

Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study

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Summary

Background Although we have shown in three out of five patients with Huntington's disease that motor and cognitive improvements 2 years after intracerebral fetal neural grafts are correlated with recovery of brain metabolic activity in grafted striatal areas and connected regions of the cerebral cortex, neural grafts are not known to have protective effects on the host brain per se. We undertook long-term follow-up of previously reported patients with the disease to ascertain the nature and extent of any secondary decline after grafting.

Methods Five patients with Huntington's disease from our pilot study were assessed annually with the unified Huntington's disease rating scale, neuropsychological tests, and MRI, for up to 6 years after neural grafting. Resting cerebral activity was recorded at 2 and 6 years.

Findings Clinical improvement plateaued after 2 years and then faded off variably 4–6 years after surgery. Dystonia deteriorated consistently, whereas chorea did not. Cognitive performance remained stable on non-timed tests, whereas progression of motor disability was shown by deterioration on timed tests. Hypometabolism also affected the brain heterogeneously, sparing the benefits in the frontal cortex and at the precise location of the grafts, but showing a progressive deterioration in other areas. Two patients who had no benefit from grafting at 2 years continued to decline in the same way as non-grafted patients.

Interpretation Neuronal transplantation in Huntington's disease provides a period of several years of improvement and stability, but not a permanent cure for the disease. Improvement of the surgical procedure and in patient selection could improve the therapeutic value, but neuroprotective treatment seems to be unavoidable in the disease.

Introduction

Patients with Huntington's disease have recently benefited from intracerebral cell therapy, which aims to substitute striatal neurons lost to the disease by striatal neuroblasts and neural precursors obtained from embryos after elective abortion. Maturation of grafted cells led to recovery of brain metabolism¹ and both motor and cognitive function in three out of five patients with Huntington's disease.^{2,3} Autopsy, undertaken 18 months after grafting,⁴ showed that the disease did not affect transplanted cells that lack the mutant huntingtin gene. Conversely, wild-type cells might not affect progression of degeneration in gene-carrying host cells.^{5,6}

Theoretical projection models suggest that the clinical effects of grafting will include an initial period of graft maturation and integration, leading to improvement, and a period of secondary decline due to the ongoing disease process in patients' brains. The duration of clinical benefit is therefore a major parameter to be taken into account when assessing the outcome of such treatment.^{3,5} The longest follow-up recorded of patients treated with these grafts is 30 months.^{2,7,8}

In 2000, we presented a preliminary report of motor and cognitive improvement over 2 years in three patients with Huntington's disease after intracerebral fetal neural grafting.² Recovery of brain metabolic activity occurred in grafted striatal areas and connected regions of the

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Patient	Demographic data			Total functional capacity				MDRS score				UHDRS motor score			
	Cod	Age at onset, years	Disease duration*	Preop	2 years	4 years	6 years	Preop	2 years	4 years	6 years	Preop	2 years	4 years	6 years
1	49	32	11	11	9†	11	9	130	140	130	138	52	47	34	53
2	43	48	13	12	11	11	10	138	138	134	127	46	52	57	77
3	41	39	12	12	11	10	10	141	135	128	129	20	25	39	68
4	51	31	13	6	4	1	..	113	93	53	..	91	77	88	..
5	44	46	10	11	9	2	2	137	122	48	25	29	47	79	91

MDRS=Mattis dementia rating scale; UHDRS=unified Huntington's disease rating scale; Cod=number of CAG repeats in the larger allele of the huntingtin gene. Preoperative values were recorded just before the first graft session; clinical motor and cognitive assessments were done 2, 4, and 6 years after the first graft. *Duration of the disease at 6 years post-graft, apart from patient 4 who was assessed for the last time at 4 years post-graft. †Total functional capacity erroneously reflects the lack of motivation in patient 1's daily life activities at the moment of testing and was corrected later when the patient became again motivated showing his real capacities.

Table 1: Demographic data and main functional, cognitive, and motor parameters at different time points

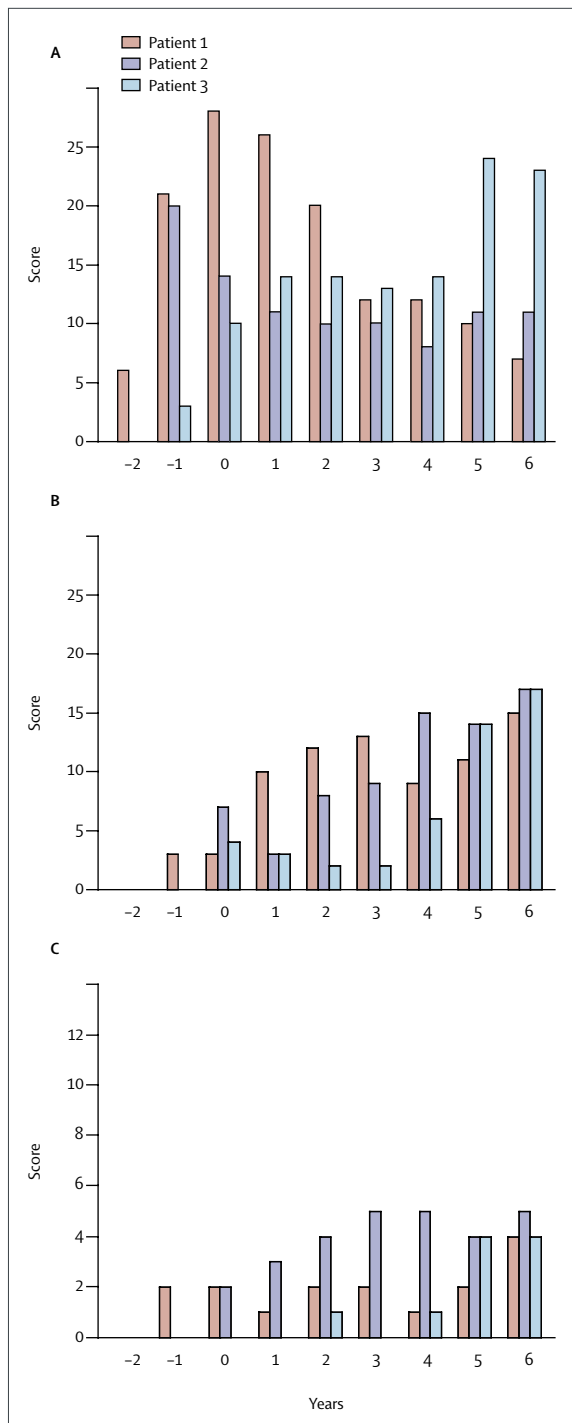


Figure 1: Results for the unified Huntington's disease rating scale motor part in grafted patients
 Scores are for chorea (A), dystonia (B), and gait parameters (C). 0 years corresponds to the preoperative assessment just before the first graft and 1 year corresponds to the assessment just before the contralateral graft.

cerebral cortex. However, because fetal neural grafts are not known to have protective effects on the host brain per se, we sought to describe the time course of clinical

benefits and improvements in resting brain metabolism over a long period in these previously reported patients.

Methods

Five patients with Huntington's disease from a pilot study² were assessed annually according to previously described protocols. Briefly, patients were followed up for 2 years and then treated with bilateral grafts in two sessions 1 year apart. Small blocks of tissue retrieved from the whole ganglionic eminence of human embryos (7.5–9 weeks old) were implanted through four to five tracks in the head of the caudate nucleus, the precommissural putamen, and the post-commissural putamen. Clinical and metabolic stability or improvement was seen in three of the five patients at 30 months of follow-up with no noticeable adverse effects.^{2,9} All patients, apart from patient 4 who died at 4 years,³ were followed up to the sixth year after grafting. Patient 4 showed an abrupt secondary deterioration, after a period of clinical improvement that lasted for more than 6 months, when the grafted tissue failed due to undetermined causes.³

We assessed the patients with the unified Huntington's disease rating scale (UHDRS),¹⁰ an extensive battery of neuropsychological tests, electrophysiological recordings, and MRI. FDG-PET scanning was done at 6 years. Neuropsychological performance was compared with that of a cohort of 22 patients with Huntington's disease at a similar stage of disease.¹¹

The study was approved by the ethics committee of Henri Mondor Hospital. All patients gave written informed consent.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In a preliminary report, patients 4 and 5 were shown to have no long-lasting clinical benefit nor improvement in brain function after grafting.² These two patients continued to decline in the following years. By contrast, patients 1, 2, and 3 showed motor and cognitive stabilisation or improvement at 2 years, consistent with an increase in brain activity in the grafted striata and in frontal and prefrontal cortices. Their results are described in detail here. At subsequent follow-up, clinical results for these three patients can be roughly split into two periods (table 1). First, performance stabilised at an improved (or similar) level to that reported preoperatively. Second, several functions showed subsequent deterioration.

For motor symptoms a plateau phase, defined by a variation of 10% or less of the scale (rounding at non-

decimal value), was observed for chorea, oculomotor symptoms, tapping, and gait parameters in all three patients. Chorea remained stable at an improved level compared with preoperative values for 6 years in patients 1 and 2, and for 4 years in patient 3 (figure 1). Tapping was both improved and stable in patient 1, but fluctuated in patient 2 with an initial improvement followed by abrupt deterioration at 3 years and subsequent improvement again until 6 years. Tapping was stable in patient 3 up to 4 years. By contrast with other motor symptoms, dystonia steadily increased in intensity over the entire follow-up period in patients 1 and 2 (figure 1), and after 4 years in patient 3. Oculomotor scores remained similar to baseline values until the end of the study in patient 1, and up to 5 years in patients 2 and 3. Gait parameters (namely tandem walking, retropulsion task, and walking) remained stable until the end of the study in patient 1, and up to 5 years in patient 3. By contrast, these parameters declined after 1 year in patient 2 (figure 1) and then remained stable until 5 years.

Table 2 shows performance before and 6 years after grafting for cognitive tasks. We set a strict criterion to define the plateau phase: the period of time when results differ no more than 1 SD from preoperative baseline values using published norms.¹¹ Thus, in patient 1 the

plateau phase for psychomotor tasks and semantic and executive tasks lasted variable times (3 years for the 1–3-digit cancellation task; 4 years for the 2-digit cancellation task and articulation rate; 5 years for the 1-figure cancellation task, trail making test B, and verbal fluency; 6 years for the 2–3-figure cancellation task and trail making test A). Measures were still stable at the end of the study for the Stroop and the symbol digit code tasks. Language was stable up to 6 years for the token test and over the entire period of examination for picture naming. Visuospatial abilities (judgment line orientation task) and global intellectual abilities (Mattis dementia rating scale, mini-mental status examination, and Raven's progressive matrices) remained stable over the entire 6 years.

Similarly, in patient 2 psychomotor tasks began to decline at various times—at 2 years the 2–3-digit and 2-figure cancellation tasks and articulation rate declined, but then remained stable until 4–5 years; at 4 years the 1-figure cancellation task declined; at 5 years the 1-digit cancellation task and verbal fluency declined; and at 6 years the 3-figure cancellation task, trail making test A and B, and Stroop colour and interference declined—or remained stable over the entire assessment period (Stroop word and symbol digit code task). The plateau was maintained up to 5 years for picture naming and over the

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Preop	6 years	Preop	6 years	Preop	6 years	Preop	4 years	Preop	6 years
MDRS	130	138	138	127	141	129	113	53	137	25
MMSE	29	28	30	28	27	25	27	16	30	10
Raven PM	36	34	35	35	34	33	23	16	35	0
Stroop word	80	62	60	52	79	60	34	16	61	18
Stroop colour	60	52	52	33	41	24	23	8	35	8
Stroop C/W	46	38	33	20	31	17	3	3	22	0
1-digit cancellation task	10	6	10	6	9	10	U	U	10	U
2-digit cancellation task	18	10	20	9	20	11	U	U	20	U
3-digit cancellation task	21	8	24	8	24	12	U	U	17	U
1-figure cancellation task	35	21	35	14	56	23	U	U	28	U
2-figure cancellation task	46	30	41	19	50	34	U	U	30	U
3-figure cancellation task	41	26	30	21	39	28	U	U	22	U
SDCT	5	6	5	9	10	ND	U	U	5	U
TMT A	80	109	95	129	52	104	U	U	72	U
TMT B	138	240	210	240	97	156	U	U	125	U
Categorical fluency	-0.9	-2	-1.4	-2	0.9	-0.8	-2.5	-2.8	-0.8	-3.6
Literal PV fluency	0	-1.85	0	-1.85	1.5	-1.7	-2.4	-2.9	1.9	-3.7
Literal M fluency	10	6	19	8	25	13	2	1	25	0
Articulation rate	6.4	8	5.8	9.8	5.8	7.3	13	U	6	36.2
Picture naming	20	20	20	19	20	18	16	15	20	15
Token test	35.5	30.5	36	36	34.5	34	22	12.5	36	13
JLOT	25	22	29	28	29	20	U	6	24	U

MDRS=Mattis dementia rating scale; MMSE=mini-mental state examination; Raven PM=Raven's progressive matrices; SDCT=symbol digit code task; TMT=trail making test; categorical fluency=fluency for fruits preoperatively and animals at 2 years and 6 years post-graft; literal PV fluency=fluency for letter V preoperatively, and P at 2 years and 6 years post-graft; literal M fluency=fluency for letter M at both time-points; JLOT=judgment of line orientation test; U=patient was unable to do the task. Z scores were used for fluency. Decreasing values indicate a decline in function, apart from for trail-making tests and articulatory rate, for which increasing values are indicative of decline.

Table 2: Scores for cognitive tasks preoperatively and at 6 years after grafting

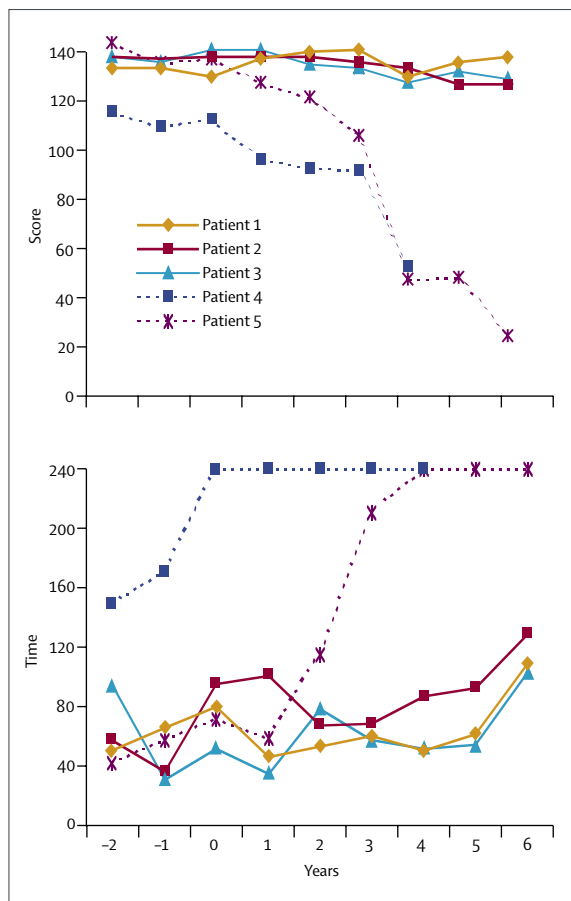


Figure 2: Individual variations over time in the Mattis dementia rating scale (top) and in the trail making test A (bottom)

Decreasing values indicate a decline in function in the Mattis dementia rating scale, but increasing time is a decline in the trail making test A, for which assessment is limited to 240 s.

whole study for language comprehension, visuospatial ability, and global intellectual abilities, apart from for the Mattis dementia rating scale, which declined at 4 years.

In patient 3, the plateau phase with psychomotor and executive tasks lasted up to 4 years for 2–3-digit and 1–2-figure cancellation tasks, symbol digit code task, and Stroop interference; up to 5 years for trail making test B; and up to 6 years for the 3-figure cancellation task, Stroop C, trail making task A, and articulatory rate. 1-digit cancellation task and Stroop word remained stable until the end. Verbal fluency declined at 3 years but then remained stable until 6 years. Visuospatial ability declined at 4 years (JLOT). Picture naming declined at 6 years, whereas language comprehension remained stable during the whole study (token test). Global intellectual abilities remained stable up to the study end, apart from the Mattis dementia rating scale, which declined at 2 years and then remained stable until 5 years. Figure 2 shows examples of time course for a non-timed (Mattis dementia rating scale) and a timed (trail making test A) task.

Total functional capacity¹⁰ decreased by only one point between years 2 and 6 after grafting (table 1). At 6 years, patient 2 continued to work part time. All patients continued activities they had lost before but regained after surgery—eg, cycling or doing odd jobs at home. However, they lost some skills after 5 years—eg, cycling or playing the guitar. At the end of the study all three patients were still able to lay the table, wash the dishes, and cook by themselves. Neuroleptics were introduced in patient 3 at 5 years to reduce chorea, and reintroduced in patient 1 at 6 years to decrease festination and treat a mood disorder.

Electrophysiological tests showed an overall stability of results up to 5 years when long latency reflexes disappeared in all patients apart from the left side in patient 1. At 6 years, a bilateral N20 wave in the somatosensory evoked potentials was still measurable in patients 1 and 2.

MRI hypointensity associated with grafts in the striatal nuclei at 2 years remained unchanged over the next 4 years. FDG-PET showed a decrease in striatal glucose consumption between 2 and 6 years in all patients (table 3), but there were no significant differences between 6 years and the preoperative state. The average decline in the cerebral metabolic rate of glucose was 7% in 6 years in patients 1, 2, and 3. Additionally, the number of hypometabolic voxels ($p < 0.0005$ compared with controls) was still lower than or equivalent to preoperative values in patients 1, 2, and 3 at 2 years and 6 years after grafting (figure 3).¹² Glucose consumption in the striatum was heterogeneous with evidence of relative preservation of improved values compared with preoperative results in parts of the striatum, whereas hypometabolism increased in surrounding areas (figure 4). Noticeably, glucose consumption, which had recovered to normal values at 2 years in the frontal cortex, remained stable up to 6 years in all three patients.

Discussion

The main result of this long-term follow-up analysis of patients with Huntington's disease who received fetal neural transplants is the prolonged benefit of the procedure, both clinically and in terms of brain activity. Altogether, a period of stabilisation of several years followed an initial 2 years of progressive clinical improvement. Within this general framework, however, the evolution was heterogeneous with, in particular, dystonia progressing more rapidly than other motor symptoms. Performance remained stable on most neuropsychological tests that did not need a timed motor response, but declined in timed tasks. Brain activity also displayed a heterogeneous pattern of evolution. The striking recovery observed at 2 years in frontal and prefrontal cortices persisted over time. By contrast, the disease continued to spread to other parts of the brain.

Patient	Preoperative	2 years	6 years
1	3.64	6.18	4.95
2	2.88	3.71	2.50
3	4.36	4.68	2.63
4	3.44	2.56	2.42
5	4.52	2.80	2.43

Absolute cerebral metabolism of glucose rates (mg/100 g tissue/min) in the whole striatum of the five patients before and 2 years and 6 years after the graft.

Table 3: Absolute glucose metabolic rates in the striatum

Because other brain regions—eg, neocortex—become affected when the disease progresses, implants in the striatum alone are unlikely to be fully effective since some cortical regions are not connected to striatal implants. Implantation of fetal stem cells into the brains of patients with Huntington's disease aims to substitute for lost cell populations but not to oppose the progression of neurodegeneration. By analogy to cancer, the treatment might only lead to remission, the value of which ultimately depends on a comparison between the extent and duration of any improvement with the discomfort and risks of the surgery and immunosuppression. The duration of the beneficial effects is thus a major issue.^{3,5} Our original analysis at 2 years reported positive clinical changes in three patients, with improvement in quality of life. We now report that the clinical benefits of striatal transplants persist for 4 years in the motor domain, and

for even longer for functional and cognitive symptoms, with no undesirable side-effects.⁹ More specifically, our patients do not follow the usual motor evolution of Huntington's disease: patient 1 maintained stable scores in the motor component of the unified Huntington's disease rating scale for 6 years (table 1); and in patients 2 and 3, the attenuation of chorea was not attributable to any increase of dystonia severity (figure 1).

These clinical changes were paralleled by results of electrophysiological tests and FDG-PET scans. Therefore, in addition to the relative safety of the procedure, the long-lasting effect of grafts reinforces the clinical relevance of transplantation. A parallel pilot study undertaken by Hauser and colleagues⁸ showed a similar trend toward motor improvement over a year, despite major differences with our study in patient selection and grafting procedures. The clinical course in patients 1, 2, and 3 differentiates them from untreated patients,¹³⁻¹⁵ even in the absence of published data with comparable follow-up from a non-operated group. In a post-hoc comparison between our three grafted patients with long-term benefit and a cohort of untreated patients with Huntington's disease followed up for 30 months,¹¹ benefits are conspicuous for total functional capacity, with slopes of evolution (at -0.2 , -0.3 , and -0.35 per year) outside the limits of the 95% CI of the control slope (-1.28 to -0.52). This is also the case for the categorical fluency and the token test. For many other

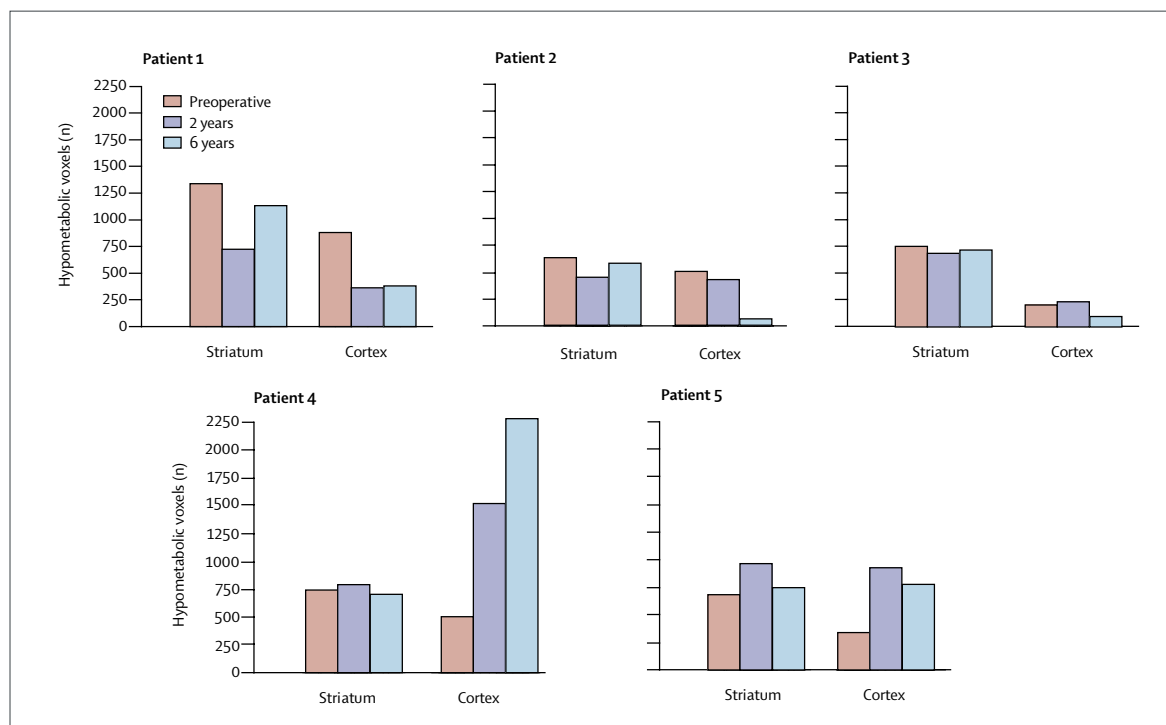


Figure 3: Local glucose consumption at different time points

PET examinations of the brain metabolism were done before the grafts, and at 2 years and 6 years after the first graft, apart from for patient 4 (last examination at 3 years). Images were compared voxel-by-voxel with the brain metabolism obtained in age-matched controls to avoid bias related to ageing on brain metabolism.¹⁹ The statistical threshold of each comparison was set at $p < 0.0005$.

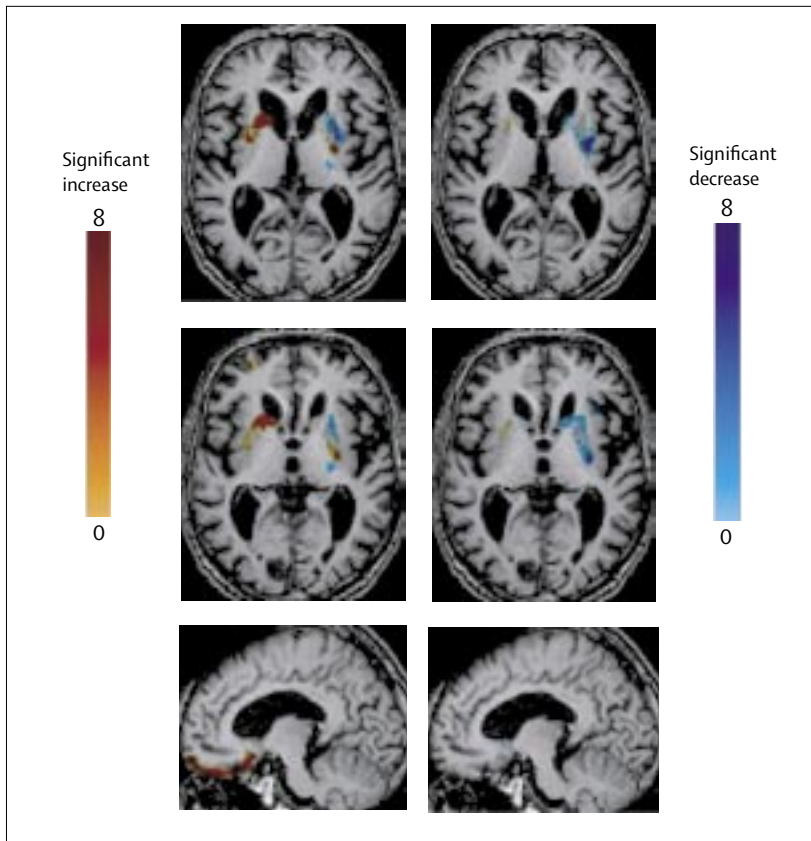


Figure 4: Significant changes in local glucose consumption in the brain of patient 1 during follow-up
T-statistic maps obtained for each stage to visualise changes in individual patients by comparing the metabolism of each patient to the corresponding controls. T-statistic maps were compared two by two to evidence the regions where the metabolism significantly improved or worsened from one examination to the next. Overlay of metabolic changes occurring at 2 years vs preoperatively (left) and at 6 years vs 2 years (right). The colour scales indicate t-values. Yellow-red colours indicate regions where a significant ($p < 0.0005$) hypometabolism compared with controls has improved between the two examinations. Blue colours indicate regions where a significant ($p < 0.0005$) hypometabolism compared with controls has worsened between the two examinations.

motor and cognitive tests, improvement was observed until the end of the plateau phase and then lost because of secondary decline near the end of the study period. One exception to this trend, however, was the evolution of dystonia, which progressed along a time course similar to that observed in untreated patients (figure 1), as if totally unaffected by the presence of grafts in the striatum. This observation could be explained by the lesser number of implantation tracks in the posterior putamen compared with the caudate nucleus and anterior putamen.¹⁶ Various patterns of change were also shown for cognitive tasks, with a clear discordance in the evolution of tasks that are timed and need a controlled movement, which deteriorated steadily, and tasks that are time-independent and were better preserved. This finding suggests that the clinical assessment of transplant patients should combine cognitive tasks with and without time constraints to disentangle specific impairments from the effects of motor dysfunction on cognitive tests.

In our analysis at 2 years, parallel improvement of clinical status and striatofrontal cortical metabolism showed that fetal striatal grafts were able to contribute to rebuilding defective corticostriothalamocortical loops.^{1,2} Striatal metabolism declines annually by 14% on average in non-implanted patients with Huntington's disease.¹⁴ Extrapolating these data, a theoretical slope of decrease in metabolic activity of close to 60% can be drawn for a 6-year period. Our results show a much smaller rate of decline, decreasing in transplanted patients by 7% on average in patients 1, 2, and 3 over 6 years. Data for the frontal and prefrontal cortices are even more striking because full recovery observed at 2 years¹ was still evident 6 years after implantation. This result suggests that striatal grafts securely rewire some neural circuits in the long term. Concomitant decline in other brain areas indicates that the implanted cells cannot prevent the natural progression of the disease. Striatal metabolic heterogeneity has already been reported after striatal neural transplantation in Huntington's disease.¹⁷ In that study, striatal metabolism decreased in four of the seven patients with grafts over 2 years (average loss of about 12% in the striatal cerebral metabolic rate of glucose) whereas it increased by up to 15% over baseline in the three other grafted patients. We speculate that there is a relation between the heterogeneous alteration of striatal activity and the opposite effects on many motor functions and dystonia discussed above. The causes of such heterogeneity are unknown. One possibility is that the success of integration of a transplant might depend more on patient-related characteristics (clinical phenotype, genotype, histocompatibility between donor and recipient, etc) than on the implantation procedure, which is similar in all patients.

Our long-term follow-up study confirms that neuronal transplantation provides a period of improvement and stability, but not a permanent cure for the disease.^{3,5} The secondary decline observed in our patients reinforces the idea that fetal neural grafts cannot completely deal with the problems of Huntington's disease alone. The therapeutic effect of fetal neural grafting is to induce a remission, with characteristics that we have defined here. Improvement of the surgical procedure and in patient selection may improve therapeutic value, but neuroprotective treatment with neurotrophic factors (eg, ciliary neurotrophic factor)^{18,19} or compounds that interfere with the molecular mechanisms of neuronal death⁶ seems to be unavoidable in Huntington's disease. The future therapeutic strategy against the disease probably relies on a combination of principles, neuroprotection, and neuronal replacement. Neuroprotection could stop the disease, but only a graft can restore lost function.

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Authors' contributions

AB was the principal investigator of the study and wrote the paper. VG analysed the PET scan data and participated in the writing of the paper. PB was responsible for neuroradiology. JL was responsible for neurophysiological testing. MB was responsible for the neuropsychological assessments. PM was responsible for methodological set-up and control, and participated in the writing of the paper. SB was responsible for the clinical database. CB was responsible for the psychiatric assessments. MJR participated in the PET-scan data analysis. PC and PH participated in the writing of the paper. PR was responsible for PET scanning, and participated in the writing of the paper. MP initiated the transplant study and was the main co-writer of the paper.

Conflicts of interest

We have no conflicts of interest.

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