FUNCTIONAL INTEGRATION OF HUMAN STRIATAL PROGENITOR GRAFTS IN A HD ANIMAL MODEL

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INTRODUCTION

Neurotransplantation represents a promising alternative for the treatment of certain localized neurodegenerative insults and pathology, such as **Huntington's disease**. To be effective, a proper cell product is required not only to survive and differentiate in striatal medium spiny neuron (MSN), but also to functionally integrate and reconstruct the damaged host striatal circuitry. Here, we present our recently published work about the **circuit reconstruction** and **functional integration** of human striatal progenitors (hSPs) grafted in a HD rat model (Scaramuzza, Ribodino et al, 2025).

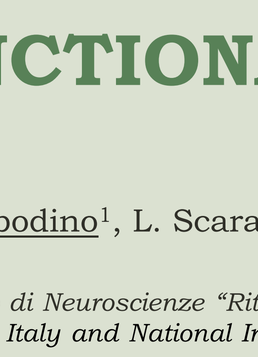
HUMAN STRIATAL PROGENITOR GRAFTS

HD rat model

Striatal monolateral injection

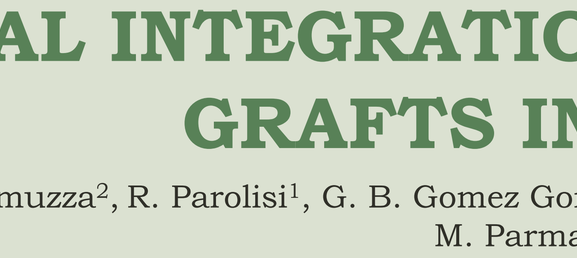
QA

Athymic nude male rats



- MSN degeneration
- Spared circuits
- Behavioral correlates

2-10MPT

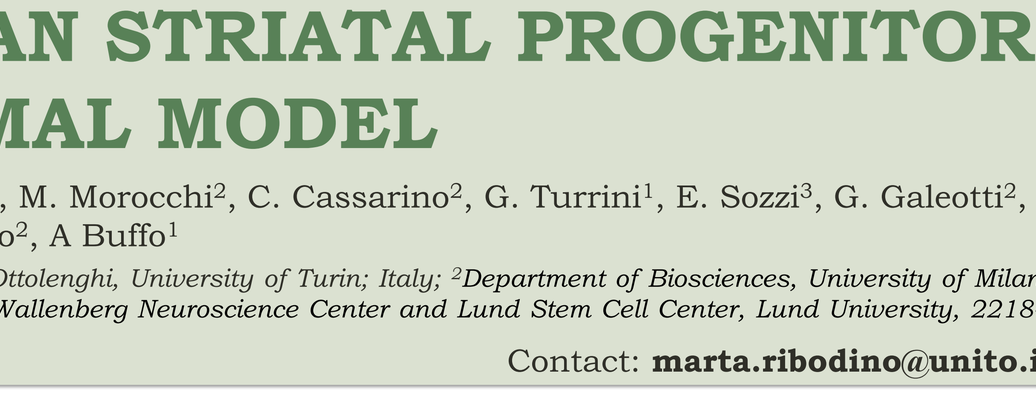


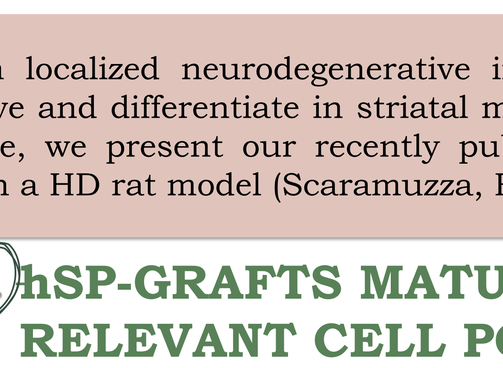
DIV15 hSPs were obtained from the differentiation of hESCs following a *in vitro* morphogen-based differentiation protocol (Conforti et al, 2022)

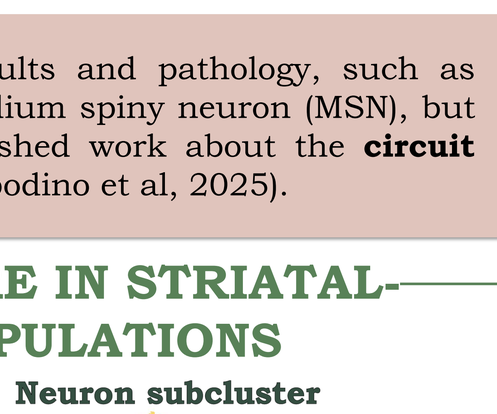
1. Graft composition
2. Anatomical integration
3. Functional responses
4. Behavioral modulation

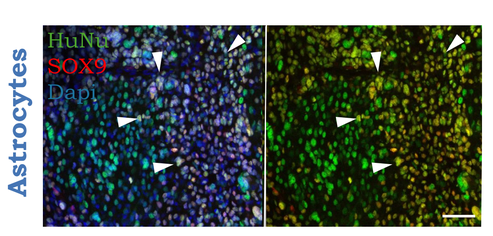
1. hSP-GRAFTS MATURE IN STRIATAL-RELEVANT CELL POPULATIONS

Neuron subcluster





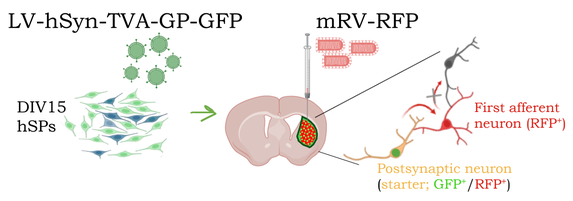


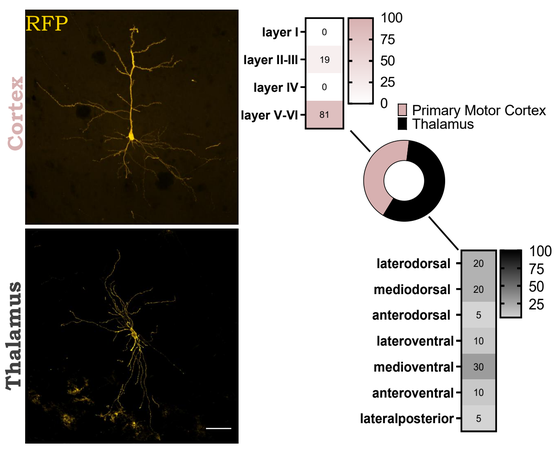


snRNAseq and IHC analyses revealed that hSP-grafts generate a diverse population **of ganglionic eminence-derivatives**, including D1- and D2-MSNs, GABA-ergic interneurons, and astrocytes.

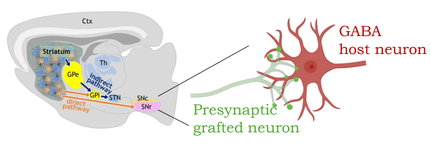
2. hSP-GRAFTS ANATOMICALLY INTEGRATE IN THE HOST STRIATAL CIRCUITRY

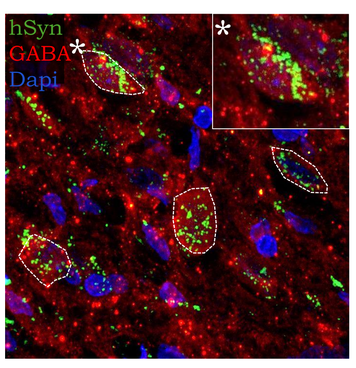
Synaptic inputs

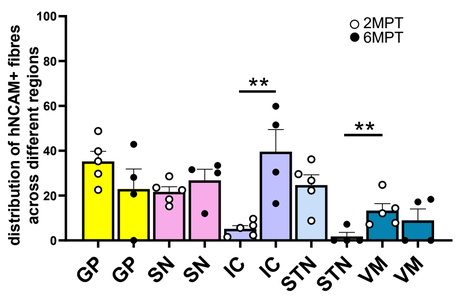




Graft-to-host innervation

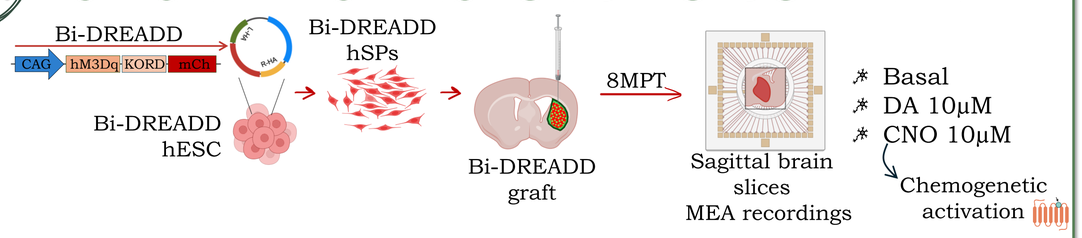


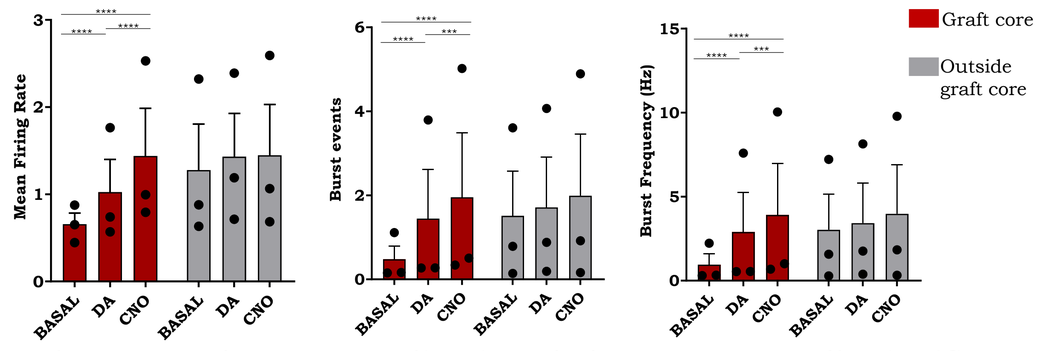




hSP-grafts **receive synaptic input** from cortical and thalamic areas endogenously projecting to the striatum, and **project** mainly toward canonical striatal targets, such as GP and SN, forming correct **synaptic contact** with resident GABAergic neurons.

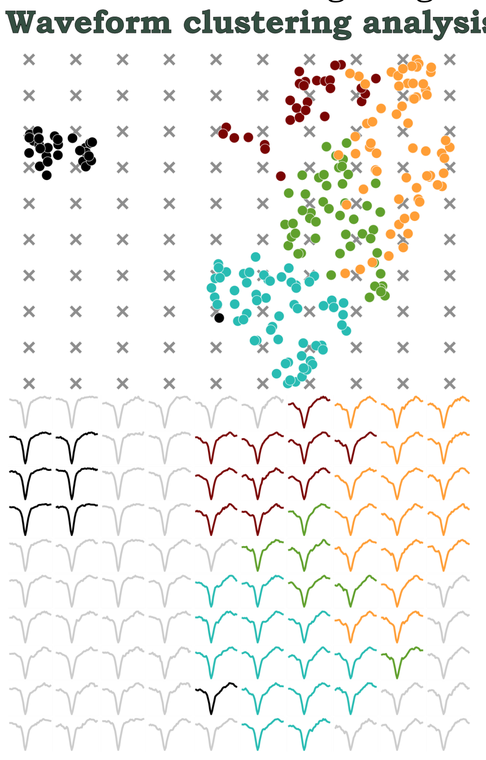
3. hSP-GRAFTS RESPOND TO DOPAMINE

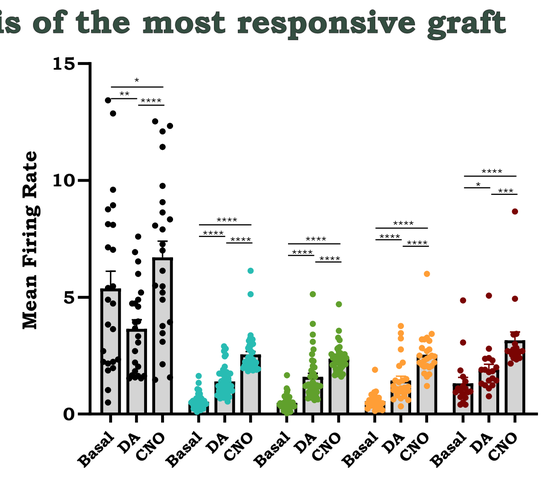


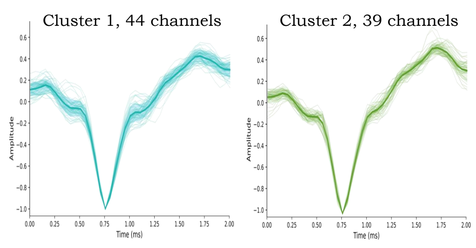


Both DA and CNO application led to an overall significant **activity increase** in graft core regions compared to cortical areas in all the analyzed animals (n=3). This indicates that dopamine- and chemogenetically-evoked responses originated from the transplanted cells, rather than from resident host neurons surrounding the graft.

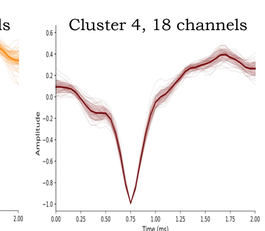
Waveform clustering analysis of the most responsive graft



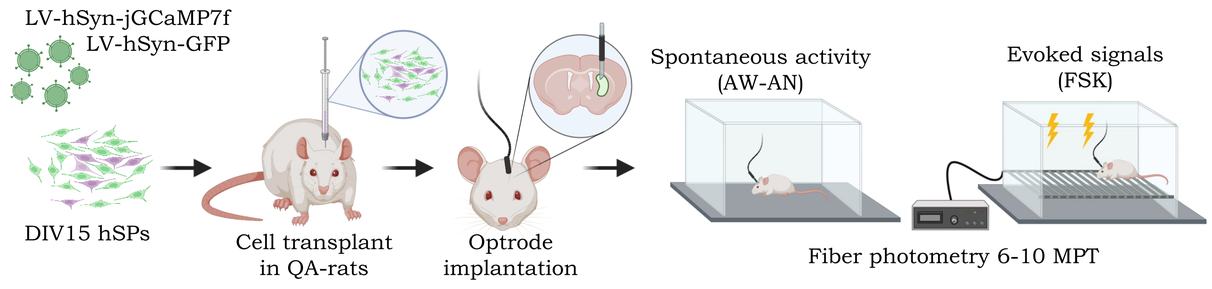


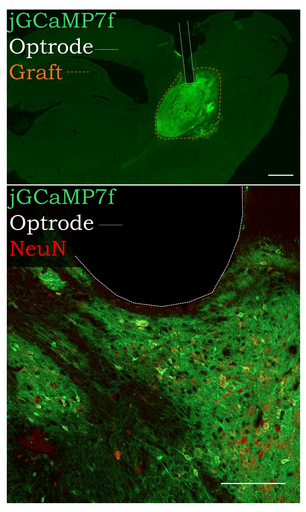


Waveform clustering of the most active (>0,12 spikes/s) channels after CNO treatment revealed **5 different waveforms** that are correlated with a specific pattern of response to dopamine, highlighting the presence of either **different maturational stages and/or functional D1- and D2-receptors**.

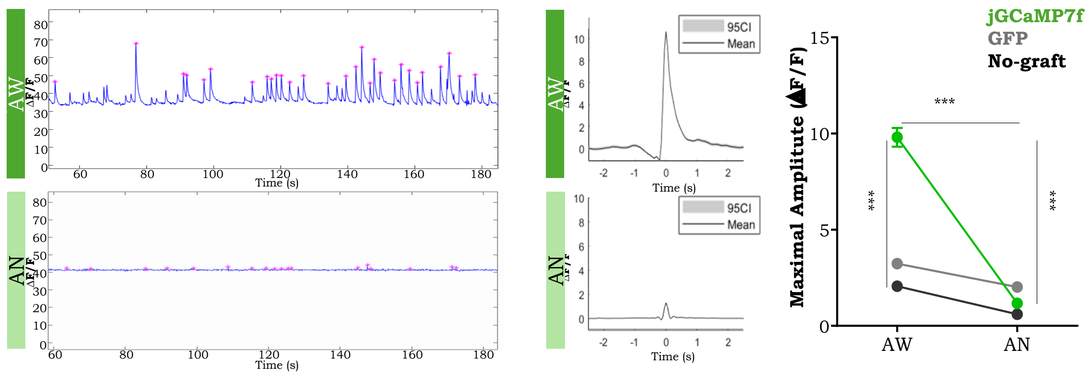


3. hSP-GRAFTS ARE FUNCTIONALLY INTEGRATED

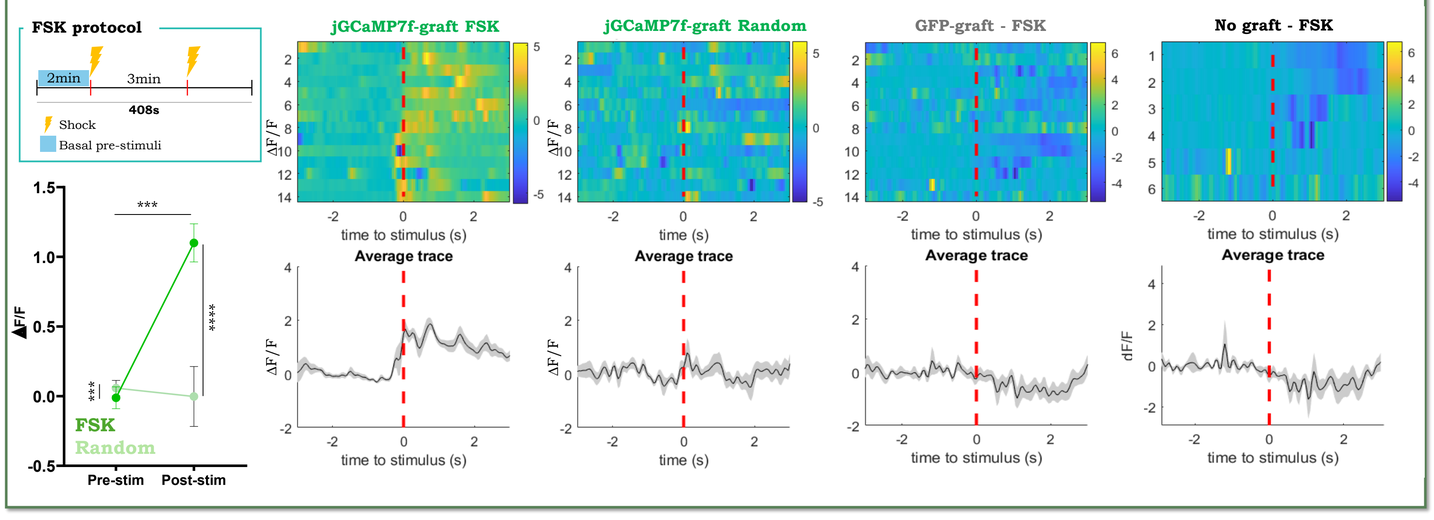




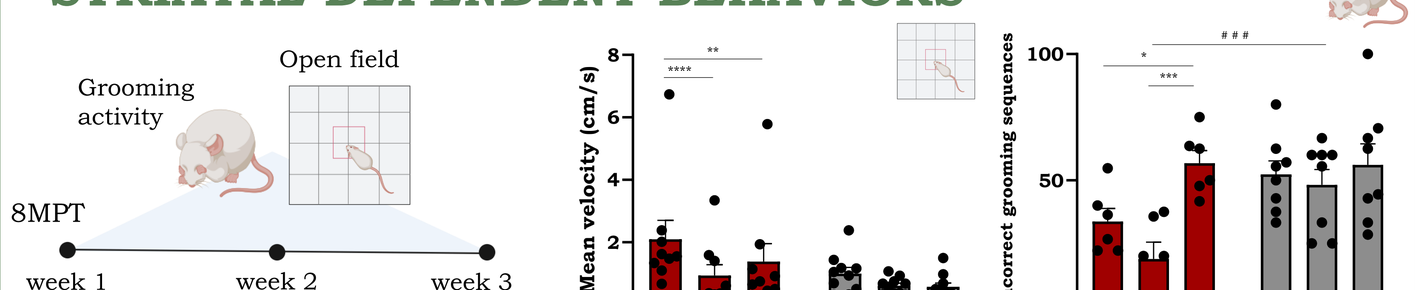
hSP-grafts are **spontaneously active**



hSPs **respond to footshock** and **participate** in endogeneous striatal circuit



4. hSP-GRAFT FUNCTIONALITY REGULATES STRIATAL-DEPENDENT BEHAVIORS



Chemogenetic modulation of graft activity, through the administration of either CNO or SALB, **modulates both voluntary motor behavior and fine motor coordination**.

CONCLUSIONS

- hSPs **mature** *in vivo* recapitulating ventral telencephalic trajectories
- hSPs achieve **anatomical integration**, reaching a **degree** of striatal circuit reconstruction
- hSPs express functional **dopaminergic receptors**
- hSPs display **spontaneous and evoked activity**
- **modulation of graft activity** translates into changes in motor behavior.

This represents, the first demonstration that **transplanted human striatal progenitors can engage with host striatal circuits at the functional and behavioral level.**

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