

# Reaction Time and Movement Time After Embryonic Cell Implantation in Parkinson Disease

Paul H. Gordon, MD; Qiping Yu, PhD; Clifford Qualls, PhD; Hal Winfield, RN; Sandra Dillon, RN; Paul E. Greene, MD; Stanley Fahn, MD; Robert E. Breeze, MD; Curt R. Freed, MD; Seth L. Pullman, MD, FRCPC

**Background:** Embryonic nigral cell implants are a novel treatment for Parkinson disease (PD). Reaction time (RT) and movement time (MT) analysis, validated quantitative measures of premovement neural processing and motor execution, can be used as objective physiological markers of motor performance in PD.

**Objectives:** To gauge the change in motor performance in patients with PD who received implants, and to determine whether the physiological findings correlate with clinical outcome measures after transplantation.

**Design:** Double-blind, placebo-controlled trial.

**Patients:** Forty patients with levodopa-responsive, Hoehn and Yahr stage III or greater PD.

**Interventions:** Random assignment to embryonic tissue implants or placebo (sham) operation.

**Main Outcome Measures:** Combined RT+MT scores measured preoperatively and at 4 and 12 months postoperatively in the "off" state.

**Results:** The difference in mean RT+MT scores between the sham and implant groups was statistically significant ( $P = .005$ ) and was greatest in those 60 years or older ( $P = .003$ ). Changes correlated with Unified Parkinson's Disease Rating Scale off scores at 4 ( $r = 0.87$ ,  $P = .001$ ) and 12 ( $r = 0.75$ ,  $P = .01$ ) months in those younger than 60 years. There was a significant deterioration in the sham surgery group at 12 months ( $P = .03$ ) that was thought to be due to worsening in subjects 60 years and older ( $P < .001$ ).

**Conclusions:** The physiological measures detected significant changes in patients undergoing embryonic nigral cell implants and correlated directly with clinical outcome measures. Comprehensive analyses of RT paradigms can document subtle changes in motor performance over time, making them useful outcome measures in therapeutic trials of PD. These findings support further research into nigral cell implantation for PD.

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From the Department of Neurology and Clinical Motor Physiology Laboratory, Columbia-Presbyterian Medical Center, New York, NY (Drs Gordon, Yu, Greene, Fahn and Pullman; Mr Winfield; and Ms Dillon); Department of Biostatistics, University of New Mexico, Albuquerque (Dr Qualls); and Departments of Neurosurgery (Dr Breeze), Medicine (Dr Freed), and Pharmacology (Dr Freed), University of Colorado, Denver (Drs Breeze and Freed).

**P**ARKINSON DISEASE (PD) IS A neurodegenerative disorder without a known cause or cure.<sup>1</sup> Advances in understanding of the basal ganglia circuitry and its role in the pathogenesis of PD coupled with refinements in imaging and improved surgical techniques have led to renewed interest in surgical treatments of PD.<sup>2</sup> Novel experimental treatments attempting to slow the progression of disease or reverse its course, including embryonic nigral cell implantation, are controversial and continually being evaluated.

Reaction time (RT) and movement time (MT) are objective quantitative physiological markers that are applicable as indexes of motor function in patients with PD.<sup>3</sup> The RT is a measure of premovement central neural processing<sup>4,5</sup> and is

prolonged by complex tasks and shortened with preparation and warning signals.<sup>6,7</sup> The MT is a physiological correlate of movement and is prolonged in bradykinesia. Tasks involving RT and MT produce both RT and MT data for every

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trial and are administered in different ways depending on experimental design. Two of the more clinically useful test designs are composed of the simple and choice task paradigms, which vary the position and timing of targets and the information given before the stimulus to move.<sup>8</sup> Simple tasks involve unambiguous information about the impending movement; choice tasks use more than one preparatory cue and result in the need to consider more than one

option when the stimulus to move is given. Thus, choice performance necessitates some degree of cognitive motor processing.<sup>9,10</sup> Both simple and choice RT/MT tasks have been shown to be abnormal in PD.<sup>11</sup> Clinical research laboratories have combined RT and MT in various ways, and RT/MT tasks have been assessed differently depending on the point of recording onset: from the first antagonist burst, from the onset of movement itself, or from the onset of the first derivative of movement.<sup>6</sup> Because central recruitment is abnormal in PD, combining RT and MT into a global score (RT+MT) provides an overall measure of total motor performance from the "go" signal to the end point of movement execution. This technique has been used in other clinical trials<sup>12,13</sup> and is the primary outcome measure in this study.

## METHODS

In the embryonic cell transplantation project, 40 patients with levodopa-responsive PD of Hoehn and Yahr stage III or greater were randomized to receive dopaminergic embryonic cell implants or placebo operations.<sup>14</sup> All patients underwent RT+MT measurements in 4 limbs preoperatively and at 4 and 12 months postoperatively in the practically defined "off" state (no dopaminergic medications for 12 hours before the evaluations). Physiological testing was done without knowing whether patients received the sham or real implant operation.

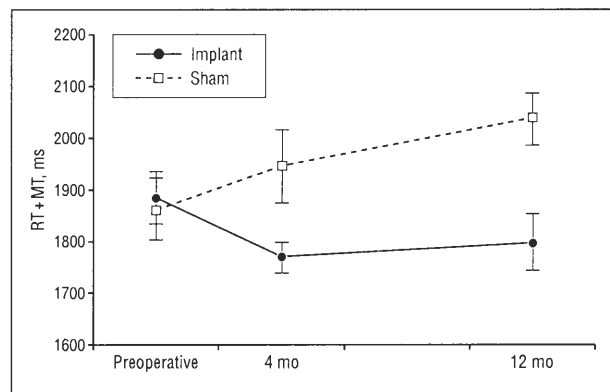
Testing was conducted in a quiet room without visual or auditory distractions. Subjects were seated in front of a series of hand and foot touch pads 1.0 m from a video monitor. After sufficient practice (10-15 trials), all subjects were instructed to move their hands and feet from a center touch pad to 1 of 2 target pads (left or right) in sets of 80 simple and choice directional RT+MT tasks. Computer-generated graphics indicated the central starting position, the go signal, preparatory cues, and targets. Simple tasks consisted of a single preparatory cue followed by the go signal; choice tasks required the need to consider more than 1 target option at the go signal. At each testing session for each limb, simple and choice trials were intermixed by means of a randomizing algorithm such that ultimately there was an equal number of trial types by the end of each testing session. The RT+MT was recorded as the time between a go signal and the moment of contact on the target.

The RT+MT averages were calculated for each limb after rejection of outlying data that included abnormally short values (<100 milliseconds) resulting from anticipation or excessively prolonged values (>4000 milliseconds) resulting from inattention or nonmotor causes.<sup>15</sup> Data were then analyzed in groups according to the type of surgery (implant or sham), limb (hand or foot), and age ( $\geq 60$  years or <60 years). Sixty years was the age used to separate older from younger patients in the transplantation study.<sup>14</sup>

Mean preoperative RT+MT was compared with the 4- and 12-month postoperative visits by repeated-measures analysis of variance. Where the analysis of variance yielded significant differences, post hoc analysis was performed with paired *t* tests comparing differences between the preoperative and the 2 postoperative dates. Pearson correlation coefficients were used to compare RT+MT with clinical Unified Parkinson's Disease Rating Scale (UPDRS) off scores, which improved in those younger than 60 years in the transplantation study.<sup>14</sup>

## RESULTS

Thirty-nine patients with PD (aged 35-76 years) completed the embryonic cell transplantation study, and all



**Figure 1.** Mean  $\pm$  SD reaction time plus movement time (RT+MT) of all limbs, grouped by type of transplant surgery. Note the deterioration at 12 months in the patients undergoing sham surgery and the trend toward improvement in the patients with implants.

were examined physiologically. Nineteen patients receiving sham and 20 receiving implant surgery completed testing. Ten patients in each group were younger than 60 years.

### SHAM VS IMPLANT SURGERY

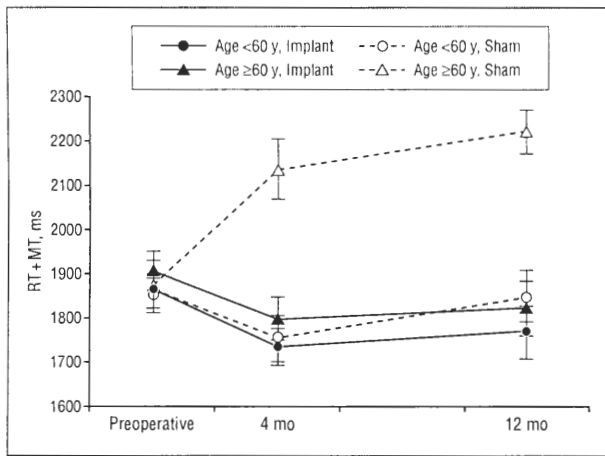
The baseline characteristics of the patients were such that they were well matched for age, sex, and initial physiological measures. There were no significant between-group differences in baseline RT, MT, or RT+MT. At study completion, there was a statistically significant difference in RT+MT between the sham and implant groups ( $P = .005$ ) (**Figure 1**). While there was significant deterioration in the sham surgery group at 12 months ( $P = .03$ ), analysis showed that the difference between groups was due predominantly to deterioration of performance in the older subset of patients receiving sham surgery ( $P < .001$ ), which steadily worsened toward the end of the study. In contrast, patients undergoing implant surgery showed improvement in RT+MT at 4 and 12 months that was not statistically significant ( $P = .09$ ). Not statistically significant improvement also was reflected when RT and MT were analyzed separately.

### AGE EFFECT

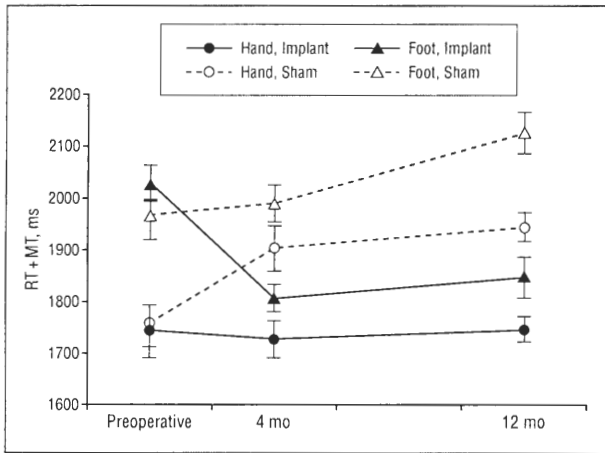
The RT+MT significantly worsened in patients 60 years or older who underwent sham surgery ( $P < .001$ ). This deterioration was significant at both 4 ( $P < .004$ ) and 12 ( $P = .001$ ) months in post hoc analysis (**Figure 2**).

The RT+MT did not change significantly in younger patients with either sham or implant surgery. However, RT+MT showed sustained improvement in both older and younger patients who underwent implant surgery. In younger patients with sham surgery, an apparent 4-month RT+MT improvement eventually returned to baseline by 12 months.

The MT correlated with improved UPDRS off scores at 4 ( $r = 0.52$ ,  $P < .001$ ) and 12 ( $r = 0.51$ ,  $P = .001$ ) months, and with UPDRS subscores for rigidity and bradykinesia at 4 ( $r = 0.87$ ,  $P = .001$ ) and 12 ( $r = 0.75$ ,  $P = .01$ ) months.<sup>14</sup>



**Figure 2.** Mean  $\pm$ SD reaction time plus movement time (RT+MT) of all limbs, grouped by age. There was a significant difference between older patients who had sham surgery and all other groups ( $P = .003$ ), a trend toward improved scores in both implant groups, and no change by 12 months in younger patients who received sham surgery.



**Figure 3.** Mean  $\pm$ SD reaction time plus movement time (RT+MT), grouped by limb. By this analysis, both hand and foot results worsened in patients who received sham surgery while there was significant improvement in foot data in patients with implants.

### LIMB PERFORMANCE

Analyzing the data by the hand or foot response showed lasting and significant ( $P < .005$ ) improvement in foot RT+MT in patients undergoing implant surgery at 4 and 12 months postoperatively (**Figure 3**). In contrast, there was no change in hand data in implant recipients. Both hand and foot RT+MT worsened about equally in patients undergoing sham surgery with significant deterioration at 4 months ( $P = .04$ ) and at 12 months ( $P = .05$ ).

### COMMENT

We measured RT+MT in the off state from simple and choice task trials preoperatively and postoperatively to gauge the change in motor performance in patients who received embryonic cell dopaminergic neurons in the first National Institute of Neurological Disorders and Stroke double-blind, placebo-controlled trans-

plantation trial.<sup>14</sup> Although recent findings from a second double-blind trial showed significant improvements in clinical measures at 6 months, there was no clinical improvement at study completion.<sup>16</sup> The purpose of this study was to determine whether there were objective physiological findings after transplantation and to correlate these with the clinical outcomes. Overall, significant differences in RT+MT measurements in patients receiving implant compared with sham surgery were found at 4 months and lasted to 12 months (Figure 1). Changes in MT correlated with clinical measures and compared directly with improvement in off UPDRS scores for rigidity and bradykinesia.<sup>14</sup> Analysis of the data showed that the worsening in the sham surgery groups was due predominantly to poorer performance in older patients; however, significant and lasting RT+MT performance occurred in subsets of implant recipient trials, particularly involving foot performance (Figure 3).

Impairments of RT and MT, first described in PD in 1925,<sup>5</sup> are related manifestations of central processes and pertain to different aspects of motor control.<sup>17</sup> Prolongations in RT and MT have been shown to correlate with nigrostriatal degeneration.<sup>18</sup> The RT measures response initiation time in motor tasks mediated in part through premovement central neural processing. The MT measures motor execution and is a physiological gauge of disability in PD that correlates with clinical bradykinesia.<sup>4</sup> The RT is prolonged in PD perhaps because of interruption in corticosubcortical circuits involving the caudate nucleus<sup>10</sup> and correlates with measures of global cognitive capacity, particularly attention and recent memory,<sup>19</sup> frontal lobe function, and motor disability.<sup>9</sup> Prolongation in RT increases as the severity of motor disability advances, and RT prolongation is more severe on the more affected side of the patient.<sup>20</sup> The RT is influenced by the medication state of the patient, and simple and choice RT may be differentially affected by levodopa replacement,<sup>15,21</sup> though overall medication state influences MT more than RT.<sup>22</sup>

The MT has been shown to correlate with Hoehn and Yahr staging, UPDRS scores, and plasma levodopa levels.<sup>4,23</sup> The MT is consistently slowed in PD, with failure of agonist muscles to exhibit abrupt discharges that normally occur in ballistic movements.<sup>17</sup> The MT is highly influenced by plasma levodopa levels<sup>4,15</sup> and improves after deep brain stimulation. Stimulation of the globus pallidus and subthalamic nucleus reduces MT equally, suggesting that disrupted pallidal output may be responsible for slowed MT in PD, without affecting preparatory processes,<sup>24</sup> although pallidotomy has been shown to improve both RT and MT.<sup>25</sup>

By combining RT+MT from simple and choice trials, we obtained broad measures of psychophysical and motor performance in patients before and after surgery. This technique provides a measure of total time needed for movement and has been used in other laboratories to assess patients with PD.<sup>12,13</sup> Analyzing simple and complex trials separately may further yield differential results, with greater changes in simple tasks with cell implantation into the putamen (which



may primarily affect motor execution), while implantation into the caudate may favor cognitive motor processing to a greater extent.<sup>10,17</sup> A differential improvement in implant recipients, and worsening in sham-treated patients, of RT+MT foot performance also was noted, perhaps reflecting the differential clinical findings affecting the upper and lower body that were found in the transplantation study.<sup>14</sup>

The greatest differences between sham and implant surgery data were due to worsening in the sham group, presumably reflecting ongoing neurodegeneration in PD, or possibly stabilization in the group receiving implants. The deterioration in patients who received sham surgery was greatest in patients 60 years and older (Figure 2). These findings show that comprehensive analyses of different reaction time paradigms can document subtle changes in motor performance over time, and indicate that there are objective markers of motor behavior that were altered with embryonic tissue implantation in patients with PD.

While the primary clinical outcome measures of this and a separate trial<sup>14,16</sup> were negative, secondary analyses including analysis of subgroups and positron emission tomographic imaging did detect changes, suggesting a potential benefit from implantation that requires further exploration. The physiological data presented herein complement these data. Greater understanding of the basic science may improve overall outcomes, and continued exploration of physiological means of measuring decline in patients with PD may increase the sensitivity of outcome measures.

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Corresponding author and reprints: Seth L. Pullman, MD, FRCPC, Department of Neurology, Clinical Motor Physiology Laboratory, Columbia University Medical Center, 710 W 168th St, New York, NY 10032 (e-mail: sp31@columbia.edu).

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