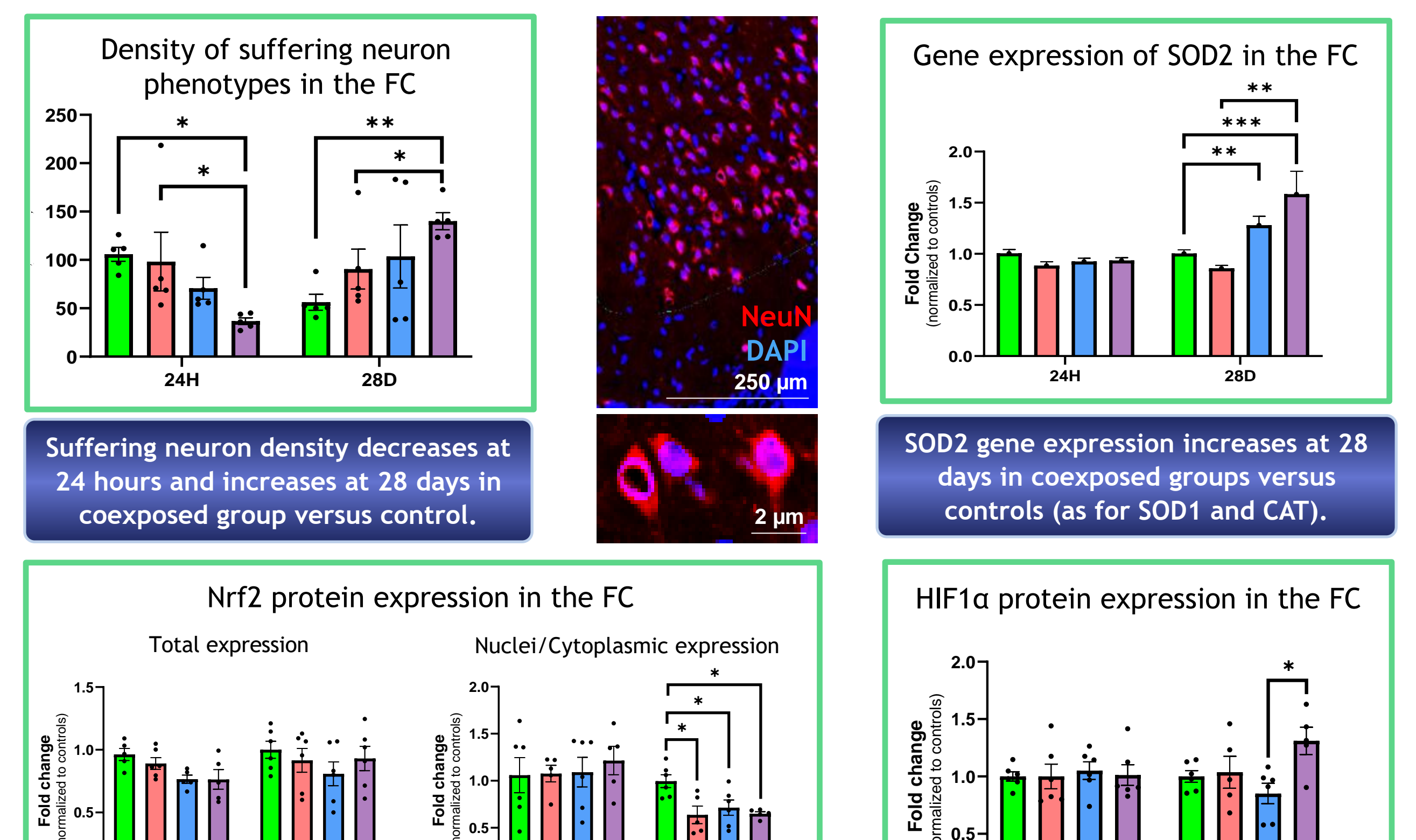
Microglial density increases at 28 days in the irradiated and coexposed group versus control in OB. When morphology is analyzed, microglial activation is observed in the tungsten group versus control at 24 hours and in coexposed group versus control at 28 days.

TNF α gene expression decreases in the coexposed group versus control at 28 days in OB. MCP1 gene expression increases in coexposed groups versus control at 24 hours in FC.

Microglial density increases at 24 hours along with IL1 β gene expression in coexposed groups versus control in FC. At 28 days, microglial density decreases in the coexposed group versus control.

Results are expressed as mean \pm SEM. * indicates a statistical difference using Ordinary one way ANOVA multicomparison and Tukey comparison test (* p \leq 0,05).

Occurrence of a neuronal suffering phenotype: a potential role for oxidative stress and hypoxia in the FC



Suffering neuron density decreases at 24 hours and increases at 28 days in coexposed group versus control.

SOD2 gene expression increases at 28 days in coexposed groups versus controls (as for SOD1 and CAT).

Nrf2 protein translocation decreases in single exposed and coexposed groups versus control at 28 days (no change of total expression and nuclei/cytoplasm ratio decreases).

HIF1 α protein expression tends to increase in coexposed groups versus control at 28 days.

Results are expressed as mean \pm SEM. * indicates a statistical difference using Ordinary One way ANOVA multicomparison and Tukey comparison test (* p \leq 0,05).

Conclusions

The coexposure paradigm causes significant effects compared to control or single stressor groups as soon as 24 hours post-exposure. These effects can be maintained or inverted at 28 days.

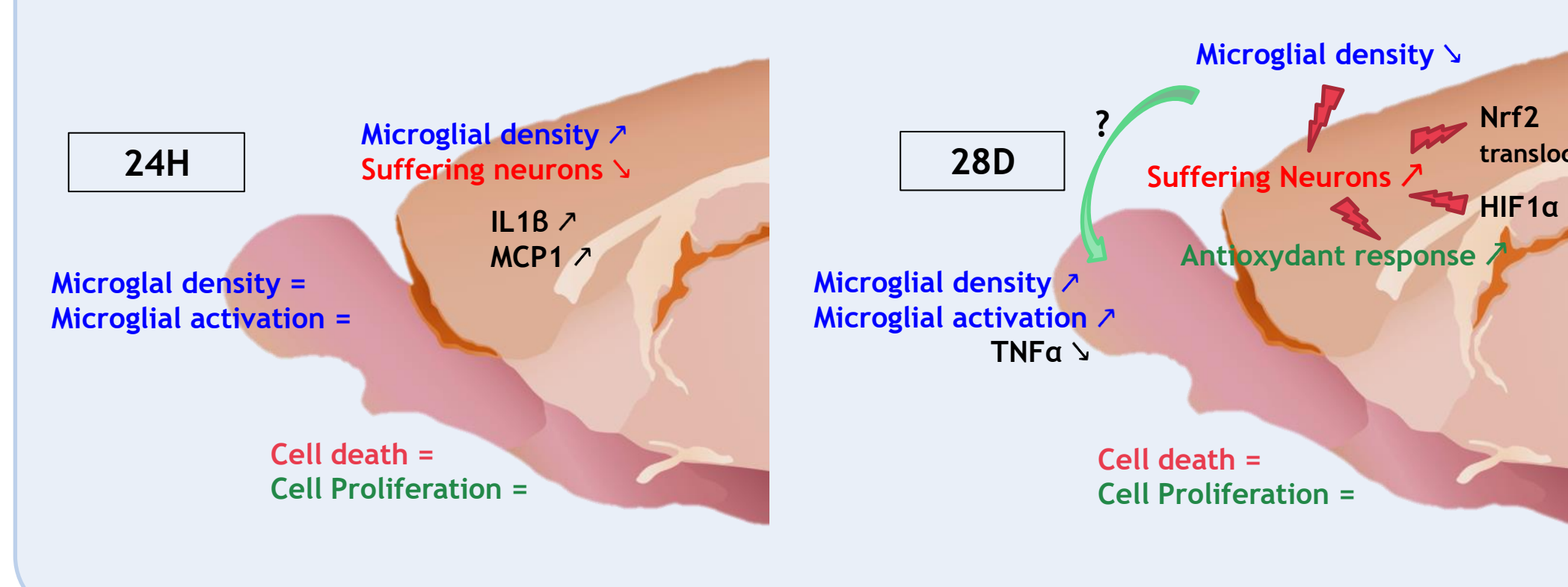
The OB and FC exhibit major differences in their biological responses in the coexposed groups.

At 24 hours, the cerebral microenvironment in FC exhibit an inflammatory response as microglial density increases along with IL1 β and MCP1 gene expression.

At 28 days post exposure, FC microglial density decreases without increase in cell death, while microglial density and activation increases in OB without proliferation. This allows us to formulate a couple of hypotheses :

- This could imply a microglial migration from FC to OB following our co-exposure
- The depletion of microglial cells in FC could contribute to the disruption of the cerebral microenvironment and thus to the increase of the neuronal suffering phenotype. The increase of the antioxidant response and HIF1 α modulation might be an attempt to compensate this loss.
- The reduction of TNF α expression in OB at 28 days while microglial activation is increased suggest an on-site anti-inflammatory microglial activation in response to our co-exposure.

Synthetic diagram of effects observed in the coexposed group



Perspectives

- Measurement of W concentrations via ICP-MS in lung, kidney, brain
- Assessment of neuronal degeneration using FluoroJade C

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