Feasibility of use of probabilistic reversal learning and serial reaction time tasks in clinical trials of Parkinson's disease

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Abstract

Introduction: The aim of this study was to investigate the feasibility of using two computer-administered neuropsychological tasks in a clinical trial involving participants with Parkinson's disease without dementia. The tasks, probabilistic reversal learning (PRL) and serial reaction time (SRT), target dorsolateral prefrontal cortex (SRT) and ventral striatal-orbitofrontal (PRL) functioning respectively.

Methods: Participants were 53 adults with idiopathic Parkinson's disease who completed both the SRT and PRL tasks at baseline in a clinical trial. Repeated measures were examined only for the placebo group (n = 20).

Results: No participants were removed from analyses due to inability to complete the tasks, and most had fewer than 10% of trials culled due to slow reaction times. Response accuracy on PRL was 81.98% and 66.65% for the two stages of the task respectively. Disease duration was associated with SRT relearning. Disease duration and stage were associated with initial learning on PRL, and there was a trend towards disease stage predicting greater errors on PRL. Among participants in the placebo group, practice effects were seen on PRL (Phase 1 errors) and SRT (relearning).

Conclusions: These results provide initial evidence for the clinical feasibility of computerized PRL and SRT tasks in clinical trials in Parkinson's disease.

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been associated with ventral striatal-orbitofrontal areas (VS-OFC) [4,5].

Behaviorally, PD patients undergoing early dopamine replacement therapy may demonstrate better performance on cognitive tasks mediated by the DS-DLPFC than tasks regulated by the VS-OFC. Brain areas such as the putamen and dorsal caudate nucleus, which atrophy early in PD, may benefit from DA replacement, whereas areas that are more intact, such as the ventral striatum and the mesocorticolimbic DA system, may be subject to a focal DA excess [4–6]. This potential DA excess suggests that early DA replacement sufficient to restore DA function to the dorsal striatum may be excessive for less affected regions of the ventral striatum. Thus, while DA replacement may remediate performance on tasks mediated by the DS-DLPFC, DA treatment may negatively impact behaviors mediated by the VS-OFC early in the disease process [4,5,7]. With disease progression, the effects of DA therapy may be altered.

1. Method

1.1. Recruitment

Participants were recruited from an outpatient movement disorders clinic by the study neurologist/movement disorders specialist (JHF), who ensured participants met criteria for diagnosis of idiopathic PD based on UK Parkinson’s Disease Society Brain Bank diagnostic criteria [10]. We explained the purpose, risks, and study requirements to potential participants and obtained written informed consent. All participants were screened for depression (score of greater than or equal to 7/15 on the Geriatric Depression Scale-Short Form [GDS-S]) [11,12], and dementia (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] [13] criteria for PDD and Modified MMSE [3MS] [14] score less than or equal to 77/100 [0.95 correlation between 3MS and MMSE]) [15]. All participants were ages 40–90, spoke English, and finished at least six years of school.

1.2. Study design

Specific details on the study design, determination of sample size, recruitment, retention, and follow-up are detailed elsewhere [9] (as the present study did not investigate galantamine effects), and the trial was registered with clinicaltrial.gov (NCT00211588). Briefly, the study was a single centre, double-blind, randomized 16-week placebo-controlled clinical trial of galantamine hydrobromide ER. The study coordinator, neuropsychologist, and neurologist were blind to group assignments. Participants were maintained on their dopaminergic and other medications during the clinical trial. Fifty-three participants completed both SRT and PRL at baseline: 33 in the treatment group (baseline performance only), and 20 participants in the placebo group who completed both tasks at Time 1 (baseline) and Time 2 (10–16 weeks later). See Table 1 for demographic information.

1.3. Cognitive measures

1.3.1. Sequential learning

We assessed implicit procedural learning using a serial reaction time task (SRT) [16]. Four squares appeared in a row on the computer screen. Participants positioned their left and right index and middle fingers on four keyboard keys corresponding to the four squares. The participant followed the position of an asterisk (*) that moved from one square to another by pressing the corresponding keys. For example, when the asterisk appeared in the left-most square, the participant pressed the corresponding key with the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 53)</th>
<th>Placebo only (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.64 (9.24)</td>
<td>70.00 (8.25)</td>
</tr>
<tr>
<td>Gender</td>
<td>40 Males 13 Males</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>14.83 (3.23)</td>
<td>14.47 (3.04)</td>
</tr>
<tr>
<td>L-dopa Dose</td>
<td>551.74 (318.41)</td>
<td>509.37 (276.93)</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>6.38 (4.54)</td>
<td>7.18 (5.03)</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr staging</td>
<td>2.12 (0.41)</td>
<td>2.26 (0.48)</td>
</tr>
<tr>
<td>UPDRS</td>
<td>16.94 (8.71)</td>
<td>19.05 (6.41)</td>
</tr>
<tr>
<td>3MS</td>
<td>94.19 (4.99)</td>
<td>94.32 (5.60)</td>
</tr>
<tr>
<td>Clock</td>
<td>8.65 (1.37)</td>
<td>8.64 (1.58)</td>
</tr>
<tr>
<td>GDS-S</td>
<td>1.87 (1.58)</td>
<td>1.58 (1.43)</td>
</tr>
</tbody>
</table>

Note: Hoehn and Yahr staging at baseline; UPDRS = Unified Parkinson’s Disease Rating Scale (motor) at baseline; 3MS = Modified Mini-Mental Status Examination at baseline; Clock = Clock drawing task performance at baseline; GDS-S = Geriatric Depression Scale-Short Form.
left middle finger. The participant worked as quickly and accurately as possible. If an error occurred, the asterisk remained in the same square until the participant pressed the correct key. The asterisk moved through a fixed sequence of 12 movements that repeated eight times per learning trial (i.e., Blocks 1–4). Block 5 was an interference trial in which the asterisk moved between the squares in a random order, and Block 6 repeated the identical 12-movement sequence used in Blocks 1–4 an additional eight times (relearning). Inter-stimulus interval was set to 400 ms. Procedural learning (difference between Block 1 and Block 4 median RTs) and relearning (difference between Block 4 and Block 6 median RTs) were examined.

1.3.2. Probabilistic reversal learning (PRL)

The PRL procedure followed that of Swainson et al. [8]. Two colored squares appeared, one red and one green, in two of four possible locations on a computer screen. The non-stimulus locations displayed a white square (distractor). Without receiving any instructions as to which of the four objects to select, the participant selected one object on each trial by clicking on that object using the touchscreen monitor. After making a selection, feedback was displayed on the screen in the form of either the word “correct,” presented with a high-pitched tone, or “incorrect,” presented with a low-pitched tone. The correct stimulus was set as the first colored stimulus selected, either red or green (Trial 1). Participants were instructed to select the object that is usually correct, even if it is sometimes wrong. Participants were also told that the correct color might change at some point.

For Trials 1 to 40 (Phase 1: simple probabilistic visual discrimination), selection of the correct stimulus was reinforced with positive feedback (“correct”) 80% of the time, but negative feedback (“incorrect”) was given 20% of the time. The incorrect stimulus was reinforced as correct on 20% of the trials and incorrect 80% of the trials. The next 40 trials then constituted Phase 2 (reversal learning). Beginning with Trial 41, and without warning, contingencies were reversed. The originally incorrect color switched to being correct and was reinforced 80% of the time (negative feedback given on 20% of the trials). A participant was considered to have “passed” a phase once they made eight or more consecutive correct responses. All participants completed 80 trials, regardless of when they learned to discriminate. For each phase, the outcomes were the percent of participants passing that phase, and for each participant, the number of errors made prior to passing the phase and the median RT across all trials for that phase.

1.4. Procedure

The study protocol and consent forms were approved by the Institutional Review Board (IRB). The current tasks were included as part of the 1 h study battery, and were presented in a randomized order. The study neurologist completed the Hoehn and Yahr scale (HY) and motor scale of the Unified Parkinson’s Disease Rating Scale (UPDRS) at baseline. All participants completed SRT and PRL at baseline (Time 1) and at the end of the clinical trial (week 10 or 16, Time 2). Total administration time was approximately 20 min. To assess practice effects, independent of the effects of galantamine, performance was compared at Time 1 and Time 2 for individuals in the placebo group only.

1.5. Data analyses

As DA levels, disease duration, and PD disease severity can be correlated with one another, all were examined in the same analyses. A series of regressions were conducted with DA equivalent dose (dopamine dose summed across all medications [17]), disease duration (in months), and UPDRS staging entered in Step 1, the two-way interactions in Step 2, and the three-way interaction in Step 3. The PRL and SRT variables were utilized as outcome variables. No problems of multicollinearity were noted in the regressions (VIF < 2.00). To examine practice effects within the placebo group, paired-samples t-tests were conducted comparing performance at Time 1 to Time 2 for both PRL (number of errors to criterion, median RT) and SRT (procedural learning, relearning).

2. Results

2.1. Objective: feasibility of use of PRL and SRT in PD clinical trials

No participants were removed from analysis due to inability to complete the tasks. On SRT, individual trial scores were removed from further analysis if they were three or more standard deviations from the block mean. Based on this criterion, each participant had 0 (0%) to 35 (36%) of their responses on each block removed (mean number removed ranged from 1.68 [Block 5] to 6.64 [Block 1]). Between 81% and 87% of participants had less than 10% of their trials culled on Blocks 1–4 or Block 6, and all participants had less than 10% of their trials culled on Block 5. We observed a decrease in RT from Block 1 (M = 764.77, SD = 218.88) to Block 4 (M = 659.46, SD = 193.90; Fig. 1), indicating participants were learning the sequence. In addition, examination of the overall RT pattern across blocks fell in the expected pattern of scores (i.e., decreases as learning occurred). On PRL, response accuracy was 81.98% (SD = 13.86) on Phase 1 and 66.65% (SD = 20.91) on Phase 2, suggesting initial learning of reward contingencies was easier than learning the reversal of reward contingencies. Collectively, these results provide evidence for the feasibility of use of the PRL and SRT tasks in the context of a clinical trial in PD Fig. 2.

2.2. Objective: practice effects

Practice effects were examined among individuals in the placebo group only. On SRT, no significant differences emerged in procedural learning between Time 1 and Time 2, t(19) = 1.51, p = .15. However, a significant difference emerged in relearning, t(19) = 3.03, p = .007, indicating greater difficulty relearning the task after distraction at Time 2 than Time 1. On the PRL task, there was a trend towards a significant difference in errors on Phase 1, t(17) = 1.83, p = .09, in that there were more errors made at Time 1 than Time 2. No significant differences emerged on Phase 2 errors to criterion, t(12) = 0.03, p = .98, or in RTs in either Phase 1, t(18) = 1.07, p = .30, or Phase 2, t(13) = −0.21, p = .83.

![Fig. 1](image-url). The x-axis represents both the time (Time 1 or Time 2) and the SRT block (Block 1–6), where Blocks 1 and 4 are compared for learning and Blocks 4 and 6 for relearning. Scores on the y-axis represent median reaction times (RTs).
3. Conclusions

Taken together, the present findings provide evidence in support of the use of computerized tasks in a diverse sample of individuals with PD without dementia. To be feasible for clinical trials, tasks need to be brief, easily understood and completed by participants, and have only low levels of missing data. The two tasks took approximately 20 min to complete, and all participants were able to complete the tasks. The low rates of culled data on SRT indicate participants were able to understand and follow task directions. In addition, the expected patterns of learning occurred, as RTs decreased across each block. Examination of PRL showed participants were able to learn reward contingencies but had some difficulty with reversal learning.

The degree of practice effects was also examined, as cognitive tasks are often administered before and after administration of a study medication. Although no practice effects were seen for SRT procedural learning, participants had greater difficulty relearning at Time 2 than Time 1 indicating potential interference from the previous administration. On PRL, there was a trend toward greater errors learning the reward contingencies (Phase 1) at Time 1 than Time 2, indicating that previous experience with the task may have helped performance on the second administration. Practice effects, although minimal, should be taken into account prior to use in longitudinal clinical trials. Researchers could, for example, conduct pre-baseline testing on these variables to reduce the largest levels of practice effects, which are typically observed after the initial point of testing [18], or covary out the influence of practice effects prior to examining whether the study medication positively or negatively affected cognition.

Minimal relationships were seen between PRL, SRT, DA dose, and disease severity (both duration and UPDRS score). DA dose was not associated with performance on either task, contrary to prediction and previous research indicating DA treatment may be differentially sensitive to DS-DLPFC and VS-OFC systems [2,4,5,7]. With regard to PD staging and performance on SRT, only disease duration emerged as a predictor of relearning. On PRL, disease duration and UPDRS score predicted performance on Phase 1 (initial learning). These results do not support the hypothesis that with disease progression, SRT performance declines but PRL performance improves as early focal DA excess would resolve. This lack of significant findings may be due to the use of a non-demented sample, as additional cognitive impairments may be found in more severe cases of PD. We also had a limited sample size, though consistent with other studies of cognitive function in PD, which limited our ability to detect small or medium effect sizes. Within the Huntington disease literature, much larger sample sizes have been needed to detect small effects with SRT and other computerized measures, and even these small effects were not consistently significant as a function of disease severity [19,20]. Our sample had a high level of education and was comprised of more males than females, which could limit generalizability. The present study did not utilize a healthy control group, so it is unclear how performance on PRL and SRT differed in individuals with PD versus controls. Motor impairment can also affect performance on computerized tasks; however, we removed individual trial scores falling greater than three standard deviations from the mean in order to minimize these effects. In longitudinal studies, calculating difference scores could be used to decrease the effects of potential outliers.

Taken together, our findings suggest that utilizing computerized SRT and PRL tasks may be useful in future clinical research with PD, as they are brief in their administration time requirements, are easy to understand and complete, and result in few missing data points, even in a diverse group of individuals with PD. On the other hand, the present study suggests that SRT and PRL may not help in
localizing cognitive difficulties to specific brain regions in the development of new pharmacological treatments.

The authors' conflicts of interest are as follows

Melissa Buelow: no disclosures.
Melissa Amick: Ortho-McNeil Pharmaceutical, Inc.
Sarah Queller: no disclosures.
Julie C. Stout: Consultancies: Prana Biotechnology, Teva Pharmaceuticals; Research funding: Teva Pharmaceuticals, Omeros Corporation, Prana Biotechnology, CHDI Foundation, National Health and Medical Council of Australia, the Australian Research Council.
Joseph Friedman: Teva (lectures); Teva, Acadia, Lundbeck, Roche, Pfizer, Auspex (consulting); National Institutes of Health, EMD Serono, Teva, Schering Plough, Avid (research); and Demos Press (royalties).
Janet Grace: no disclosures.

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References


