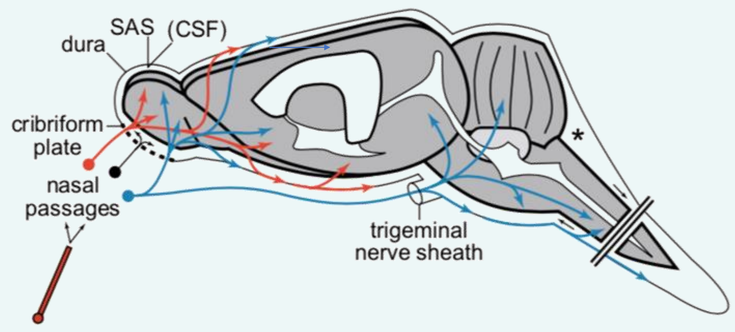
FIVE-WEEK NERVE GROWTH FACTOR TREATMENT IS SAFE FOR BRAIN REPAIR

Nina Colitti*, Franck Desmoulin*, Wafae Labriji*, Alice Le Friec*, Lorenne Robert*, Amandine Michaux‡, Fabrice Conchou‡, Carla Cirillo*, and Isabelle Loubinoux*,
*Toulouse NeuroImaging Center (ToNIC), Inserm, University of Toulouse UPS, Toulouse, France ; ‡National Veterinary School of Toulouse, University of Toulouse, Toulouse, France

1 Introduction

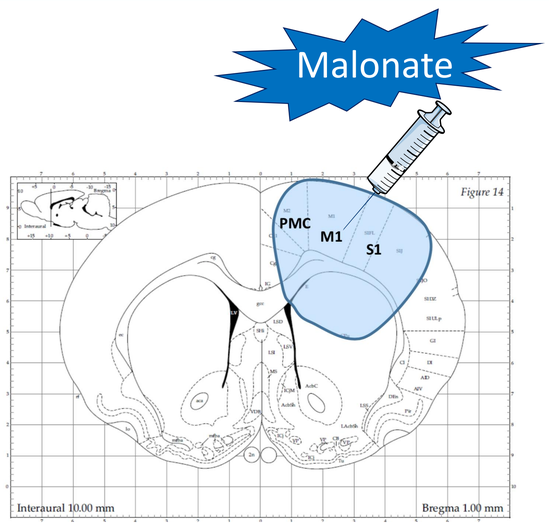
- Stroke is the leading cause of acquired severe motor disability in adults.
- The brain has limited ability to reconstruct itself by generating new neurons from stem cells.
- New neurons survival is too low (0.2%) to induce recover.
- Low survival is also due to the lack of growth factors.



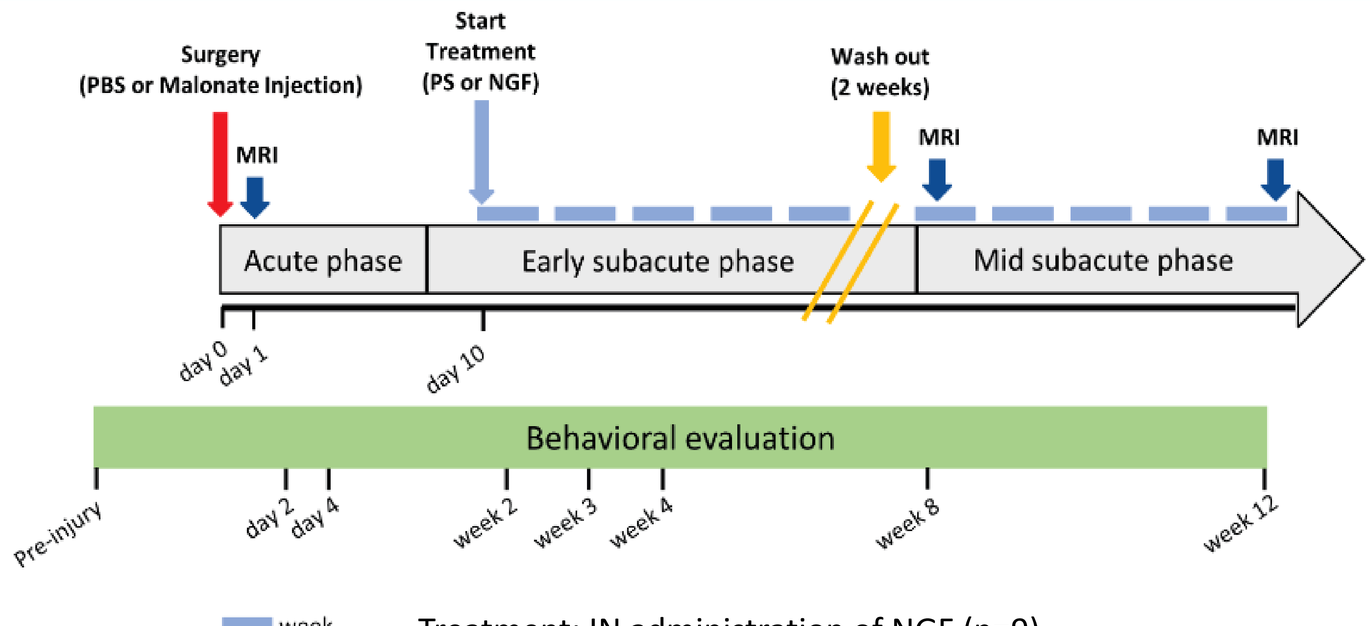
This study focuses on Nerve Growth Factor (NGF) : neuroprotective/anti-inflammatory/stimulating neurogenesis effects.
The intranasal (IN) pathway was chosen as delivery route.

2 Materials & Methods

Malonate was used to induce M1 cortex and adjacent structure lesion in rats (n=19)



Sensorimotor function was evaluated by:
- Grip strength test
- Neurological severity score assessment
- Limb-use asymmetry test



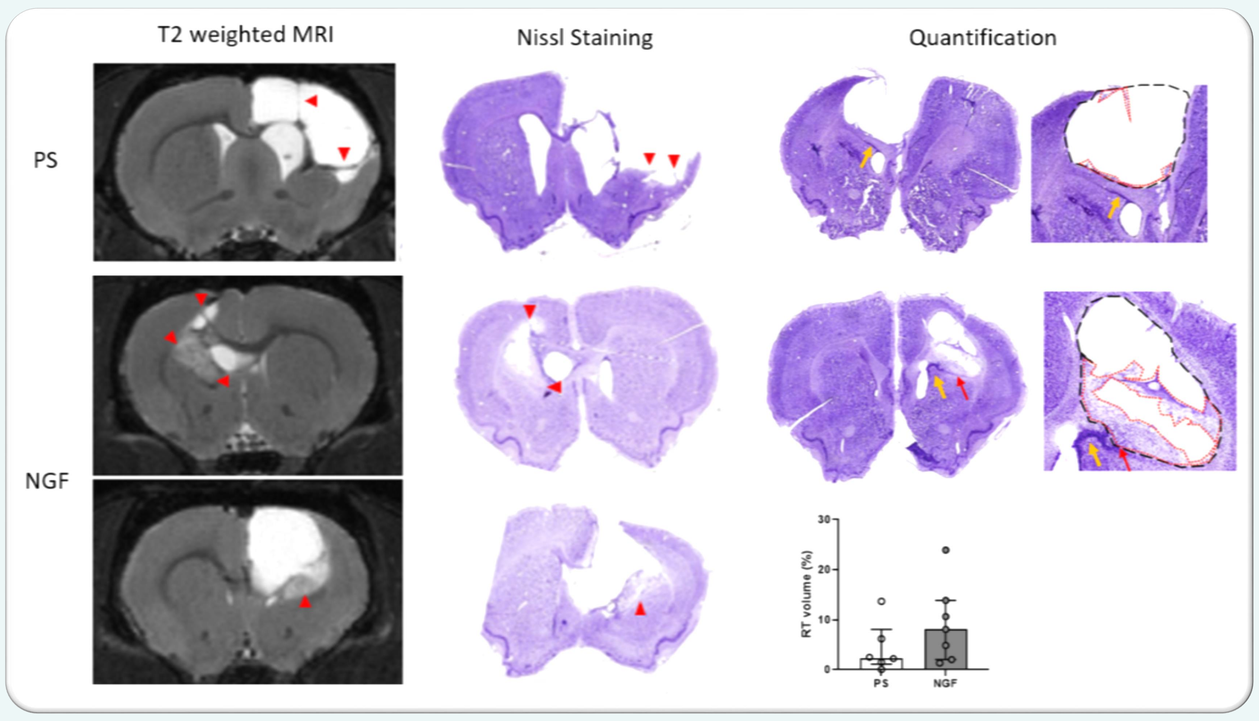
Treatment: IN administration of NGF (n=9)
Control: IN administration of Physiological Serum (PS ; n=9)

Lesion volume and Reconstructed Tissue (RT) identification were evaluated by:
- MRI T2 weighted images
- Nissl staining coloration (RT calculated on Case viewer software ; % of RT is normalized to the size of the lesion)
- Immunostaining: GFAP: glial scar/astrocytes; Iba1: microglia; PDGFRb: vessels/pericytes; Doublecortin: neurons progenitors; beta 3 tubulin: immature neurons; NeuN: mature neurons

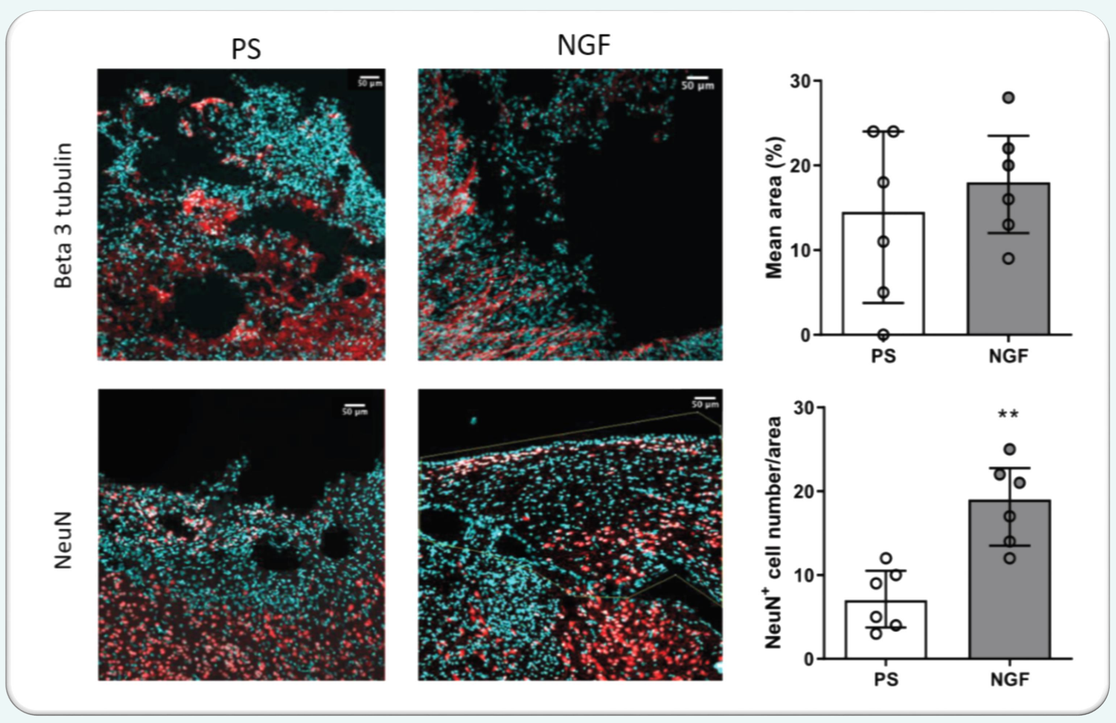
3 Results

- MRI T2 weighted might be a reliable biomarker for reconstructed tissue evaluation
- Migration pathways coming from the anterior part of the ventricle until the edge of the lesion
- Long-term NGF treatment promotes tissue reconstruction and remodeling
- NGF induces a significant increase in the percentage of mature neurons in the reconstructed tissue compared to PS (*p=0.0043*)
- Five-week NGF treatment is safe; however ten-week treatment retarded motor recovery *(p=0.01)*

Identification and quantification of reconstructed tissue



Immunofluorescence of reconstructed tissue brain section



4 Discussion

- First study with long-term NGF treatment
- Reconstructed tissue characterized for the first time at 3 month post injury
- The nose-to-brain pathway is a valid strategy for repeated and non-invasive administrations : Hope for chronic stroke treatment

5 Conclusion

In this preclinical study, we show that five-week intranasal NGF treatment is safe and promotes tissue regeneration with a significantly higher proportion of neurons observed twelve weeks after brain injury.

Donnan GA et al., Stroke, 2008 ; Arvidsson A et al., Nat Med, 2002 ; Khelif Y et al., Theranostics, 2018 ; Zhu W et al., Drug Deliv, 2011 ; R. G. THORNE et al., Neuroscience, 2004 ; Davoust C et al., Stem Cells Res Ther, 2017

- Nina Colitti - iDREAM team Toulouse NeuroImaging Center - nina.colitti@inserm.fr -