The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease.

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RESEARCH PAPER

The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington’s disease

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ABSTRACT

Huntington’s disease (HD) is a fatal autosomal dominant neurodegenerative disease involving progressive motor, cognitive and behavioural decline, leading to death approximately 20 years after motor onset. The disease is characterised pathologically by an early and progressive striatal neuronal cell loss and atrophy, which has provided the rationale for first clinical trials of neural repair using fetal striatal cell transplantation. Between 2000 and 2003, the ‘NEST-UK’ consortium carried out bilateral striatal transplants of human fetal striatal tissue in five HD patients. This paper describes the long-term follow up over a 3–10-year postoperative period of the patients, grafted and non-grafted, recruited to this cohort using the ‘Core assessment program for intracerebral transplantations-HD’ assessment protocol. No significant differences were found over time between the patients, grafted and non-grafted, on any subscore of the Unified Huntington’s Disease Rating Scale, nor on the Mini Mental State Examination. There was a trend towards a slowing of progression on some timed motor tasks in four of the five patients with transplants, but overall, the trial showed no significant benefit of striatal allografts in comparison with a reference cohort of patients without grafts. Importantly, no significant adverse or placebo effects were seen. Notably, the raclopride positron emission tomography (PET) signal in individuals with transplants, indicated that there was no obvious surviving striatal graft tissue. This study concludes that fetal striatal allografting in HD is safe. While no sustained functional benefit was seen, we conclude that this may relate to the small amount of tissue that was grafted in this safety study compared with other reports of more successful transplants in patients with HD.

INTRODUCTION

Huntington’s disease (HD) is an inherited, progressive neurodegenerative disorder characterised by involuntary movements, psychiatric and cognitive symptoms and signs. It is caused by an expansion of the CAG repeat in exon 1 of the huntingtin (Htt) gene. Patients with 36 or more CAG repeats in this gene develop HD. Htt is now recognised to be involved in a variety of cellular, metabolic, transcription and maintenance processes throughout development and in the adult.1 2 Abnormal CAG expansion in HD results in neuronal dysfunction, aberrant intracellular aggregation of mutant protein fragments and, eventually, cell death. Cellular dysfunction and loss is regionally specific within the brain, with early prominent atrophy occurring within the caudate nucleus and putamen, as well as the neocortex, and eventually extending to additional areas of the brain with advancing disease.3 The condition is currently incurable with the patient usually dying within 15–30 years of disease onset.4 5

Current therapies provide only partial relief of some of the symptoms of HD, and no disease-modifying therapies are yet available. One experimental therapeutic strategy has been to seek to replace the damaged and dying cells of the striatum with fetal striatal transplants, with some benefits reported in initial small studies.6–8 These studies reported motor and cognitive improvements and stabilisation over 5–6 years, consistent with data from positron emission tomography (PET) scans showing striatal metabolic activity at the site of graft placement.7–10 However, improvement has not been consistent in all studies, and the safety of such transplants, at least in patients with advanced disease, has been questioned11 12 (see refs 13 and 14 for discussion).

The NEST-UK multicentre study was initiated in 1998 as the second of two European centres to evaluate the safety and efficacy of bilateral fetal striatal transplantation in HD (ISRCTN no 36485475).15 This pilot study was designed to evaluate the feasibility, as well as providing preliminary data on the tolerability, of serial bilateral striatal transplantation in 10 patients with mild HD. The study was designed as a learning rather than a confirming trial and, as such, sought to describe what was seen, rather than being powered to show an effect. In this last issue, a confirmatory study would need to be much larger as our study only has an effect size of 0.74, so is not (and was not intended to be) powered to formally assess efficacy. If the trial had been designed for this purpose, then...
a further 21 patients would be needed in the transplant arm to detect a clinically meaningful difference of five points on the Unified Huntington’s Disease Rating Scale (UHDRS) motor scale at 10–12 years postsurgery.

The operations were undertaken in five patients between 2000 and 2003. A preliminary report of safety of the surgical procedures has been published from the first four patients after unilateral transplantation. Following this, the second phase of the trial commenced, in which these patients received contralateral transplants, and one additional patient received simultaneous bilateral transplants. At that time, the European Union published the Tissue and Cells directive, which required that full pharmaceutical-grade standards be applied to the processing of all cells and tissues for human application, including in small academic pilot studies. Implementation of the tissue directive into UK regulation led to suspension of the NEST-UK trial, pending full compliance with the new European standards, and this process is still ongoing. Since the completion date for the original study is further extended for at least 4 years, we consider that progress in the first five patients with grafts is informative, in comparison with 12 HD patients without grafts included in the initial cohort, and warrants an interim report, which we present here.

**METHODS**

Full details of the methods can be found in Rosser et al., briefly given in what follows.

**Patient cohort**

Initial plans for fetal cell transplantation in HD originated from the European Biomed network for striatal transplantation in HD (NEST-HD) in 1990–1993. The NEST-HD program coordinated a series of preclinical experimental studies and established a core assessment protocol for the longitudinal evaluation of patients within transplant trials (Core Assessment Program for Intracerebral Transplantations (CAPIT)-HD). The UK arm of this program was established as a collaboration between six centres (NEST-UK: Belfast, Aberdeen, Manchester, Cardiff, Cambridge, London) coordinated from Cambridge, with recruitment into the longitudinal assessment cohort taking place from 1994 to 2000. Separate ethical permission for undertaking transplantation was granted in 1999 (approval number: 99/099M) to commence a clinical trial of the safety and feasibility of fetal striatal transplantation. The first five patients were all selected for grafting from the Cambridge cohort of 17 patients recruited into the CAPIT-HD longitudinal assessment program. The present report is based on 8–10 years progression in these five patients, in comparison with the 12 patients from the longitudinal cohort who were assessed as being equally suitable for transplantation, but who were not randomly selected for the surgery.

**Tissue preparation and neurosurgical procedures**

Full details of tissue procurement, preparation, immunosuppression, safety assessment and implantation of the first four unilateral implants has been fully reported elsewhere. 15 17 23 24 The present report is based upon the progress of these same four patients following their second, contralateral implant, and a fifth patient who received bilateral transplants in a single surgical session, following the same protocols. Surgical and donor tissue parameters are shown in table 2. Doses of the three immunosuppressive drugs were slowly withdrawn a year after the second transplant.

**Clinical assessment**

All patients underwent a longitudinal assessment which included the full CAPIT-HD protocol plus additional motor and cognitive assessments. UHDRS5 6 motor, functional, behavioural and cognitive scales; and the following timed motor tests, 12 m walking, hand tapping in 30 s7 and time to drink 120 ml of water, were assessed at 6-month intervals: The UHDRS cognitive scale, the extended CAPIT-HD cognitive battery, and additional automated cognitive neuropsychological assessments were undertaken annually (see table 1). The five patients with transplants had pre- and postsurgical MRI and raclopride PET scans. 15 Raclopride (RAC) PET was carried out at baseline and after transplantation for 1–2 years postgrafting to assess striatal dopamine D2 receptor status and graft survival, assuming the grafts contained mature/differentiated striatal tissue which would express such receptors. The PET scanning protocol is as described previously. Six of the patients without transplants

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics at time of recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measure</strong></td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Sex (M:F)</td>
</tr>
<tr>
<td>Age at recruitment</td>
</tr>
<tr>
<td>Age at transplant</td>
</tr>
<tr>
<td>Education age</td>
</tr>
<tr>
<td>UHDRS</td>
</tr>
<tr>
<td>Total functional assessment</td>
</tr>
<tr>
<td>Total functional capacity</td>
</tr>
<tr>
<td>Independence score</td>
</tr>
<tr>
<td>Mini mental state exam</td>
</tr>
<tr>
<td>WAIS (vocab)</td>
</tr>
<tr>
<td>WAIS (block design)</td>
</tr>
<tr>
<td>NART</td>
</tr>
<tr>
<td>VOSP battery (total score)</td>
</tr>
<tr>
<td>VOSP battery (n of pass)</td>
</tr>
<tr>
<td>Boston naming test</td>
</tr>
<tr>
<td>Token test</td>
</tr>
</tbody>
</table>

*All differences are non-significant at p<0.10, with the exception of the NART scores, p<0.01.
N.B: As patient recruitment took place more than 12 years ago, while genetic data were not available, we do not have a valid power calculation for a further 21 patients being needed in the transplant arm.

also received RAC PET and acted as the controls for the patients with transplants.

Most patients have been assessed over 10–15 years; 3–5 years prior to and 7–10 years following the transplant selection period. Full details of all tests are provided in both the supplementary materials (information about participants drug regimes prior to and 7–10 years following T0, and in the methods section).

Statistical analyses

The five patients with transplants are compared with the remaining 12 patients recruited into the longitudinal NEST-HD cohort and similarly available for selection for transplantation prior to trial suspension (‘Reference control group’). Surgery in the patients with transplants was undertaken approximately 4–5 years following recruitment into the programme and all longitudinal data is referenced to the date of first transplantation (=T0). The patients selected for transplant surgery were slightly younger with higher UHDRS motor scores than the remainder of the reference group at the time of first recruitment, although these differences were not significant (table 3). The only significant difference between the two groups was the National Adult Reading Test (NART) scores which suggested that the group with transplants had slightly higher premorbid IQ (table 1, t15=3.11, p<0.01), but with no correction for multiple comparisons.

For longitudinal analysis of progression in control patients, T0 was designated as 4 years following first recruitment into the programme (although other arbitrary time shifts have no effect on the results).

According to the CAPIT protocol, neurological assessments were undertaken at 6-monthly intervals, and neuropsychological assessments at yearly intervals, although there were inevitably small variations in the precise scheduling of tests, and occasional missed assessments (less than 5% overall). For purposes of analysis, the scores on each test were averaged for each patient in 2-year blocks over 12 years, referenced with regard to >2 years pre-T0, 2–0 years prior to T0, and in 2-year blocks up to 6–8 years following T0. Longitudinal progression of impairments on each neurological and neuropsychological test was analysed by a two-factor analyses of variance (Genstat v11, VSN International, Hemel Hempstead). Missing values were entered in the dataset for patients who died or withdrew before the end of the 12-year assessment window, or where consecutive tests were omitted. The Genstat analysis programme is powered to estimate missing values by an iterative minimum variance routine that reduces the degrees of freedom in the estimates of error variance to correct for regression towards the mean, allowing unbiased inclusion of all patients’ data.

RESULTS

Demographics: adverse events

There were no major adverse events, in line with the initial safety report on the first four patients receiving unilateral transplants of fetal striatal tissue.15

The patients all showed a transient and anticipated decline in renal function post-transplantation, secondary to the cyclosporine immunotherapy they were receiving. This resolved when the treatment was eventually discontinued. Immunosuppression was also thought to be responsible for a transient anaemia in Patients 1 and 3, which again resolved on stopping the medication.

Soon after the second transplant, Patient 3 experienced a problem with lumbar disc disease, but this spontaneously resolved without recourse to surgery.

Table 3  Demographics of patients, grafted and non-grafted. The table shows the age at time of operation (for patients without grafts, the time of surgery is taken as May of the year 2000; which is the average date of the operations of the first four patients) along with their disease characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>M: F</th>
<th>Duration of disease at time of first surgery</th>
<th>Duration of disease at last assessment</th>
<th>UHDRS total motor score at surgery</th>
<th>Last recorded UHDRS total motor score (months after first graft)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>50</td>
<td>F: 7</td>
<td>17</td>
<td>31</td>
<td>37 (120 mo)</td>
<td>58 (108 mo)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>52</td>
<td>M: 9</td>
<td>15</td>
<td>46</td>
<td>66 (96 mo)</td>
<td>87 (36mo)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>53</td>
<td>M: 7</td>
<td>16</td>
<td>32</td>
<td>25 (78 mo)</td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>45</td>
<td>M: 6</td>
<td>15</td>
<td>78</td>
<td>54.6±10.9</td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>44</td>
<td>M: 4</td>
<td>10</td>
<td>12</td>
<td>40.5±19.7</td>
<td></td>
</tr>
</tbody>
</table>

- It should be noted that the UHDRS motor scores, especially the last recorded scores of the patients without grafts were very variable, ranging from 17 to 79 (maximum score is 124). UHDRS, Unified Huntington’s Disease Rating Scale.
Patient 1 developed a renal cell carcinoma following the first transplant which was resected with no residual tumour and no metastatic spread. The occurrence of this tumour was thought to be unrelated to either the transplant or immunosuppressive medication, and as such, the patient completed a full course of immunosuppression following the second transplant without any adverse events.

Clinical assessment
An average of 22.5 months after the first transplant, patients 1, 2, 3 and 4 had a second transplant to the contralateral striatum. The first three of these patients then continued to attend for regular assessments for the next 3 years. Patient 4 was unable to attend further appointments after 2005, 2 years after his second transplant. He died on 25 December 2009; the cause of death was recorded as aspiration pneumonia. No postmortem was conducted, nor unfortunately, was the brain collected for analysis. Patient five received a bilateral transplant and is still being followed-up 6 years after his operation. Details of drug treatments and performance on assessments additional to the CAPIT protocol are included in the supplementary data.

Motor assessments
UHDRS total motor score
The total UHDRS motor score of the five patients with transplants was compared with that of the 12 patients without grafts. Over a 13-year follow-up, the UHDRS score increased progressively in all patients, signifying a slow progressive worsening of motor signs (figure 1). The best fit regression lines to the annual means of each group indicated a highly significant rate of disease progression in both groups (Transplant, r = 0.628, t12 = 2.80, p < 0.02; Reference controls, r = 0.708, t12 = 3.47, p < 0.01), and the slopes of the best regression fits in the two groups did not differ. Analysis of individual patients revealed some apparent improvements. Thus, Patient 1 showed improvement after the first unilateral transplant, with the UHDRS motor score falling from 37 to 18 in the first 6 months after transplantation. After the second transplant, (at T = 22.5 on the graph) the UHDRS motor scores became and continued to get progressively worse. The final UHDRS score recorded 10 years after the first transplant was 37. This patient has never received any drug treatment for her chorea. Patient 2 also improved his motor score from 37 to 18 in the transplant. He died on 25 December 2009; the cause of death was recorded as aspiration pneumonia. No postmortem was conducted, nor unfortunately, was the brain collected for analysis. Patient five received a bilateral transplant and is still being followed-up 6 years after his operation. Details of drug treatments and performance on assessments additional to the CAPIT protocol are included in the supplementary data.

Full CAPIT neurological assessment
Neurological assessments were conducted at 6-monthly intervals according to the CAPIT protocol. For purposes of analysis, the scores on each test were averaged for each patient in 2-year blocks over 12 years, referenced with regard to >2 years pre-T0, 2–0 years prior to T0, and in 2-year blocks up to 6–8 years following T0. As shown in table 4, all test measures showed a clear and very highly significant (Years, F5,69 = 4.63–44.63, all p < 0.001) worsening over time. However, none of the tests showed any difference between the transplant and reference control groups, either overall, nor following transplant surgery, with the sole exception of the timed walk subtest, in which the interaction term reached significance if no correction is made for multiple testing (Groups × Years, F5,69 = 2.67, p < 0.05). However, although it does appear that the group with transplants shows a slowing of impairment on this one test, the only significant difference relates to the last time point 10–12 years after initial recruitment 6–8 years postsurgery, and not in the period immediately following transplantation.
(Groups×Years, $F_{5,69}=4.52$, $p<0.001$, uncorrected for multiple comparisons). By contrast to the conventional neuropsychological tests, we found the CANTAB automated touch screen measures to be less sensitive to the longitudinal progression of the disease (see supplementary table 2).

### Imaging MRI

Postoperative MRI scans confirmed appropriate surgical targeting with increased FLAIR signal along the implantation tracts. No occult haemorrhage was identified. Subsequent imaging was unable to identify any implanted material, and there were no mass lesions seen to develop in or around the transplant site. No volumetric studies were undertaken as MRI was employed for safety assessments only. All patients continued to have mass lesions seen to develop in or around the transplant site. No occult haemorrhage was identified. There were no implanted material, and there were no mass lesions seen to develop in or around the transplant site.

### PET

As the first four surgical subjects received implantation into the right striatum initially, their left striatal binding potential (BP) acted as an internal control for the contralateral side prior to the second implantation. Averaging the PET results of the first four subjects who received unilateral transplants, the rates of decline of striatal RAC BP were slightly higher on the right (transplanted side) after the first implantation, but this difference disappeared after the second implantation. The overall rate of progression from baseline to 1 year after the second operation were similar on both sides, and were not significantly different from those of non-grafted HD controls (figure 2), in line with previous longitudinal studies in HD using this ligand.

Subject 5 was scanned using a different PET camera and hence, his data could not be compared directly with the rest. The rates of progression of his striatal RAC BP at 1 year post-transplantation were 8.9% and 7.3% per annum for the right and left sides respectively. He did not receive further RAC PET scans as he was started on quetiapine for a psychotic episode, which interferes with RAC binding.

### DISCUSSION

This study reports the long-term safety, motor, cognitive and psychiatric effects of bilateral fetal striatal allografts in five patients with mild to moderate HD, in comparison with a reference group of 12 patients from the same cohort who were similarly suitable for transplantation but not selected for surgery, but were followed in an identical way.

There were no significant differences in any of the measures chosen when comparing patients with transplants with this reference cohort at baseline and followed-up for up to 10 years postsurgery, using identical protocols of assessment. In small open label studies with multiple outcome measures, it is

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### Table 4 CAPIT UHDRS and motor assessments

<table>
<thead>
<tr>
<th>Tests</th>
<th>Years</th>
<th>Control Mean±SEM</th>
<th>Transplant Mean±SEM</th>
<th>$F_{1,15}$</th>
<th>$F_{5,69}$</th>
<th>$F_{5,69}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHDRS (total motor scale)</td>
<td>0–2 years</td>
<td>20.3±3.2</td>
<td>27.9±3.8</td>
<td>1.16</td>
<td>26.38**</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>2–4 years†</td>
<td>24.0±3.5</td>
<td>30.4±3.6</td>
<td>1.87</td>
<td>30.28**</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>4–6 years‡</td>
<td>28.2±3.9</td>
<td>37.8±4.2</td>
<td>2.20</td>
<td>38.02**</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>6–8 years§</td>
<td>31.2±4.0</td>
<td>42.1±5.6</td>
<td>3.30</td>
<td>41.28**</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>8–10 years</td>
<td>34.4±5.1</td>
<td>46.0±6.7</td>
<td>3.80</td>
<td>45.03**</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>10–12 years</td>
<td>37.6±6.2</td>
<td>52.6±7.8</td>
<td>4.30</td>
<td>51.09**</td>
<td>0.30</td>
</tr>
<tr>
<td>Fahn score</td>
<td>Control</td>
<td>91.7±3.9</td>
<td>95.0±4.4</td>
<td>0.46</td>
<td>98.83**</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Transplant§</td>
<td>101.7±4.6</td>
<td>105.6±5.4</td>
<td>0.64</td>
<td>103.83**</td>
<td>0.25</td>
</tr>
<tr>
<td>Fahn score</td>
<td>Control</td>
<td>95.0±4.4</td>
<td>95.0±4.4</td>
<td>0.00</td>
<td>95.0±4.4</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Transplant§</td>
<td>105.6±5.4</td>
<td>105.6±5.4</td>
<td>0.00</td>
<td>105.6±5.4</td>
<td>0.00</td>
</tr>
<tr>
<td>Cognitive battery (total scores)</td>
<td>Control</td>
<td>232±12</td>
<td>232±12</td>
<td>0.00</td>
<td>232±12</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Transplant§</td>
<td>232±12</td>
<td>232±12</td>
<td>0.00</td>
<td>232±12</td>
<td>0.00</td>
</tr>
<tr>
<td>Timed tests (walk)</td>
<td>Control</td>
<td>220±22</td>
<td>220±22</td>
<td>0.00</td>
<td>220±22</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Transplant§</td>
<td>220±22</td>
<td>220±22</td>
<td>0.00</td>
<td>220±22</td>
<td>0.00</td>
</tr>
<tr>
<td>Timed tests (hand tap L&amp;R)</td>
<td>Control</td>
<td>86.8±7.2</td>
<td>86.8±7.2</td>
<td>0.00</td>
<td>86.8±7.2</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Transplant§</td>
<td>86.8±7.2</td>
<td>86.8±7.2</td>
<td>0.00</td>
<td>86.8±7.2</td>
<td>0.00</td>
</tr>
<tr>
<td>Timed tests (drink)</td>
<td>Control</td>
<td>82.8±10.1</td>
<td>82.8±10.1</td>
<td>0.00</td>
<td>82.8±10.1</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Transplant§</td>
<td>82.8±10.1</td>
<td>82.8±10.1</td>
<td>0.00</td>
<td>82.8±10.1</td>
<td>0.00</td>
</tr>
</tbody>
</table>

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**$p<0.001$; *$p<0.05$ (not significant when correcting for multiple comparisons); transplant improved (+), or impaired (−) with respect to the reference controls.

UHDRS (total motor score): 0–124, 124 worse; UHDRS (functional assessment): 25–50, 50 worse; UHDRS (ADL scale): 0 worse; UHDRS (independence scale): 0–100, 0 worse; Fahn score: 0–13, 0 worse; Cognitive battery: 0 worse; Timed tests (walk, hand tap (L & R) and drink): 0 worse.

CAPIT, Care assessment program for intracerebral transplantsations; ADL, activities of daily living; UHDRS, Unified Huntington’s Disease Rating Scale.

Note: all significant results are identified in bold.
Table 5  CAPIT neuropsychology battery assessments

<table>
<thead>
<tr>
<th>Tests</th>
<th>Years</th>
<th>Control (n=12)</th>
<th>Control (n=5)</th>
<th>Transplant (n=5)</th>
<th>Transplant (n=5)</th>
<th>Control (n=12)</th>
<th>Control (n=5)</th>
<th>Transplant (n=5)</th>
<th>Transplant (n=5)</th>
<th>Groups</th>
<th>Time</th>
<th>Group×Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal fluency (letters)</td>
<td>0–2 years</td>
<td>31.8±1.9</td>
<td>31.3±2.1</td>
<td>30.2±2.1</td>
<td>27.7±3.5</td>
<td>25.7±3.6</td>
<td>23.9±5.5</td>
<td>0.93</td>
<td>7.42**</td>
<td>2.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal fluency (animals)</td>
<td>0–2 years</td>
<td>18.0±0.9</td>
<td>16.2±2.8</td>
<td>13.1±2.2</td>
<td>11.4±2.0</td>
<td>10.2±1.2</td>
<td>9.0±3.0</td>
<td>0.01</td>
<td>15.93**</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol digit</td>
<td>0–2 years</td>
<td>34.6±3.3</td>
<td>30.1±2.2</td>
<td>27.0±3.5</td>
<td>22.5±3.3</td>
<td>21.7±4.6</td>
<td>29.2±6.7</td>
<td>0.18</td>
<td>40.18**</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop (colours)</td>
<td>0–2 years</td>
<td>55.7±3.0</td>
<td>48.5±2.9</td>
<td>45.8±2.9</td>
<td>38.4±3.5</td>
<td>34.0±3.3</td>
<td>33.7±5.1</td>
<td>0.08</td>
<td>38.70**</td>
<td>0.48</td>
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<tr>
<td>Stroop (words)</td>
<td>0–2 years</td>
<td>76.4±4.7</td>
<td>67.7±4.9</td>
<td>59.8±5.4</td>
<td>50.7±5.3</td>
<td>47.0±5.7</td>
<td>41.3±7.3</td>
<td>0.09</td>
<td>44.63**</td>
<td>0.71</td>
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<tr>
<td>Stroop (interference)</td>
<td>0–2 years</td>
<td>31.1±2.1</td>
<td>29.9±2.0</td>
<td>26.0±1.8</td>
<td>22.2±2.2</td>
<td>18.5±2.7</td>
<td>17.6±3.4</td>
<td>0.09</td>
<td>27.44**</td>
<td>0.54</td>
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<tr>
<td>MMSE</td>
<td>0–2 years</td>
<td>28.1±0.5</td>
<td>27.9±0.5</td>
<td>27.3±0.6</td>
<td>27.3±0.8</td>
<td>25.7±1.3</td>
<td>25.7±1.3</td>
<td>0.02</td>
<td>10.98**</td>
<td>0.57</td>
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<tr>
<td>Hopkins (test 1)</td>
<td>0–2 years</td>
<td>5.6±0.4</td>
<td>5.7±0.5</td>
<td>5.4±0.5</td>
<td>4.8±0.5</td>
<td>4.7±0.7</td>
<td>4.7±0.9</td>
<td>0.36</td>
<td>6.42**</td>
<td>0.43</td>
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<tr>
<td>Hopkins (test 2)</td>
<td>0–2 years</td>
<td>7.4±0.4</td>
<td>7.4±0.6</td>
<td>7.1±0.5</td>
<td>6.7±0.6</td>
<td>6.9±0.7</td>
<td>6.5±1.2</td>
<td>0.12</td>
<td>11.42**</td>
<td>2.06</td>
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<tr>
<td>Trails test (form A)</td>
<td>0–2 years</td>
<td>8.3±0.9</td>
<td>8.3±0.7</td>
<td>7.6±0.8</td>
<td>7.0±0.7</td>
<td>8.1±0.7</td>
<td>6.6±1.7</td>
<td>0.00</td>
<td>7.98**</td>
<td>1.97</td>
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<tr>
<td>Trails test (form B)</td>
<td>0–2 years</td>
<td>8.8±0.8</td>
<td>8.3±0.8</td>
<td>8.1±1.0</td>
<td>6.2±1.1</td>
<td>6.7±0.4</td>
<td>7.0±1.0</td>
<td>0.07</td>
<td>9.63**</td>
<td>0.54</td>
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<td>WCST (categories)</td>
<td>0–2 years</td>
<td>5.3±0.4</td>
<td>5.7±0.3</td>
<td>5.4±0.3</td>
<td>5.4±0.3</td>
<td>5.4±0.2</td>
<td>5.7±0.3</td>
<td>2.86</td>
<td>5.12**</td>
<td>4.52**</td>
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<td>WCST (errors)</td>
<td>0–2 years</td>
<td>4.7±0.8</td>
<td>4.9±1.0</td>
<td>4.6±0.9</td>
<td>4.5±0.7</td>
<td>4.3±1.1</td>
<td>1.5±1.5</td>
<td>2.02</td>
<td>4.90**</td>
<td>3.54*</td>
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<tr>
<td>Trails test (form A)</td>
<td>0–2 years</td>
<td>11.9±4.7</td>
<td>9.0±5.6</td>
<td>10.4±4.5</td>
<td>13.5±4.8</td>
<td>11.9±4.5</td>
<td>25.5±8.5</td>
<td>1.01</td>
<td>13.62**</td>
<td>0.85</td>
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<tr>
<td>Trails test (form B)</td>
<td>0–2 years</td>
<td>118.5±12.2</td>
<td>162.7±34.9</td>
<td>135.7±16.6</td>
<td>135.9±18.5</td>
<td>157.4±54.1</td>
<td>0.48</td>
<td>10.44**</td>
<td>0.53**</td>
<td>0.46</td>
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<tr>
<td>Recognition memory</td>
<td>0–2 years</td>
<td>10.7±0.4</td>
<td>10.7±0.5</td>
<td>10.2±0.7</td>
<td>10.7±0.4</td>
<td>10.1±0.5</td>
<td>10.0±0.5</td>
<td>0.17</td>
<td>0.83</td>
<td>0.24</td>
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<tr>
<td>Digit span (forward)</td>
<td>0–2 years</td>
<td>11.3±3.0</td>
<td>10.8±0.5</td>
<td>10.7±0.5</td>
<td>10.0±0.9</td>
<td>10.5±0.7</td>
<td>10.0±3.0</td>
<td>0.21</td>
<td>9.03**</td>
<td>0.97</td>
<td></td>
<td></td>
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<tr>
<td>Digit span (backward)</td>
<td>0–2 years</td>
<td>7.4±0.3</td>
<td>7.5±0.4</td>
<td>7.4±0.5</td>
<td>6.6±0.3</td>
<td>7.1±0.5</td>
<td>6.2±0.9</td>
<td>0.09</td>
<td>6.50**</td>
<td>0.46</td>
<td></td>
<td></td>
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<tr>
<td>Rivermead (immediate)</td>
<td>0–2 years</td>
<td>5.5±0.5</td>
<td>5.1±0.5</td>
<td>5.1±0.6</td>
<td>5.3±0.9</td>
<td>3.5±0.8</td>
<td>4.0±0.0</td>
<td>0.03</td>
<td>9.42**</td>
<td>1.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivermead (delay)</td>
<td>0–2 years</td>
<td>5.5±0.5</td>
<td>5.1±0.5</td>
<td>5.1±0.6</td>
<td>5.3±0.9</td>
<td>3.5±0.8</td>
<td>4.0±0.0</td>
<td>0.01</td>
<td>4.63**</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional associates</td>
<td>0–2 years</td>
<td>34.1±6.8</td>
<td>30.1±6.0</td>
<td>33.0±7.2</td>
<td>39.3±7.2</td>
<td>35.6±9.7</td>
<td>26.0±11.1</td>
<td>0.01</td>
<td>4.63**</td>
<td>0.85</td>
<td></td>
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</tbody>
</table>

**p<0.001; *p<0.05 (not significant when correcting for multiple comparisons); Transplant improved (+), or impaired (−) with respect to the reference controls. For Trails test parts A and B, and conditional associates, a LOWER scores indicates a BETTER performance. For all other tests 0 is worse.

CAPIT, Core assessment program for intracerebral transplantations; MMSE, Mini Mental State Examination; WCST, Wisconsin Card Sorting Test.

Note: all significant results are identified in bold.
A primary concern when we were designing the NEST-UK trial was the possibility for embryonic striatal tissue to overgrow. This was first observed in some human striatal xenografts in the rat brain, but has also been seen in at least two clinical trials in HD patients. In our first study of safety and feasibility, we therefore undertook implants of relatively small amounts of tissues—typically 5–10 x 10^6 cells from two or occasionally three ganglionic eminences from one or two donor embryos. The imaging results showed change in FLAIR signal along the surgical tracts consistent with minor tissue trauma. However, no significant graft deposits could be identified on serial imaging, using either MRI or RAC-PET. These observations are consistent with our previous experience with similar small graft volume protocols in rats and primates in which the implanted tissue volume was too small to exert any clear functional benefit. Rather, the dissociated cell suspension protocols employed here appear to be safe, but now warrant scaling up to implant larger numbers of cells to yield grafts of comparable size and integration to those that have been seen to be effective in animal studies. At the same time, attention still needs to be paid to accurate tissue dissection, since misdissection to include any meningeal cells can yield clear overgrowth and proliferation of non-neuronal tissues within neural grafts.

There has been considerable debate about the extent to which positive results in previous open label transplant studies—in particular in Parkinson’s disease, but also in HD—reflect placebo effects when neither the subjects nor the investigators are blind to the experimental condition. The present study is similarly open label, and none of the testing was undertaken blind. Nevertheless, although the present patients with grafts were highly motivated and exhibited clinically strong expectations of success, we saw no evidence for any clear placebo effect when patients were assessed long-term on a well-validated CAPIT test battery, and in spite of expectation of benefit, the patients with grafts exhibited no clear changes on test scores in comparison with the reference control group. Rather, the motor and cognitive features progressed at a very similar rate over the subsequent 8–10 years in both groups. A similar result has been recorded in an otherwise negative longitudinal clinical trial of riluzole in HD (R Roos, personal communication). Whereas we recognise the need for well-designed double-blind placebo-controlled studies of a candidate cell therapy just like for any
other medicinal product before it is released for widespread distribution in a standardised format, we consider that placebo effects in open label studies can be overemphasised, and that small case-control studies provide a more efficient and cost effective study format within which to refine and optimise protocols while the methods are still at a relatively early stage of development. 4,5

Although not its primary aim, the present data provide what is probably the longest longitudinal study of functional progression in HD using standardised neurological and neuropsychological tests. For this purpose, both motor and cognitive measures in the UHDRS offered reliable and stable measures of disease progression. All the neurological measures and all but one of the neuropsychological measures yielded a highly significant change across the years, as has been reported previously for non-surgical patients from this cohort over a 3–6-year time span. 6,7 While recognising the invalidity of ‘concluding the null hypothesis’, the very high values for the F ratios of the main effects of tests (within subjects) increases the impact of the absence of any significant differences over time between the two experimental groups (see tables 4 and 5). The data also attest to the continuing utility of the UHDRS and its subscales as an outcome measure of longitudinal progression in experimental and clinical HD research, although the sensitivity of these measures to detect subtle changes is still unclear. By contrast, whereas some subtests of the CANTAB battery have proved powerful for analysing the precise profile of functional impairment in HD, for instance, with the demonstration of patients particular susceptibility to impairments in extradimensional set-shifting, 8,9 we found the CANTAB automated touch screen measures to be less sensitive to the longitudinal progression of the disease. A further difference is that it is only on several of the CANTAB subtests that effects of the neurosurgical treatment were seen to show any significant interactions in this trial. However, the significant changes all involved a late-stage deterioration rather than benefit in the group with transplants; and since the effects were restricted only to the last tests applied 8–10 years post-transplantation, it is not yet clear whether this reflects a stable long-term impairment in specific aspects of prefrontal cognition, or a late-stage decline in individual patients close to the end of their lifespan.

In conclusion, the first five patients in the NEST-UK tolerability and feasibility study of striatal cell transplantation in HD confirms the absence of any long-term adverse effects and, we conclude, based on a limited number of patients followed long-term, that the surgical procedure is itself safe and feasible. Moreover, we found no significant clinical benefit of cell transplantation in these patients in any of the neurological, neuropsychological or imaging assessments. However, as a tolerability trial, we started with a low number of cells implanted, similar to the strategy adopted in dose escalation studies of novel pharmacotherapeutics, and since the imaging revealed no obvious graft masses, the absence of efficacy is not remarkable. To build on these findings, work to establish the optimum tissue selection, preparation and transplantation protocols are now key if efficacy is to be demonstrated. As an adjunct we have followed a group of 12 patients without grafts from the same cohort for more than 10 years, who showed clear and consistent progression of disability over a longer time frame than has been systematically evaluated hitherto. Although conducted as an open label study, it is notable that the patients with grafts showed no evidence whatsoever of a placebo effect, on the basis of which we can conclude that informative pilot data on efficacy can continue to be explored in open label studies with long-term follow-up prior to further refinements in the protocols to a stage where a fully blinded, controlled study is warranted.

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Colleagues

The NEST-UK collaboration involved six centres in the Universities of Aberdeen (SA Simpson, J Moore), Belfast (PJ Morrison, TFG Esmonde, N Chada), and Manchester (D Craufurd, J Snowden, J Thompson), along with Cambridge, Cardiff (P Harper, R Glew, R Harper) and London (as above).

Contributors

The following authors were involved in the concept and design of the study: RAB, TPH, BJS, PJ, DIB, WC, AER, SBD and the NEST-UK collaboration. The following authors were involved in the acquisition of data: RAB, SLV, TPH, RAS, AKH, MR, ES, TS, HC, AR, TP, SE, CA, YYT, PN, WC, JD, AER, SBD and the NEST-UK collaboration. The following authors were involved in analysis and interpretation: RAB, SLV, RAS, PP, YYT, DIB, PN, AER, SBD and the NEST-UK collaboration. The following authors were involved in drafting and/or revising the manuscript: RAB, SLV, TPH, RAS, PP, YYT, DIB, PN, WC, AER, SBD

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Competing interests

None.

Ethics approval

Cambridge Research Ethics Committee.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

All data relating to this study has been included in the publication. However, where mean values have been reported, the raw data is available upon request to the corresponding author (in anonymised format).

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The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease

Roger A Barker, Sarah L Mason, Timothy P Harrower, et al.

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