Host-integration of Neural Precursors in Parkinsonian monkeys: outcome on clinical, cognitive, circadian and DA function

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INTRODUCTION

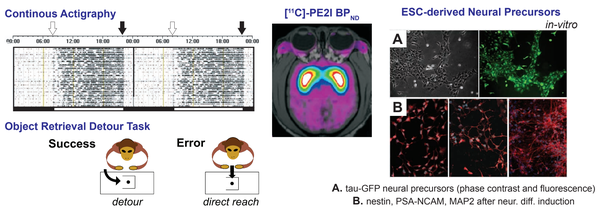
Cell-therapy offers tremendous potential for neurodegenerative diseases treatment. However, proof-of-function in preclinical models with multidisciplinary approaches is still lacking.

In Parkinson's disease , both human patients and animal models express cognitive performance deficits, disorders of sleep and biological rhythms in addition to the cardinal motor disturbances (Simuni and Sethi, 2008; Vezoli et al., 2011).
The non-motor symptoms significantly contribute to the decline in the quality of life in PD patients and may stem from widespread neurodegenerative processes of both dopaminergic and non-dopaminergic systems.

Here we assessed the therapeutic potential of bilateral grafts of neural precursors in parkinsonian macaque monkeys following motor symptoms, non-motor markers and *in-vivo* DA levels of functional recovery.

MATERIAL AND METHOD

Six middle-aged female macaca fascicularis (11-15 years old, 4-6 kg) intoxicated with repeated low-dose MPTP injections (0.2mg/kg, i.m.).



A. tau-GFP neural precursors (phase contrast and fluorescence)
B. nestin, PSA-NCAM, MAP2 after neur. diff. induction

Clinical Score - 3-5 days a week, 3 observers, Parkinsonian Monkey Rating Scale- PMRS (Vezoli et al., 2011).

Cognitive performances - throughout protocol, Detour Task, largely used to assess frontal functions (Decamp & Schneider, 2004).

Rest-Activity cycles - followed continuously in homecage (CAMS, Dkhissi-Benyahya et al., 2007).

DA function - in 4 cases, *in-vivo* PET-imaging of [11C]-PE2I and [18F]-Dopa, BP_{ND} measure with Cynomolgus Atlas Template (Costes et al., 2010).

Grafted cells - Neural precursors derived from a rhesus ESCs line stably expressing tau-GFP (LYON-ES; Wianny et al., 2008-2011).

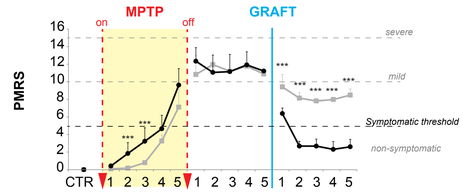
Bilateral transplantation - MRI guided, targets: posterior Putamen, anterior Caudate and SN.

Sham-Grafts - in 2 cases, to assess effects on behavior and function and compare to cell-transplantation effects.

RESULTS

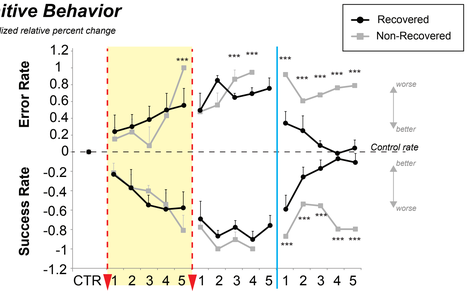
MULTIPARAMETRIC FOLLOW-UP OF SYMPTOMS

Clinical Score



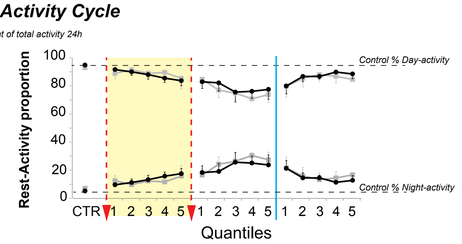
Cognitive Behavior

normalized relative percent change



Rest-Activity Cycle

percent of total activity 24h

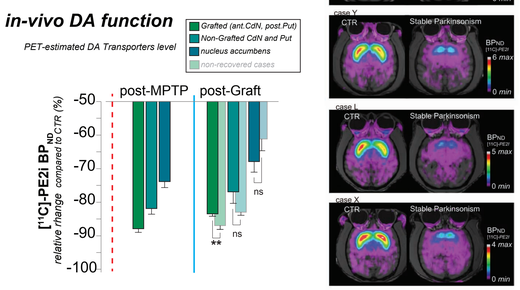


Quantiles duration in days (MEAN±SD)

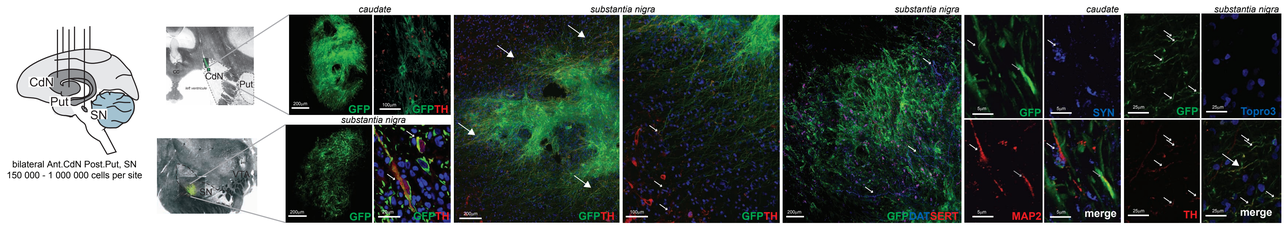
	CTR	MPTP	post-MPTP	post-GRAFT
recovered	*24±4*	*8±4*	*15±9*	*39±1*
non-recovered	*28*	*12±7*	*22±8*	*45±22*

in-vivo DA function

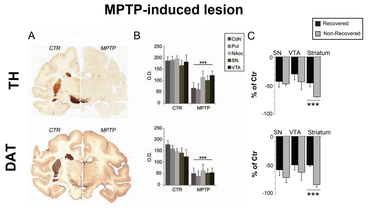
PET-estimated DA Transporters level

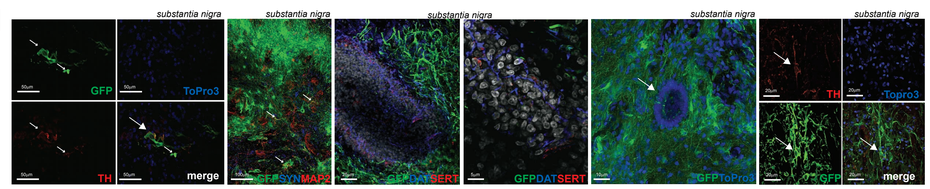


HOST-INTEGRATION OF GRAFTED CELLS CORRELATES WITH BEHAVIORAL RECOVERY



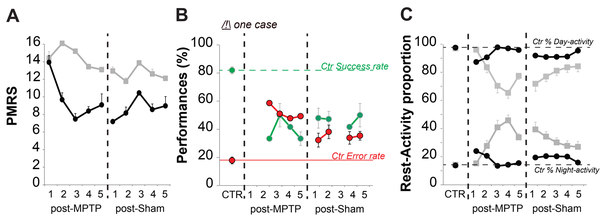
MPTP-induced lesion





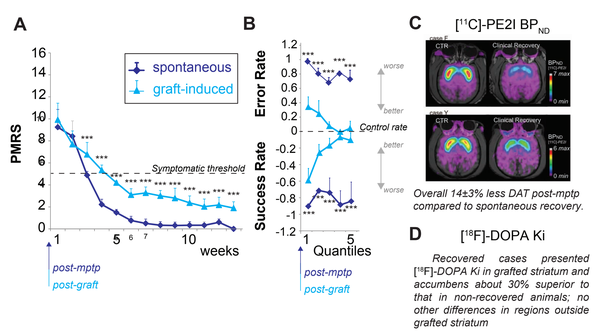
neural precursors survived in parkinsonian monkeys that presented behavioral recovery following transplantation. Evidences of graft integration with surrounding host-cells (TH+ prolongements, synatic contact), differentiate into mature neurons and a proportion of TH+ cells (~20%).

SHAM-GRAFTS INDUCED NO CHANGES



SPONTANEOUS CLINICAL RECOVERY vs. GRAFT

Before inducing stable Parkinsonism, MPTP halted in 3cases to observe potential spontaneous clinical recovery



Overall 14±3% less DAT post-mptp compared to spontaneous recovery.

D [18F]-DOPA Ki

Recovered cases presented [18F]-DOPA Ki in grafted striatum and accumbens about 30% superior to that in non-recovered animals; no other differences in regions outside grafted striatum

CONCLUSIONS

In three out of five grafted monkeys, clinical and cognitive recovery was induced by neural precursors grafts while long-lasting deficits remained in the non-recovered group.

Sham experiments revealed no behavioral effect and comparison between spontaneous and graft-induced recovery confirmed the positive effects of grafts on behavior.

in-vivo DAT level in the grafted Striatum of recovered animals was less reduced compared to non-recovered and Dopa function was also less affected (Ki ~30% superior).

These results shows that transplantation of neural precursors is efficient in MPTP-treated monkeys provided, however, that the DA-lesion is not too advanced. Indeed, the degree of host-integration of grafted cells correlated with measured *post-mortem* TH-DAT lesion.

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