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COMBINATION OF EXERCICE ANS STEM CELL-BASED STRATEGIES TO IMPROVE CORTICAL REPAIR

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► **To cite this version:**

Valentin Fernandez, Annousha Govindan, Marie-Laure Bonnet, Eric Balado, Sébastien Brot, et al.. COMBINATION OF EXERCICE ANS STEM CELL-BASED STRATEGIES TO IMPROVE CORTICAL REPAIR. 25th biennial meeting of the international society for developmental neuroscience, Sep 2024, Montpellier, France. <hal-05517125>

HAL Id: hal-05517125

<https://hal.science/hal-05517125v1>

Submitted on 18 Feb 2026

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INTRODUCTION

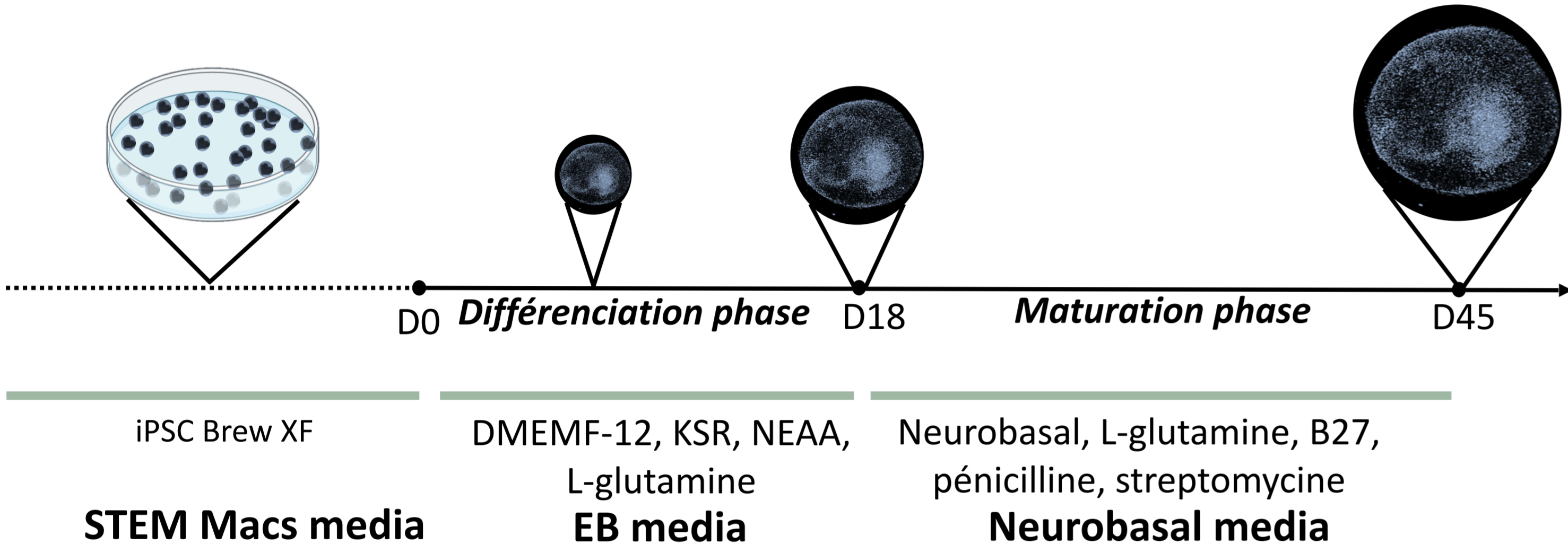
Traumatic brain injury (TBI) is among the leading cause of death and disability with limited treatment options available. We have previously shown that cortical neurons derived human pluripotent stem cells grafted into injured motor cortex of adult mice allow partial neuroanatomical and functional restoration of degenerated cortical pathways. Furthermore, voluntary exercise has long been known to be neuroprotective and to increase brain plasticity through a wide range of action. It has already been reported in several studies beneficial effects of physical activity after TBI. The aim of the present study is to investigate whether the combination of cell therapy and physical activity improves neuroanatomical and functional outcomes in a TBI mice model.

For this, we generated motor cortical neurons from human induced pluripotent stem cells and these cells into injured motor cortex of adult Rag2^{-/-} mice.

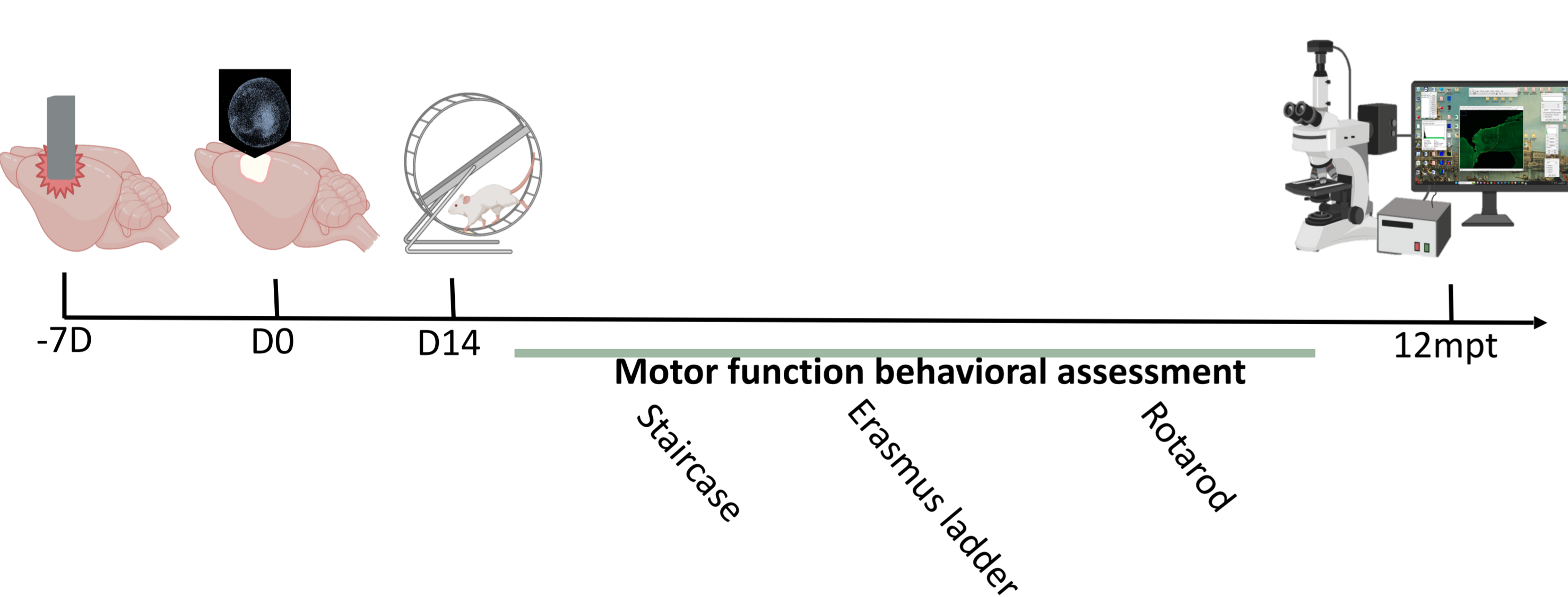
For voluntary exercise, activity wheels were placed in the mice's housing cages for the entire duration of the study. Control animals were housed in the same cage with the wheels removed.

METHODS

Generation of 3D motor cortical neurons from hiPSC



In vivo evaluation of motor cortical neurons derived hiPSC



RESULTS

Generated neurons expressed the appropriate cortical layer markers

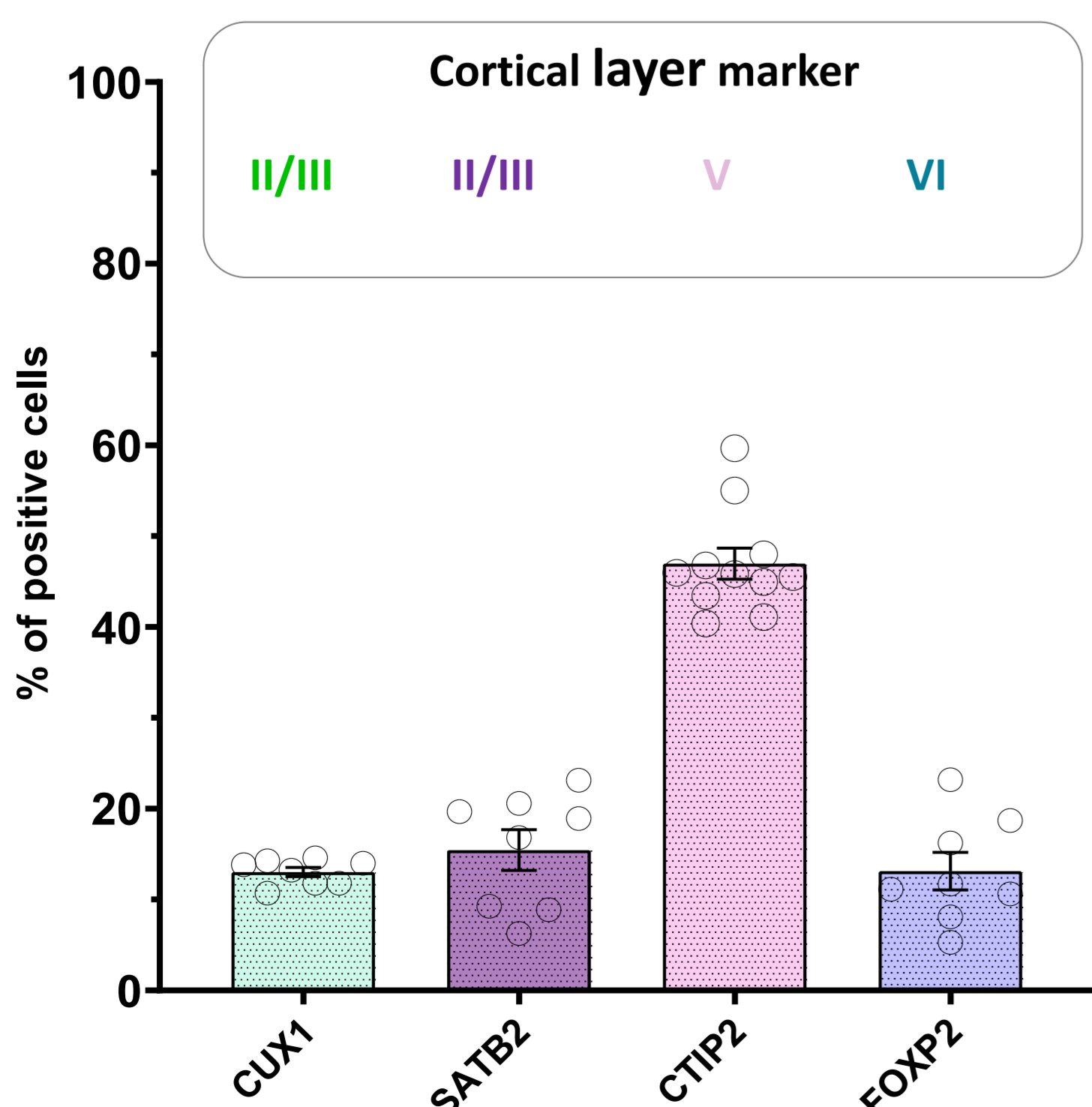
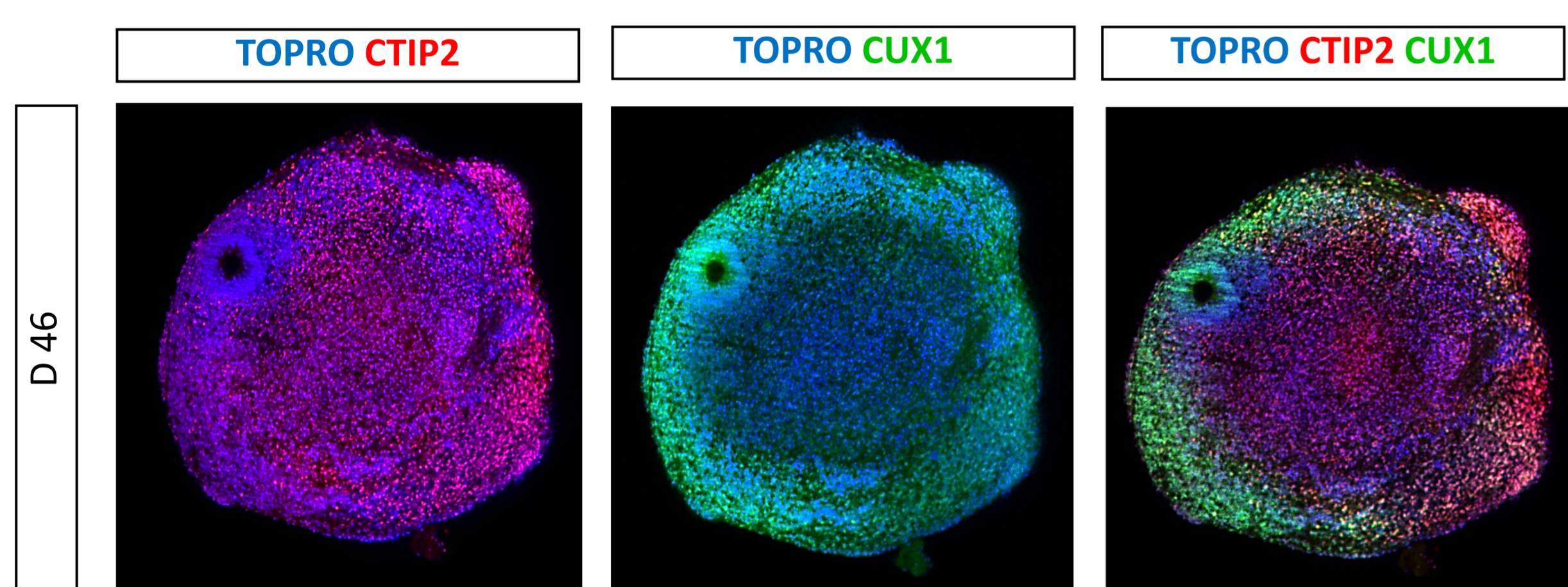


Figure 1: At D46 of differentiation hiPSC-derived neurons expressed all neuronal markers specific for cortical layers: II/III (CUX1, SATB2), Layer V (CTIP2+) and Layer VI (FOXP2) with layer V superior to other cortical markers.

RESULTS

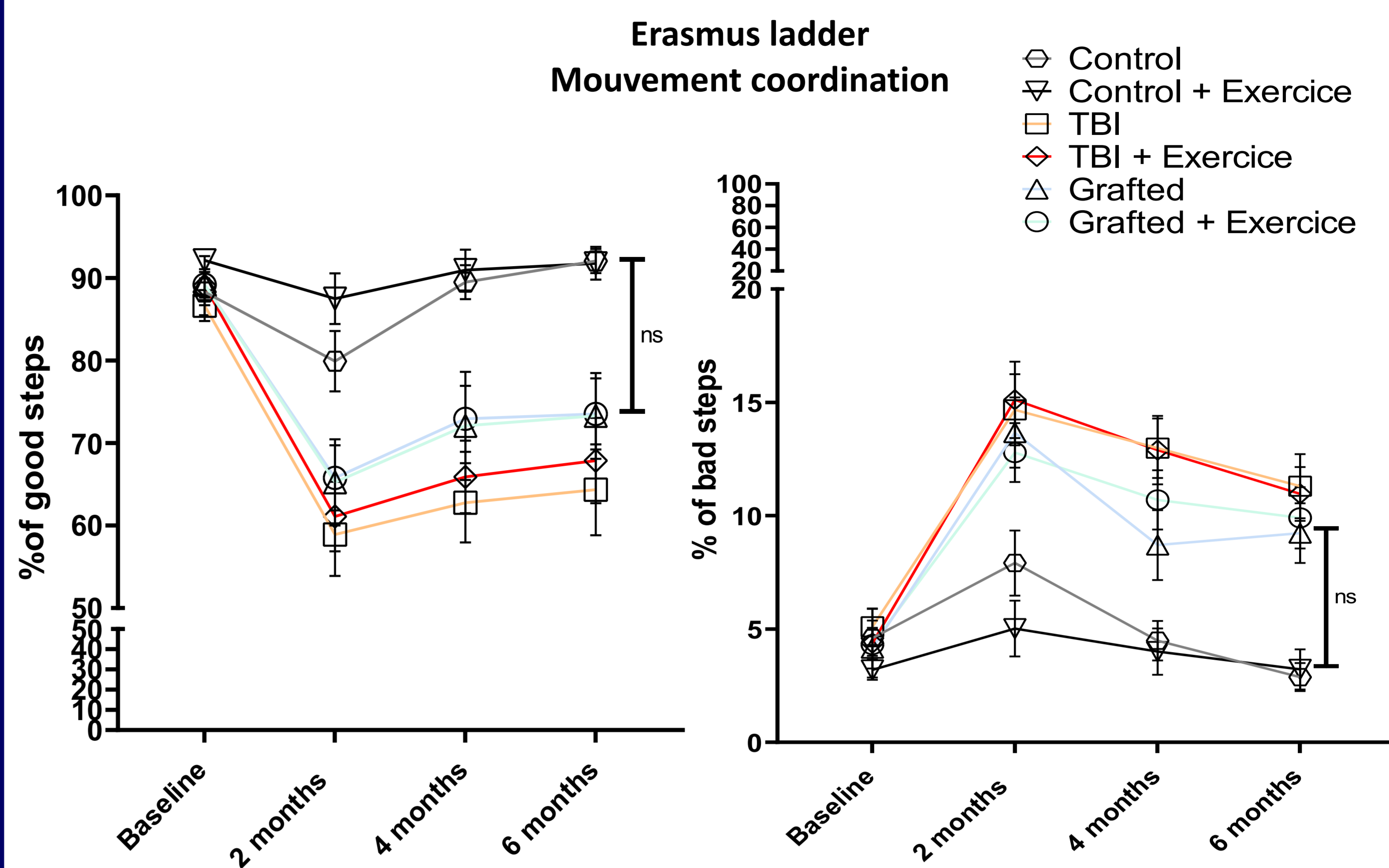


Figure 2: Evaluation of motor coordination using the Erasmus ladder

Good and bad steps percentages on the contralateral paw to the lesion in the Erasmus ladder test in control, injured and grafted groups with and without physical activity before transplantation and at 2, 4 and 6 months post-transplantation. We found an improvement in motor coordination in grafted group with physical activity. These studies are currently underway to evaluate the long-term effects of transplantation with or without physical activity.

Staircase Fine motor skills

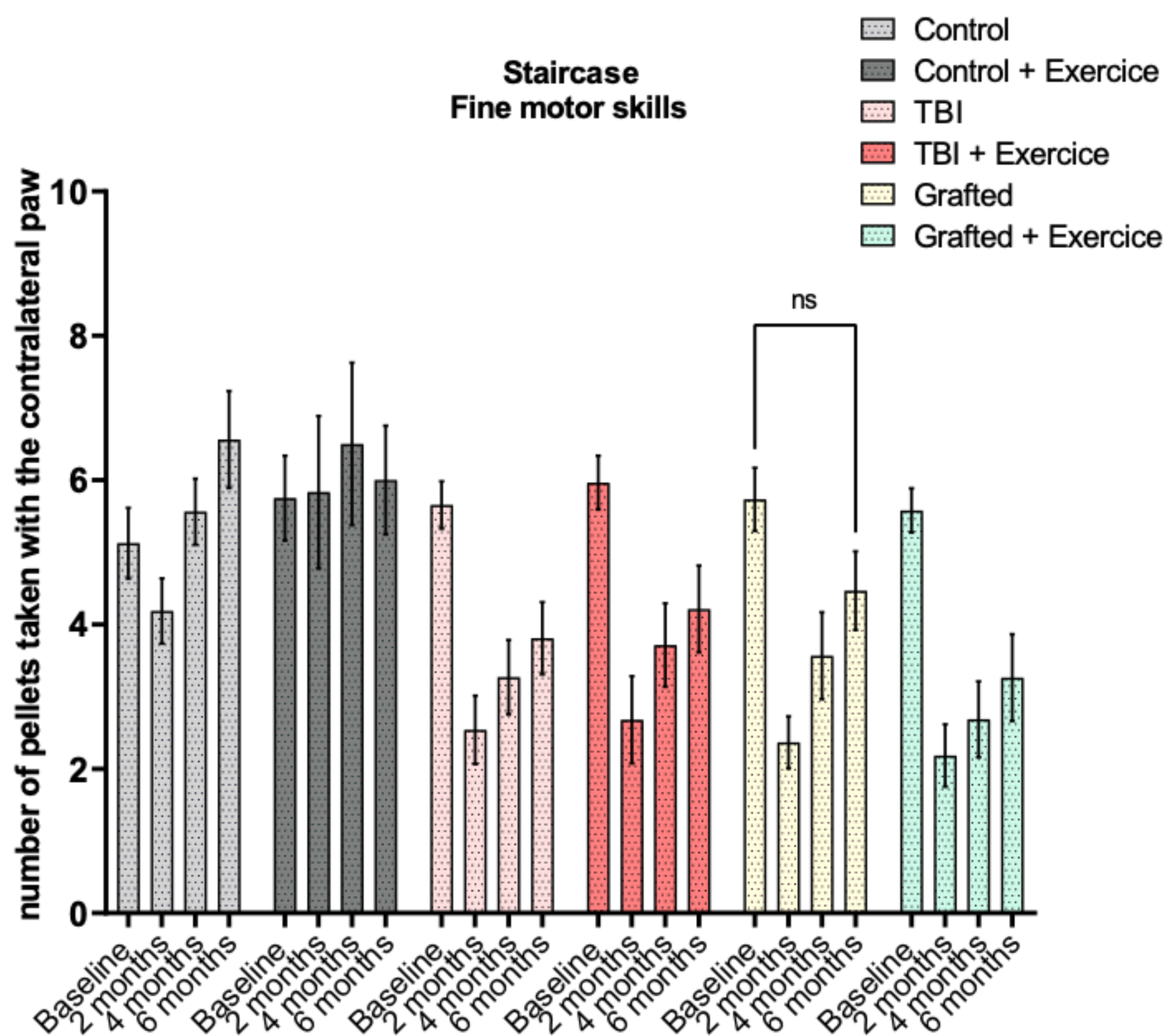


Figure 3: Evaluation of fine motor movements with the Staircase

Number of pellets taken with the contralateral in the control, TBI and grafted groups, with and without physical activity at 2, 4 and 6 months. We found an improvement in fine motor movement in grafted group. Indeed, the score of the grafted group returned to baseline, indicating an improvement in fine motor skills.

CONCLUSION

The aim of our study is to see whether transplantation in combination with physical activity improves the efficacy of transplantation. Our initial results show a beneficial effect of physical activity on motor coordination in transplanted animals subject to physical activity after 6 months post-transplantation.

These studies are currently underway to evaluate the long-term effects of transplantation with or without physical activity. At the end of the behavioral tests, we will evaluate the neuroanatomical integration of the transplanted neurons and see whether physical activity leads to a more complete restoration of the damaged motor pathways.