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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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Cognition is targeted as an outcome in many clinical trials of Parkinson's Disease (PD). Neuropsychological measures in these trials typically are individually administered, paper-and-pencil measures, ranging from brief global measures, such as the Mini-Mental Status Exam (MMSE), to domain-specific measures, such as the Hopkins Verbal Learning Test. Little research has examined the feasibility of computerized neuropsychological tests, specifically those assessing procedural sequence learning and probabilistic reversal learning, in clinical trials in PD [1–3]. Those studies

that have utilized computerized cognitive assessment were generally not part of clinical trials, with little focus on repeated assessment. In this study, we examine the feasibility of use of these tasks, which target specific dopamine (DA) sensitive brain regions, in a heterogeneous sample of non-demented individuals with PD. The present study furthers current research by examining these tasks as part of a clinical trial, to determine their feasibility for use in PD and with a repeated-measures paradigm. These two tasks have been linked to specific DA sensitive frontal-subcortical circuits. Specifically, spatial working memory, including procedural sequence learning, has been associated with the dorsolateral prefrontal cortex (dorsal-striatum-DLPFC circuit, DS-DLPFC) [1,4], whereas probabilistic reversal learning (PRL) has

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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. Further atrophy of the dorsal striatum may result in less benefit in performance mediated by the DS-DLPFC, whereas later PD-stage changes to the ventral striatum may result in improved performance on cognitive tasks mediated by the VS-OFC, such as PRL, and negate the focal DA excess.

Serial reaction time tasks (SRT) evaluate spatial working memory by having participants respond to cues in specific locations by pressing corresponding keys as quickly as possible. Although participants are not told they are seeing a fixed sequence, reaction time decreases as the spatial sequence is learned (implicit learning) [1]. By contrast, PRL involves adapting to changes in stimulus-reward contingencies [8]. A typical PRL task involves participants first learning a stimulus-reward pairing (Phase 1), and later shifting to learn an opposite stimulus-reward pairing (Phase 2). Among individuals with PD, non-medicated participants performed better on PRL than spatial working memory tasks, suggesting PRL is relatively preserved in early PD [1]. By contrast, among individuals with PD treated with DA replacement therapy, learning the PRL task reward contingencies had reversed was impaired but task-set switching on a separate task was enhanced [2]. Thus, these two tasks (PRL, SRT) are likely sensitive to the differential effects of DA replacement on different DA circuits.

We previously examined the utility of galantamine hydrobromide ER (Razadyne ER, formerly Remnyl) to improve cognition in non-demented PD patients [9]. Treatment with galantamine resulted in no significant improvements in attention, memory, or visuospatial perception over placebo. As part of the same study protocol, PRL and SRT computerized tasks were administered. The present study sought to examine feasibility of use of these computerized measures in longitudinal clinical trials, and to determine their sensitivity to a focal DA excess and the detection of differences in DS-DLPFC and VS-OFC functioning. We hypothesized that patients with a higher DA equivalent dose (dopamine dose summed across all DA sensitive medications) would perform worse on PRL but not SRT, consistent with research by Cools et al. [2] If PRL and SRT are sensitive to DA dose in a broad sample of non-demented PD participants, as indicated in Vallancourt et al. [4], then these computerized tasks could be utilized in clinical trials to detect the cognitive impact of medication-induced changes in DA levels within PD participants. We predicted better performance on PRL would be seen with later PD staging, and the opposite would be found on SRT, as earlier in the disease process DA therapy may lead to a focal DA excess in regions associated with PRL performance (i.e., VS-OFC). Lastly, we examined potential practice effects, which are especially important in longitudinal clinical trials in which cognition may be tested at baseline and various intervals after treatment onset. If there are strong practice effects, this could limit feasibility of their use in clinical trials.

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 clinicaltrials.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 1
Study data presented as mean (standard deviation).

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

Note: H&Y = 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.

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