# Neural transplantation therapies for Parkinson's and Huntington's diseases

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**Parkinson's and Huntington's diseases are progressive neurodegenerative disorders of the central nervous system for which symptomatic but not curative therapies are available. Therapeutic strategies have been developed to try and repair the brain in these conditions, including the use of grafts of foetal neural tissue. Here, we consider the merits of this approach and discuss the extent to which neural transplantation has successfully been translated into clinical studies for these diseases.**

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Neurodegenerative disorders are a group of diseases in which there is a loss of a defined populations of neurons within the central nervous system (CNS), leading to progressive neurological disease. This loss can occur through genetic causes, as in Huntington's disease (HD), or through less-well-defined processes, such as idiopathic Parkinson's disease (PD). The loss of neurons leads to the development of a range of clinical features, some of which respond to symptomatic drug treatment but none of which are amenable to cure[1–4], because the treatments simply try to replace missing or disordered transmitters rather than to arrest or replace the lost neurons. Therefore, even though the drug treatments can help, especially early in the disease, they ultimately fail as the progressive neuronal loss continues.

Attempts have been made to reduce or reverse the rate of cell loss through the provision of neuroprotective or neurotrophic factors – for example, ciliary neurotrophic factor in HD and glial-cell-line-derived neurotrophic factor (GDNF) in PD[5–7]. These agents have been shown experimentally to rescue striatal and dopaminergic neurons, respectively, and thus have shown promise as novel therapeutic agents. However, clinical trials to date with these neurotrophic factors are limited. For GDNF, at least, its intraventricular delivery in PD is ineffective[8] but improved delivery of the agent intraparenchymally to the site of pathology might prove more effective, as might its use in conjunction with neural grafts. In this article, however, we will discuss not neurotrophic factors but the clinical and pathological aspects of PD and HD that make them candidates for curative neural transplant therapies[9].

## The diseases

PD is a common neurodegenerative disorder of the CNS with a lifetime incidence of 2.5% and a prevalence that rises exponentially with age. It affects at least 120,000 people in the UK, costing £400 million annually. Although the condition responds well in the early stages to drug therapy, the treatment is not curative and, with time, the effects of treatment become less predictable. Therefore, attempts have been made at more curative approaches that seek to restore the lost dopaminergic nigral neurons that lie at the heart of the pathology of this condition[1].

The clinical features of Parkinson's disease are classically motor in nature with tremor, rigidity and bradykinesia[2,3]. However, there is an increasing realization that this condition has a significant number of cognitive deficits associated with it, which can range from subtle frontal lobe dysfunction to a florid dementia. In addition, autonomic problems are not uncommon in PD and many of these non-motor aspects of the disease might actually be made worse by pharmacological treatment[10] (Table 1).

HD is an inherited neurological disease that affects around 6,000 patients in the UK and comprises progressive motor, cognitive and psychiatric symptoms. In the early stages of the condition, any one of these sets of symptoms might predominate. Its core pathology involves degeneration of the basal ganglia, in

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**Table 1. Symptomatic treatment of Parkinson's and Huntington's disease**

| | Parkinson's disease | Huntington's disease |
|---|---|---|
| Drug therapy | Motor symptoms:<br>Drugs that stimulate dopaminergic network:<br>• L-dopa<br>• Dopamine agonists<br>• Inhibitors of dopamine breakdown (MAO and COMT inhibitors) | Motor symptoms:<br>Anti-chorea medications<br>• Antagonists of the dopaminergic network<br>• Anti-dystonia medication<br>L-dopa |
| | Psychiatric symptoms:<br>Atypical anti-psychotic drugs, some of which work at specific dopamine receptors within the brain. | Psychiatric symptoms:<br>Standard anti-depressants and anti-psychotics along with mood stabilizers (e.g. carbamazepine. Olanzapine, sodium valproate) |
| | Cognitive symptoms:<br>Some of the cholinergic agents advocated for Alzheimer's disease can help in some cases (e.g. rivastigmine) | Cognitive symptoms:<br>None |
| Surgical therapy | Stereotactic lesions:<br>• Subthalamic nucleus<br>• Internal part of globus pallidum<br>Deep brain stimulation:<br>• Subthalamic nucleus<br>• Internal part of globus pallidum | |
| | Neural transplantation | Neural transplantation |

particular the caudate and putamen, and is caused by a single autosomal gene encoding a mutant form of the protein huntingtin[11]. HD is a progressive disorder that usually starts in midlife and leads to complete dependence and death over a period of 15–20 years. At present, the only treatment available in HD are symptomatic (Table 1).

## Why might PD and HD be suitable for transplantation?

The failure of drug treatment in PD and HD to offer anything other than symptomatic benefit has led to the exploration of curative repair strategies that use tissue transplantation to replace those cells that are lost as part of the disease process. Both conditions are attractive in this respect because of their well-defined core pathology: the loss of the dopaminergic nigrostriatal tract in PD[12] and the loss of the GABAergic striatal output neurons in the early stages of HD[13]. Thus, the main target for restorative transplantation in PD is the dopaminergic neurons[14–16], whereas it is the striatal output neurons in HD[17]. It should be stressed, however, that more widespread pathological abnormalities develop with disease progression, which might account for some additional features of these diseases. Targeting treatment to specific sites might thus ultimately be limited by pathology at extranigral and extrastriatal sites in PD and HD, respectively. Nevertheless, given that the dopaminergic system and the striatal output neurons bear the brunt of the damage early in the course of these diseases, targeting these sites with transplanted tissue is a logical first approach.

## Neural transplants for PD and HD: the experimental evidence

Several surgical alternatives have been developed for the treatment of symptoms in advanced PD, including making strategic lesions in the outflow pathways of the basal ganglia (pallidotomy, subthalamotomy and thalamotomy) or implantating electrical stimulators at these sites[18,19] (Table 1). Although these surgical approaches can be effective at controlling certain symptoms, they do not represent a reparative approach. Transplantation, by contrast, strives to do this by replacing the dopaminergic neurons lost from the diseased basal ganglia in PD, with the goal of achieving lasting survival and repair of the underlying degeneration. The extent to which this occurs depends on the tissue transplanted – at its simplest level, this might take the form of dopamine-secreting cells that replace the transmitter in a nonspecific fashion, although a better approach might be to recreate the host dopaminergic circuitry, as has been attempted with embryonic nigral tissue.

HD, by contrast, has not been the subject of such intense neurosurgical intervention. It is also likely to represent a greater challenge in terms of the capacity of graft cells to repair damaged neuronal circuits than PD, in which the deficit can be more clearly seen to be pharmacological in nature. In other words, in PD, grafts might largely work by the nonspecific release of dopamine, whereas, in HD, the grafts will only function by making appropriate connections to and from the brain. In this respect, not only are clinical trials of neural transplantation in HD important to

evaluate the benefit of this approach in this devastating and incurable disease but they will also provide a prototype for other neurodegenerative disorders.

### *Parkinson's disease*

The first transplants that were considered for PD involved the adrenal medulla, but clinical trials produced no consistent, sustained benefit[20,21]. As a result, attention turned to grafts of embryonic ventral mesencephalic (VM) tissue, the isolation, preparation and implantation of which uses a well-validated procedure (Fig. 1) that is essentially identical to those used for other embryonic neural tissue, including human foetal tissue in clinical trials[22].

The development of VM grafts in animal models has clearly shown that the efficacy of the grafts is critically dependent on several factors.

- The donor embryonic tissue used must be of the right age (in the case of humans, this is 6–8 weeks of gestation[23]).
- Enough dopaminergic cells must survive. Currently, only 5–10% of those harvested survive, which means that many foetuses are required per patient transplanted, creating major practical problems in the clinical domain[24].
- The tissue must be properly dissected[25].
- The tissue must be correctly placed in the donor brain, as VM allografts are only effective at a behavioural level when grafted ectopically into the striatum of the host and not the substantia nigra. Furthermore, the site at which the tissue is implanted within the striatal complex determines the repertoire of behavioural recovery, on both motor and cognitive tests[26,27].
- Survival is best using tissue from the same species. Tissue from other species (a xenograft) creates immunological problems of rejection[28,29].

Experimentally, grafts of embryonic VM tissue have been shown to survive transplantation in the hemi-parkinsonian rat brain (Fig. 2), to receive and make connections from the host brain, to release dopamine in a controlled fashion, and to ameliorate behavioural deficits using a range of tasks[9]. These original studies in rats have now been extended to non-human primates[30] and so there is a substantial experimental basis for believing that this treatment will work for patients with PD. However, there are serious practical and ethical concerns to be addressed with the use of human foetal tissue for transplantation, which makes such a translation a complex and sensitive issue[31].

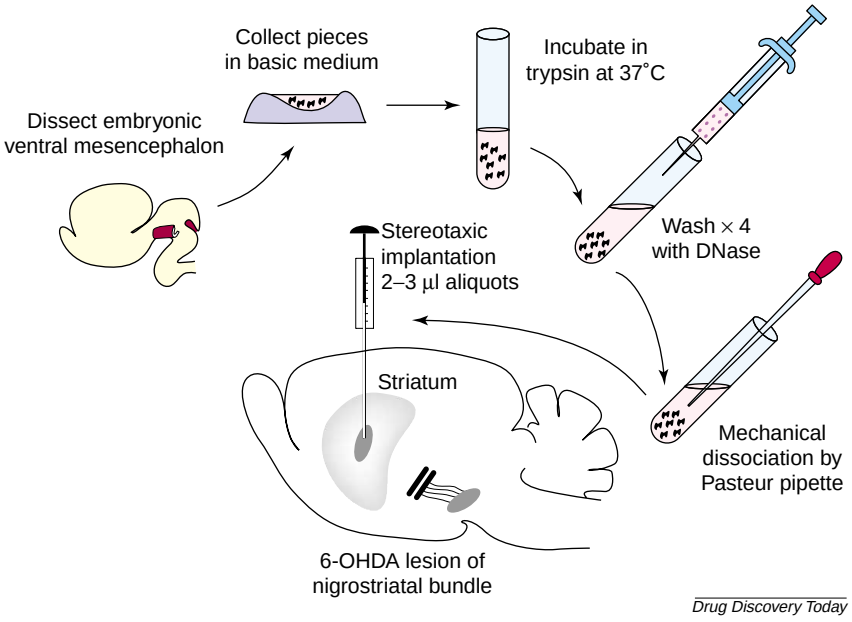


**Figure 1.** Schematic figure of basic transplantation procedure for embryonic ventral mesencephalic tissue used in the 6-hydroxydopamine (6-OHDA; a neurotoxin) rat model of Parkinson's disease. The animals receive a unilateral 6-OHDA lesion into the nigrostriatal bundle, which depletes the striatum of dopamine on that side. The developing dopamine cells of the substantia nigra are dissected as part of the embryonic ventral mesencephalon and then prepared using trypsin, DNase and trituration. This preparation of the tissue generates a cell suspension that can then be stereotaxically implanted into the dopamine-depleted striatum. In animal models of Huntington's disease, the striatum itself is lesioned with an excitotoxic agent such as quinolinic acid and then cells from the developing foetal striatal primordium are grafted into the lesioned striatum.

### *Huntington's disease*

The experimental approach to neural transplantation in animal models of HD is similar to that seen in PD. In brief, animal models of HD involve an excitotoxic lesion of the striatum (e.g. using quinolinic acid) and the intrastriatal grafting of appropriately aged embryonic striatal tissue, which appears to be E14–16 in rats[32,33]. In contrast to the relatively poor survival of dopaminergic neurons in VM grafts, striatal grafts survive well (Fig. 2), thus reducing some of the practical difficulties in their clinical use.

The ability of striatal grafts to recreate circuits is thought to be fundamental to their efficacy and has been demonstrated using a number of markers in experimental animals. The output from the grafts can be visualized using various tracers, which can be injected either directly into the graft itself so that the targets of the axons coursing


**Figure 2. (a)** A nigral allograft of rat E14 ventral mesencephalic tissue stained for tyrosine hydroxylase (TH) grafted into the striatum of the 6-OHDA-lesioned hemiparkinsonian rat brain. The dopamine cells can be seen on the borders of the graft with fibre outgrowth both within and out of the graft. **(b)** A striatal xenograft derived from an 8-week-old human embryo grafted into the quinolinic-acid-lesioned rat striatum and stained for acetylcholinesterase (AChE). The normal striatum can be seen surrounding a graft that contains patches of AChE positive striatal material. (Photographs courtesy of Carrie Hurelbrink.)

from it can be followed (so-called anterograde labelling) or into the normal target sites for the graft tissue so that the marker will be in the cells within the graft if they have projected into their target (so-called retrograde labelling). Both of these techniques show that striatal grafts have fibres that grow out towards their normal targets in the striatum (the globus pallidus and the substantia nigra)[32,33]. Indeed, the verification of this anatomical connectivity of the grafts has even been shown at the level of electron microscopy[34] and thus the evidence of circuit reconstruction is perhaps now stronger for this model system than any other, including VM grafts in PD. Of course, it is more difficult to determine whether graft connectivity, as demonstrated above, has any role in the functional efficacy of such grafts to the animal.

Further work to confirm that the graft makes functionally significant connections comes from a number of studies. One approach is the use of neurophysiological tests to show that the grafts respond normally to stimulation at sites of striatal input (e.g. host cortex or thalamus)[35,36]. A second approach is to monitor changes in gene expression in target cells in responses to changes in their inputs. It has now been shown that the patterns of expression of genes in the grafts that are regulated by the host dopaminergic input behave in an identical fashion to normal striatum[37]. The third approach is the use of *in vivo* measurements of neurotransmitter turnover to monitor the activity of inputs and outputs of the grafts, which has also confirmed a restoration of circuitry[38].

These various approaches all suggest that the re-formed host cortical, thalamic and dopamine inputs making synaptic connections with GABA output neurons are indeed capable of relaying functional information from the host brain to neurons of the graft. Furthermore, the grafts can transduce that information to exert a reciprocal influence on the appropriate neuronal circuits within the host brain. This in turn translates into behavioural benefits in the grafted animal, although this functional effect of the graft is in some cases only brought out after retraining of the animal on the original behavioural task, implying that the graft is relearning lost striatal functions[39,40].

## Clinical results of VM and striatal transplants in patients with PD and HD

At the time of writing, a clinical transplant programme is still an experimental procedure, despite the wealth of animal data to support its use. As a result, some aspects of the transplantation programme might evolve as techniques improve. This means that, even within one transplantation centre, the procedure might vary between patients, making comparative studies difficult. Moreover, even though many patients have received foetal VM transplants in PD, only a minority of these have been fully reported in the necessary detail, which is set out in the internationally recognized assessment protocols [e.g. CAPSIT-PD and CAPIT-HD (Refs 41,42)]. These protocols involve the assessment over time of patients using a number of well-validated rating scales in conjunction with structural and functional imaging studies. The initial assessments require a relatively long run-in period in order to establish a stable base line, and this is vital in ascertaining whether the graft is of benefit to the patient. The adoption of these protocols is essential if meaningful results are to be obtained from individual centres and compared across centres and studies. Failure to do this often negates the results from any given centre.

### *VM grafts in PD*

Many human VM transplants for PD have been undertaken over the past 10 years, estimated at over 200 in a recent review[14]. Although they have been targeted at PD

[including three patients with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism], diagnostic difficulties in this condition[43] have meant that patients with other diseases have occasionally received transplants. Probably the best-studied patients are those from the large series from Sweden, who have reported on VM transplants in 17 PD patients over the past 10 years with encouraging results[44]. In particular, such grafts in PD have been shown:

- to improve L-dihydroxyphenylalanine (L-dopa) drug efficacy;
- to reduce the amount of time the patient spends 'off' (time when patient is parkinsonian because treatment is not working); and
- to mediate a dramatic improvement in the speed with which PD patients can perform timed motor tasks, in particular during the 'off' state.

All of this has been seen in the context of increased dopaminergic activity in the graft using fluorodopa (a marker that labels presynaptic dopamine terminals in the brain) positron-emission tomography (PET) scans. PET is currently the only method that can provide information on the survival of dopaminergic neurones within the grafts *in vivo*. Whereas the fluorodopa uptake signal continues to decrease with the progression of the disease in the untransplanted caudate nuclei and the putamen, there is a dramatic and highly significant restitution of signal in grafted caudate and putamen[45]. Although the degree and extent of this improvement has been different for each individual, all participants in the Swedish series after the first two patients have shown increased fluorodopa signal on PET scanning, and this has also been seen in other centres[46,47].

The demonstration of surviving grafts in patients with clinical improvement gives credence to the view that clinical efficacy is directly related to the survival and integration of VM grafts and not just to the nonspecific consequences of surgery, placebo effects and heightened expectation and optimism. This is further supported by the clinical results from other centres and the limited postmortem studies in patients receiving foetal nigral grafts[48]. The early postmortem studies in patients who had received grafts were disappointing, primarily because the tissue implanted was suboptimal in its preparation[49]. However, the most recent postmortem studies from a US team (a collaboration between South Florida and Chicago) show healthy grafts with abundant cells and fibre outgrowth into the host striatum. In both cases, the deaths were unrelated to the transplantation procedure and occurred 18–19 months after they had received their grafts. These cases therefore clearly show that embryonic VM grafts can survive in the parkinsonian human brain, extend processes and provide extensive dopaminergic innervation of the striatum. This agrees with the experimental findings for rat and monkey allografts, and supports the hypothesis that these grafts work by comparable mechanisms in animals and humans.

However, a recent controversial randomized double-blind, placebo-controlled trial of VM grafts in PD has been undertaken in the USA with results that have alarmed some in the field[50]. In this study, patients were randomized to receive either a foetal human VM graft or sham surgery, and were followed longitudinally; the placebo group were later offered a transplant if efficacy was shown. This study showed there was a significant placebo effect of the surgery but that this subsided with time compared with those patients that received grafts. This clinical improvement only correlated with improved fluorodopa uptake in those patients under the age of 60 and, more worryingly, some of the grafted patients went on to develop major dyskinesias in the absence of any L-dopa medication. This has not been seen in other transplant studies but might relate to the different amounts of tissue and its preparation, along with the adoption of a novel grafting procedure by the surgical team in this study.

Overall, although VM grafts mediate good recovery by many measures, all of the patients remain parkinsonian, even years after receiving a successful transplant, and this also applies to the grafted MPTP-induced parkinsonian patients. Some patients have shown no benefit with grafts and this almost certainly relates to them not having PD but some other form of parkinsonism.

### *Clinical transplants in HD*

There is very little published literature on the results of clinical neural transplantation in HD but such reports are now appearing from a number of centres worldwide[33], including a recent study from Marc Peschanski (Creteil, France). This group have published a safety study[51] and, more recently, an efficacy study (see below). Previously, a safety evaluation had been published on three HD patients from a team based in Los Angeles. In this study, each patient received bilateral grafts from multiple donors in a single-stage operation. The grafts survived in all patients, as assessed by magnetic resonance imaging (MRI), and grew within the implanted striatum without causing any displacement of surrounding tissue during a 1-year follow-up period. No patients suffered any adverse effects of the surgery or the associated cyclosporin immunosuppression, nor did any patient deteriorate following the procedure[52].

The safety report on the first five patients from the Peschanski study has now been published and is based on at least two years' preoperative assessment and one year's postoperative follow-up[51]. No major adverse effects were

**Table 2. Alternative sources of cells being considered for transplantation in PD and to a lesser extent HD**

| Molecular replacement | Neuronal replacement |
|---|---|
| Peripheral neurones and ganglia | Peripheral neurones and ganglia |
| Slow release polymers and matrices | Neuronal cell lines |
| Secretory cell lines | Neural stem cells |
| Encapsulated cell lines | Immortalized neuronal cell lines |
| Genetically engineered cells | Xenografts |
| Genetically modified cell lines | |
| *In vivo* gene transfer | |

reported, although they did note some minor psychological problems in both patients and carer, and some compliance difficulties with the immunosuppression.

The functional efficacy of these transplants has now been evaluated for two years after implantation and is the subject of a recent report[53]. Three of the five patients showed a significant improvement in activities of daily living as well as on functional scales, and these correlated with improvement in glucose uptake on deoxyglucose PET scans within the striata and grafts seen on the MRI scan. The south Florida group, which has also transplanted five HD patients, found some improvements three days after grafting that have remained stable and not changed over 18 months[54]. One of these patients unfortunately died 18 months after receiving the transplant and was found to have a healthy graft containing all the normal constituents of the striatum[55]. However, this group used a different dissection of the human foetal striatum to the French group and grafted the tissue only into the post-commissural putamen rather than other structures of the striatum. It is therefore hard to compare these two studies in terms of whether striatal grafting is beneficial for patients with HD.

## Alternatives to the use of human foetal tissue for grafting in PD and HD

The difficulties with using human foetal tissue have meant that alternative sources of cells have been examined experimentally (Table 2), of which porcine xenografts and neural stem cells have entered or are about to enter clinical trials. In a US study, porcine embryonic VM tissue has been grafted into 12 patients with PD, half of whom received immunosuppression with Cyclosporin A (CyA); the rest received a masking antibody to one of the major immunogenic molecules present on the tissue, MHC class-I antigens[56]. Of these 12 patients, 2–3 have shown a significant improvement 1–2 years after implantation, although in none of these patients is this correlated with changes in their fluorodopa PET scans, and so the interpretation of their recovery is not straightforward. Furthermore, one of the grafted patients died 7–8 months after grafting from unrelated causes and was found at postmortem to have only a few surviving dopaminergic cells within the graft[57]. The reason for this is not known but probably relates to the immunological rejection of the xenograft. Indeed, this problem of rejection currently represents one of the two major problems with such tissue, the other being the risk of infection, especially from porcine endogenous retroviruses[29,58]. As a result of these difficulties, further experimental data is felt to be necessary before any clinical trials are started in Europe[59], although further clinical trials on embryonic porcine tissue for PD continue in the USA. Porcine xenotransplants have also been also been performed in HD patients without benefit[60].

Other tissues have been considered for use in the transplantation of PD and HD, of which one exciting possibility is neural stem cells[61,62]. These precursor cells are found throughout the developing embryonic brain as well as in the adult, and are distinct from totipotent embryonic stem cells. The major problem confronting the field is in persuading neural precursor cells to differentiate into the phenotype required (dopaminergic neurons in the case of PD). Despite this, some commercial companies are keen to embark on clinical trials with these cells. A number of other approaches are also being considered for PD and HD, including the use of neurotrophic factors. However, to date, no other replacement approaches using cells or viral vectors have entered the clinical arena for the treatment of either condition, although several trials are being considered[63,64].

## Is there a future for treating PD and HD using neural grafts?

PD and HD are incurable chronic neurodegenerative disorders that have as part of their core pathology the loss of specific subsets of neurons. Pharmacological treatment of PD is successful in the early stages, although the treatment produces its own problems with time but no such therapy exists for HD in any stage of the disease. However, in PD, none of the currently available drug therapies offers a cure and thus new approaches are being developed with the hope of offering such a possibility. Neural grafts of human embryonic VM tissue have been shown to be successful in PD when implanted by appropriately trained personnel in neural transplant centres, and there are preliminary reports

that human foetal striatal transplants might be of benefit in HD.

Major practical and ethical problems still confront the field of neural grafting, which means that clinical transplant programmes using human foetal VM tissue are unlikely to be widely adopted. Thus, alternative strategies are being explored that might ultimately prove to be more successful. However, whether such grafts will ever truly offer a cure remains unresolved, and this will continue to be the case until the etiology and pathogenesis of these conditions are better understood. Nevertheless, the development of new tools for manipulating and growing cells in culture make it possible that new and exciting curative cell therapies will emerge for the treatment of these common neurodegenerative disorders.

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