NeuroRehabilitation 46 (2020) 311–320
DOI:10.3233/NRE-192940
IOS Press

Time course of cognitive training in Parkinson disease

Hoang M. Nguyen[a,b], Ashwin Aravindakshan[c], Jessica M. Ross[d] and Elizabeth A. Disbrow[a,b,e,*]
[a]*Department of Pharmacology, Toxicology, and Neuroscience, LSUHSC-Shreveport, Shreveport, LA, USA*
[b]*LSU Health Shreveport Center for Brain Health, Shreveport, LA, USA*
[c]*Graduate School of Management, UC Davis, Davis, CA, USA*
[d]*Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard Medical School, Boston MA, USA*
[e]*Department of Neurology, LSUHSC-Shreveport, Shreveport, LA, USA*

Abstract.
BACKGROUND: People with Parkinson disease (PD) have difficulty initiating internally generated movements. We have shown that computer-based cognitive training can improve movement initiation. However, little is known about the optimal duration of training.
OBJECTIVES: To determine the optimal training duration for computer-based neurorehabilitation of internally represented movement initiation in people with PD.
METHODS: Nineteen PD and twenty-one age-matched control participants, ages 50–85 years, were included in analysis of pre- and post-training evaluation and 30 training sessions. Computer training consisted of cued and un-cued movement trials. The presentation of a cue (a combination of numbers on either the right, left or both sides of the screen) indicated that participants should respond by typing the numbers. Successful cued trials were followed by un-cued trials consisting of a green filled circle. Participants re-enter the cued sequence, thus producing an internally represented (IR) movement. The training was adaptive. Outcome measures were reaction time and error rate, and cumulative sum (CUSUM) analysis was used to identify peak training improvement.
RESULTS: Participants with PD were divided into impaired (IPD) and unimpaired (UPD) groups, based on mean control group pre-training performance. All three groups showed improved RT and error rates for IR trials; however, the IPD group demonstrated significantly greater improvement in reaction time. Training was most effective in participants with greater disease severity and duration. Peak day of training improvement for the IPD group was 8 days.
CONCLUSION: Optimal training duration was relatively short and the IPD group demonstrated the most gain, indicating that cognitive training should be tailored to individual needs.

Keywords: Movement initiation, neurorehabilitation, adaptive training

1. Introduction

The timely production of a movement involves motor planning and movement initiation (Haith et al., 2016), both of which are impaired in Parkinson disease (PD; Siegert et al., 2002). Akinesia is a classic sign of PD which includes impaired movement preparation and initiation (Hallett, 1990) ranging from delayed reaction time to freezing (Spay et al. 2019). Slowness of movement impacts a wide range of functions including reach and grasp (Amano et al., 2015; Castiello et al., 2000), gait (e.g. Morris et al., 1994), physical activity level (Lana et al., 2015) and

*Address for correspondence: Elizabeth Disbrow, Department of Neurology, LSU Health Sciences Center, Shreveport, 1501 Kings Highway, Shreveport, LA 71130, USA. Tel.: +1 318 675 7184; E-mail: edisbr@lsuhsc.edu.

activities of daily living (Candan and Ozcan, 2019) in people with PD.

1.1. Movement initiation deficits

Deficits in movement initiation have been well described in Parkinson disease (PD). Specifically, internally represented movements are impaired while externally cued movements are relatively spared (Glickstein and Stein, 1991; Martin et al., 1994; Jahanshahi et al., 1995; Siegert et al., 2002). For example, Martin and colleagues (1994) measured the ability of people with PD to draw shapes while varying the level of visual input available. Reducing visual cues resulted in movements that were less stable and accompanied by signs of hypokinesia. The authors attributed the performance deficits to problems with internal cuing in people with PD. Similarly, Siegert and colleagues (2002) tested the hypothesis that people with PD initiated externally cued movements faster than self-initiated ones. PD and control subjects were given a two-button computer task simulating a traffic scenario to measure their reaction time with varying external cueing. Results showed that while controls had faster reaction times when self-initiating a button press, PD subjects had slower reaction time during self-initiated trials. The authors attributed slower reaction time during self-initiation trials and trials without a visual cue to deficits in movement initiation and planning, respectively, in PD.

1.2. Cognitive training

Cognitive neurorehabilitation is a growing field (Alzahrani and Venneri 2018) and in recent years, cognitive training has been shown to improve performance in elderly and PD populations (see Leung et al., 2015; Shah et al., 2017 and Walton et al., 2017 for reviews). In PD, training programs have targeted planning, switching, processing speed, attention and working memory. For example, Angelluci and colleagues (2015) reported improved planning ability related to cognitive training. For twelve 45-minute sessions over one month, seven PD participants in the experimental group were given adaptive cognitive training designed to improve set shifting ability. The training evaluation had two phases, an unstructured navigation task with minimal instruction and a similar task with specific sequence instructions. Following set shifting training, PD participants were able to perform the unstructured task with fewer errors.

While akinesia is not well controlled with dopamine replacement therapy (Favre et al., 2013; Fox, 2013), there is accumulating evidence that links akinesia to executive dysfunction (see Spay et al., 2019 for review). For example, Heremans and colleagues (2013) reviewed behavioral and neuroimaging studies of the link between cognitive function and akinesia (freezing of gait), and concluded that cognition is an important contributing factor. Furthermore, they identified the development of adequate rehabilitation strategies as an important target for future research. In fact, we have shown that computer-based neurorehabilitation can improve movement initiation (Disbrow et al., 2012). PD and control subjects participated in a 10-day computer-based neurorehabilitation program targeting internally represented button press number sequences. We found that training significantly reduced error rate and reaction time for sequence initiation. Furthermore, Walton and colleagues (2018) evaluated the impact of cognitive training on freezing of gait. Participants in the experimental condition received training targeting inhibitory control, set shifting, working memory, processing speed and visuospatial skills. The authors argued that executive dysfunction is a pathophysiological mechanism of freezing of gait. They found that cognitive training reduced freezing time during the Timed Up and Go task performed on dopamine replacement therapy. Thus, cognitive training can positively impact performance in PD, however optimal training parameters have not yet been identified.

1.3. Duration of cognitive training

Duration of training is an important factor that must be optimized to ensure efficiency. However, cognitive training duration varies widely across studies. For example, in a relatively short intervention Burki and colleagues (2014) used a 10-session protocol over the span of 2–4 weeks to evaluate working memory training with latent growth curve modeling (LGCM) in young and older adults. They examined 63 younger (average age = 24.85 years) and 65 older (average age = 67.98 years) adults who were assigned to one of three groups (working memory training, implicit sequence training, or no-contact control), and reported that both the younger and older groups exhibited improvement after training. In contrast, using a longer training period of 24 weeks, totaling 72 sessions, Klusmann and colleagues (2010) randomized two hundred and fifty-nine older female

participants (70–93 years old) into one of three groups: computer training, exercise training, or no-contact controls (Klusmann et al., 2010). Participants in the computer training group showed improved delayed story recall and maintained their performance level for delayed word recall, whereas the control group showed declining performance. While Burki et al., 2014 trained participants for 10 sessions over 2–4 weeks, Dahlin et al., 2008 trained participants for 15 sessions over 5 weeks, Cerasa et al., 2014 trained participants for 12 sessions over 6 weeks, Smith et al., 2009 trained participants for 40 sessions over 8 weeks, and Klusmann et al., 2010 trained participants for 72 sessions over 24 weeks, positive results are consistently reported. In fact, a recent review of cognitive training in PD (Alzahrani and Venneri 2018) lists a range of training duration from 3 weeks to 6 months, with the number of sessions varying from 4 to 180. In addition, the frequency of training sessions varied from once a day to once a week. Thus, cognitive neurorehabilitation in PD has been quite effective irrespective of the type of intervention (Alzahrani and Venneri 2018), however data on the optimization of training duration is sparse. Optimizing duration is important for maximizing returns, reducing fatigue and limiting patient burden, thereby potentially improving compliance. Furthermore, streamlining training administration could simplify distribution and improve cost effectiveness. Thus, we have evaluated gains in cognitive training over a 30-session bimanual computer-based training program for improving internally represented movement initiation in people with PD to identify peak improvement time.

2. Methods

2.1. Participants

Twenty subjects with PD (12 males, 8 females) and twenty-one controls (13 males, 8 females) were recruited from the VA Northern California Health Care System, Martinez, CA and Overton Brooks VA Medical Center in Shreveport, LA. This study was also registered with ClinicalTrials.gov, Identifier: NCT01085968. Participants were between the ages of 50–85. Participants with PD had a clinical diagnosis of PD and a history of good clinical response to levodopa and/or dopamine agonist treatment. Exclusion criteria were traumatic head or spine injury, brain tumor, stroke, history of drug abuse, significant symptoms of depression (Geriatric Depression Scale >20, to exclude possible "severe depression") and Mini-Mental State Exam score <20, to exclude possible "moderate dementia". In addition, participants with PD were given the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Rating Scale (H&Y). All participants with PD were treated using dopamine replacement therapy including levodopa with carbidopa, dopamine agonists, and/or COMT inhibitors. All participants provided written, informed consent prior to eligibility screening and the study was approved by an institutional review board.

2.2. Instruments

Subjects performed tests in a private room and testing lasted about an hour. The test battery was presented in a pseudorandomized order across participants. Each participant was evaluated twice: first during the initial visit (pre-training) and again during the return visit (post-training). Participants with PD were tested during their best ON medication state, for instance after taking their morning dose of medication. Best ON medication state was determined based on patient self-report.

Descriptive measures

- Hoehn and Yahr scale (H&Y; Hoehn & Yahr, 1967): A measure of PD severity.
- Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975): Estimates general cognitive function from orientation, registration, attention and calculation, recall, and language.
- National Adult Reading Test, Revised (NART-R; Blair & Spreen, 1989): The participant is asked to pronounce a series of 61 irregularly spelled words, and the tallied score estimates premorbid intellectual function.
- Geriatric Depression Scale (GDS; Yesavage et al., 1982): A measure of depressive symptoms in the form of a 30-item self-report.
- The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987): A clinical scale used to evaluate PD severity in multiple domains. A nurse practitioner trained in the use of the UPDRS administered the UPDRS interview and evaluation.

2.3. Computer-based training

Training was performed in-home, on a study-provided desktop computer with a QWERTY keyboard as the input device. Target input was limited to the following eight keys: A, S, D, F, J, K, L and:. For both hands, the index fingers, middle fingers, ring fingers, and little fingers corresponded to the numbers 1, 2, 3, and 4, respectively (Fig. 1). Training stimuli were presented on the computer monitor and performance was recorded using Neurobehavioral Systems, Inc. Presentation software.

The training program incorporated bimanual input into the training program previously described by Disbrow and colleagues in 2012. Each finger corresponded to a number from 1 to 4 (Fig. 1A). Subjects viewed a blank screen divided down the middle (Fig. 1B). A cue appeared consisting of numbers on the right, left or both sides of the screen (Fig. 1C-D). Participants typed the cue number combination. An externally cued (EC) response trial was followed by an internally generated (IG) response trial consisting of a green dot (Fig. 1E), signaling the participant to re-enter the cue number combination. The training component of this program was adaptive, beginning with easier (shorter) combinations followed by longer combinations based on performance. Training was adapted to maintain 87% accuracy rate.

Participants were evaluated with a non-adaptive version of the computer program before and after training. Performance was measured as reaction time from presentation of stimulus to sequence initiation (first button press) for correct response trials as well as error percentage. Incorrect response trials were not

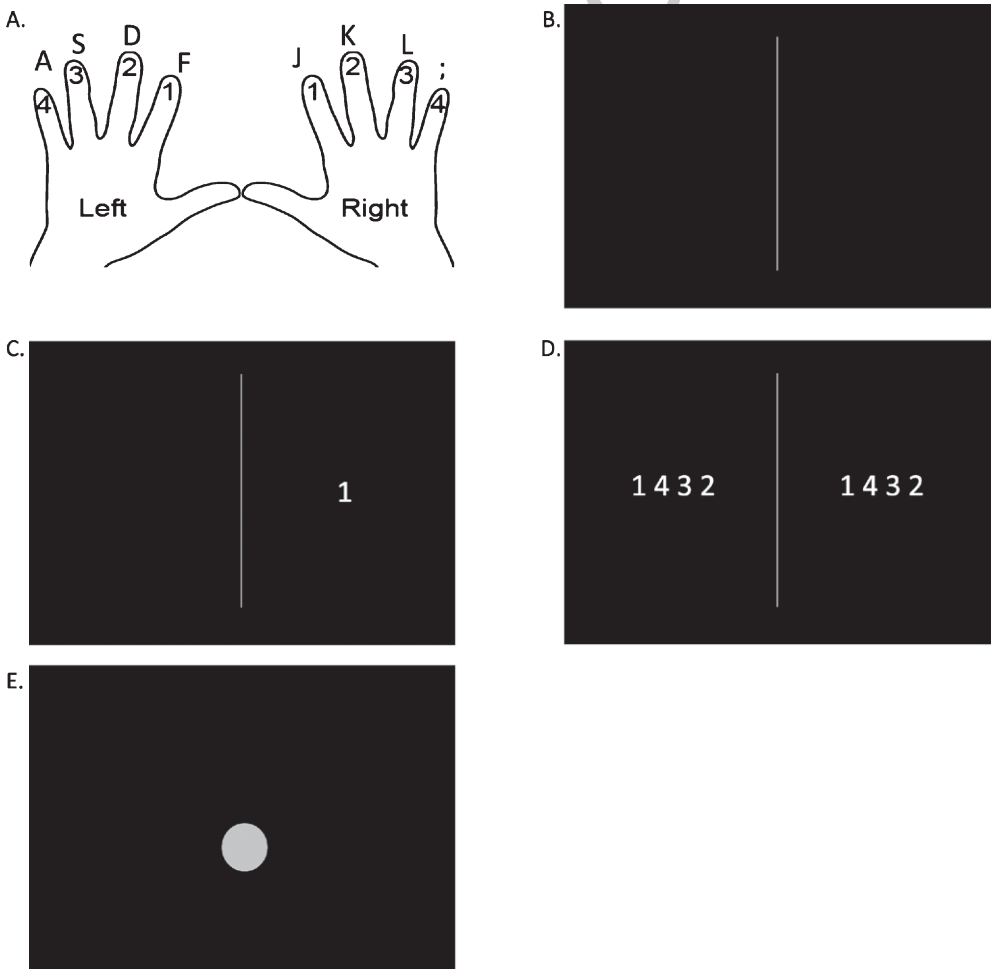

Fig. 1. Computer-based cognitive training on-screen display. A. Graphical representation of the finger digit-keyboard relationship, posted under the computer screen at all times. B. Inter-trial interval display. C. Example of single sided 1-digit stimulus. D. Example of bimanual 4 digit stimulus. E. Circle (green filled during training), representing stimulus for internally represented trial.

included in reaction time calculations. For the pre- and post-tests of the computer program, error percentage rate for each trial type was measured as the number of correct responses for that trial type divided by the sum of the number of errors plus the number of correct responses for that trial type. Reaction times and error rates were recorded for each trial of the pre- and post-tests. As in our previous work, a subset of the PD group performed similarly to the healthy control group. The control group's reaction times for the bimanual IR 4-digit trials were averaged and used as the value to differentiate the PD participants into either the impaired PD group (IPD) of the unimpaired PD group (UPD; Disbrow et al., 2012). This procedure, which was designed a priori, was the reason for collecting data from a healthy control group. We identified 11 IPD participants, and 9 UPD participants.

Participants trained for 30 sessions over a 6-week period and training time was about 40 minutes per day. Participants were instructed to train 5 days a week, at the same time each day, and date and time of training was recorded as part of the output file. All subjects completed the training program, however data from 1 PD subject was excluded because he completed multiple additional training sessions on a single day on multiple days. Participants were provided with a lab cell phone number to call if they experienced technical difficulties. Technical difficulties were minimal as the study computer displayed only 2 icons, one for the training program and one for the non-adaptive pre- and post-test. A few participants called to ask about which icon was which. The most common problem was that participants unplugged the computer, for example to vacuum or plug in a lamp, and then forgot to plug the computer back in. In these instances, an investigator went back to the home to clarify or troubleshoot. No adverse effects related to the training were reported throughout the study period.

2.4. Data analysis

Between groups analysis was performed using SPSS (SPSS version 23; http://www.ibm.com/analytics/us/en/technology/spss/). Between groups comparisons were made using Multivariate Analysis of Variance (MANOVA). Repeated measures ANOVA was used to determine within group interactions for pre- and post-training reactions times.

Cumulative sum charts were used to monitor the small gains in performance for the 4-digit bimanual trials for each day throughout the 30 days of training (Noyez 2009). For the cumulative sum (CUSUM) analysis, the number of sessions was equal to the number of days of training (30 days), therefore the x-axis units are in days. The CUSUM equation used was as follows:

$$\mathrm{CUSUM} = \mathrm{RT}_{\mathrm{Previous\ day}} + (\mathrm{RT}_{\mathrm{Current\ day}} - \mathrm{RT}_{\mathrm{Average\ (30\ days)}})$$

Using this equation, we determined the progress made on each day relative to the average performance over the span of 30 days. The maximum cumulative sum value was taken as the change point, corresponding to the training day with the greatest change in performance and thus the peak of training improvement. We completed a CUSUM chart for each study participant, then averaged the CUSUM values of each day for all participants in a given group to generate the group-based CUSUM values. The resulting CUSUM chart provided group specific analysis of training progress. For verification of CUSUM analysis results we used a bootstrap analysis with $n = 100{,}000$ samples. This analysis generated samples which randomly reordered the observed data in order to determine the likelihood that our data occurred at random (Chatterjee and Qiu 2009). For this analysis we used estimators of magnitude change (S_{Diff}) calculated from the difference of the minimum CUSUM value from the maximum CUSUM value. Confidence levels were reported as percentages, with greater percentage indicating higher likelihood that the original data set did not occur at random.

3. Results

Our training program consisted of a cue/target button-press task. First, subjects responded to externally cued (EC) trials comprised of digit sequences displayed on a computer screen. Subjects typed the sequences left-handed, right-handed, or with both hands sequentially. Digit sequences ranged from 1 to 4 digits and were identical on both sides for bimanual trials. Second, subjects were prompted by a green circle to produce the same sequence without the visual representation of the number sequence on the computer screen (internally represented trials; IR). PD subjects were differentiated into two groups, impaired (IPD) versus unimpaired (UPD), based on pre-training reaction time on the 4-digit bimanual IR trials. Outcome variables were reaction time and error

rate before and after training as well as day-to-day reaction time during the training program.

3.1. Pre-training group differences

Multivariate ANOVA was used to evaluate differences in pre-training data for demographic variables across the three groups (IPD, UPD, and Control; Table 1). Before training, the IPD, UPD, and control groups were similar for descriptive measures of age ($F(2,37) = 1.149$, $p = 0.328$), years of education ($F(2,37) = 0.937$, $p = 0.401$), mental status (MMSE; $F(2,37) = 0.499$, $p = 0.611$), and pre-morbid IQ (NART-R; $F(2,37) = 0.612$, $p = 0.547$). Gender distribution was evaluated via Chi-Square analysis and revealed no significant differences between groups ($X^{(2)} = 0.189$, $p = 0.910$). PD participants were on dopamine replacement therapy (dopamine equivalents; Table 1). The IPD group had greater disease severity and longer disease duration than the UPD group according to the UPDRS Total score (UPDRS, $F(1,17) = 5.241$, $p = 0.035$) and participant reported disease duration ($F(1,17) = 6.938$, $p = 0.017$). Additionally, the median H&Y score for the IPD group was 2.5 while the median H&Y score for the UPD group was 1.0 (Table 2). A significant main effect was also found for a measurement of depression (GDS; $F(2,37) = 6.380$, $p = 0.004$). Tukey's honestly significant difference (HSD) *post-hoc* pairwise comparisons indicated no difference between the Control group and the UPD group for depression (GDS; $p = 0.940$). However, the IPD group had significantly higher depression scores (IPD vs Control $p = 0.006$, IPD vs UPD $p = 0.016$; Table 2).

A one-way ANOVA was used to evaluate difference in pre-training data for IR reaction time across groups. We identified a significant main effect of group for 4-digit bimanual IR reaction time, $F(2,37) = 13.143$, $p < 0.001$. Tukey's HSD *post-hoc* pairwise comparisons indicated no difference between the Control group and the UPD group for 4-digit IR reaction time ($p = 0.401$). However, the IPD group had significantly longer reaction times than the Control group ($p < 0.001$) and the UPD group ($p < 0.001$; Fig. 2). A one-way ANOVA was also used to evaluate differences in pre-training 4-digit bimanual IR error rates across groups. We found a significant main effect for group, $F(2,37) = 4.541$, $p = 0.017$. Tukey's HSD *post-hoc* pairwise comparisons indicated no difference between the Control group and the UPD group ($p = 0.732$) as well as no difference between the IPD group and UPD group ($p = 0.206$). However, results showed that the IPD group had significantly higher error rates than the Control group ($p = 0.013$).

3.2. Pre- versus post-training differences

We used a repeated measures ANOVA to evaluate group differences in pre- versus post- training reaction times and error rates for the 4-digit bimanual IR response trials. We identified a significant main effect of training (decreased response time; $F(2,37) = 12.157$, $p < 0.001$). Tukey's HSD *post-hoc* pairwise comparisons revealed that the IPD group showed greater improvement in the 4-digit bilateral internally represented response trials as a result of the training compared to the Control group ($p < 0.001$) and the UPD group ($p = 0.001$). There was no

Table 1
Demographic Measures

	N	Age (years)	Education (years)	Dopamine equivalent (mg)
Control	21 ($F = 8$)	65.38 (7.10)	15.71 (3.48)	–
IPD	11 ($F = 5$)	68.91 (5.05)	14.91 (3.67)	598.41 (333.62)
UPD	8 ($F = 3$)	66.50 (6.63)	17.00 (1.85)	416.06 (405.24)

Table 2
Descriptive and PD specific measures

	NART-R	MMSE	GDS*†	Disease duration (years)†	UPDRS Total score†	H&Y (median)
Control	114.21 (7.74)	29.00 (1.00)	3.86 (4.25)	–	–	–
IPD	114.26 (8.34)	28.73 (2.24)	9.18 (5.19)	8.36 (3.98)	43.82 (17.81)	2
UPD	117.56 (6.12)	29.37 (0.52)	3.25 (3.24)	4.25 (2.19)	27.44 (11.08)	1.00

*IPD vs CO, $p < 0.05$. †IPD vs UPD, $p < 0.05$.

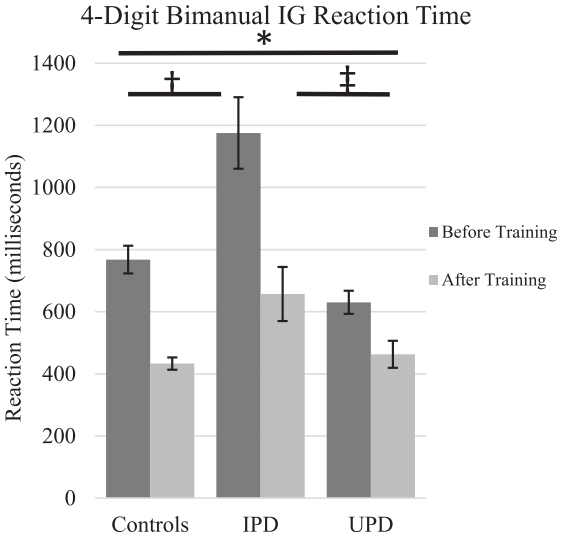

Fig. 2. Average reaction times for the control, IPD and UPD groups for the 4-digit bimanual internally generated response trials, before and after training. *Reaction time before vs after by group; $p < 0.05$. †CO vs IPD Repeated Measures ANOVA; $p < 0.05$. ‡IPD Vs UPD Repeated Measures ANOVA; $p < 0.05$. Error bars represent standard error.

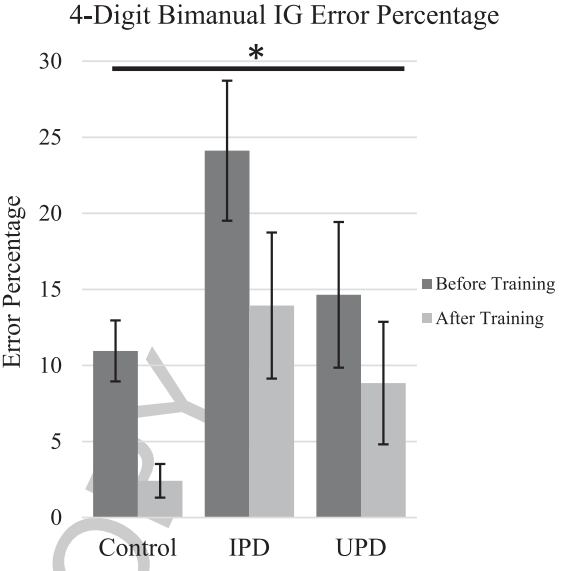

Fig. 3. Error percentage for the control, IPD and UPD groups for the 4-digit bimanual internally generated response trials before and after training. Conventions as in previous figures. *Error percentage before vs after training by group; $p < 0.05$.

significant difference between the Control group and the UPD group ($p = 0.799$) (Fig. 2). We identified improvement over time for all groups 4-digit IR error rates, $F(1,37) = 17.017$, $p < 0.001$, indicating improvement post- versus pre-training for all 3 groups. However, there was no significant interaction for Training x Group, $F(2,37) = 0.332$, $p = 0.720$ (Fig. 3).

3.3. Cumulative sum analysis

We used a Cumulative Sum (CUSUM) analysis, which is typically used to detect small changes in performance over time, to determine the time to peak improvement. The Control group attained maximum training improvement in 10 days. The IPD group attained peak training improvement in 8 days. The UPD group attained peak training improvement in 9 days (Fig. 4). To verify these results, we performed a bootstrapping analysis, which showed the confidence level to be 100%, 100% and 99.81% for the control, IPD and UPD groups, respectively. The resulting confidence levels obtained from the bootstrap analysis demonstrate that our CUSUM analysis results were statistically significant and did not occur at random.

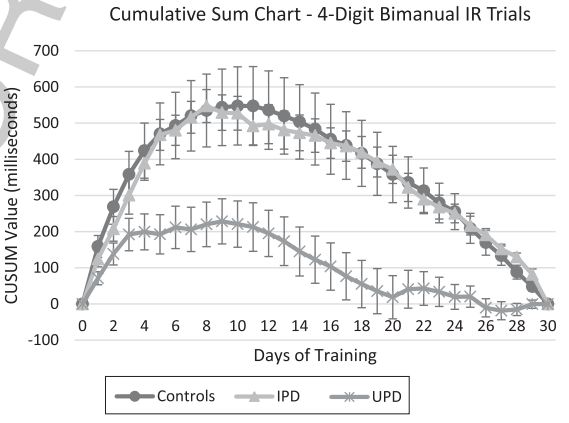

Fig. 4. Cumulative sum chart of the 4-digit bimanual internally generated response trials. Error bars represent standard error. Maximum points in the curve indicate the peak day of training. For the IPD, UPD, and control groups, the peak days of training are 8, 9, and 10 days, respectively.

4. Discussion

The purpose of our study was to determine the optimal training duration for computer-based cognitive rehabilitation of movement initiation in people with PD. First, we showed that our cognitive training resulted in performance improvement in participants with movement initiation deficits prior to training. Though subject groups were similar for most demo-

graphic variables, the impaired group, which showed the greatest training improvement, had significantly greater disease severity and longer disease duration. Second, we used CUSUM analysis to determine the optimal training duration for this task. The CUSUM chart revealed that the peak training day of improvement for the control, IPD and UPD groups were 10, 8, and 9 days, respectively.

4.1. Training effectiveness

As in our previous work (Disbrow et al., 2012) we found that improvements in reaction time were greater in PD participants with pre-training deficits. Previously we studied 30 PD subjects and 21 healthy controls who participated in a 10-day computer-based neurorehabilitation program. The program consisted of an adaptive externally cued and internally represented button press paradigm. As in the current study, PD participants were classified as "impaired" or "unimpaired" based on performance on the pre-training assessment. Results showed that after training, PD and control groups showed similar improvement for sequence initiation and sequence completion for the externally cued trials. However, PD subjects with impairment before training displayed significantly greater improvement in error rate and reaction time for sequence initiation for the internally represented trials compared to age-matched controls and PD participants who were not impaired before training (Disbrow et al., 2012). Similarly, Walton and colleagues (2018) showed freezing of gate improvement after training in a group of PD participants who were impaired on the outcome measure before training. This group consisted of participants who were severely impaired enough to show freezing of gait in the lab during evaluation. We divided participants into two groups, one showing impairment and one performing close to control level, because there is likely a performance ceiling limiting further improvement in the group performing at or near control levels. Furthermore, the interaction between training and group demonstrates that within the PD population, there are subgroups that are more likely to respond to training that can be identified based on pre-training deficits.

Deficit specific improvements may also explain discrepancies in the literature about the effectiveness of cognitive training. For example, Tusch and colleagues (2016) used event-related potentials (ERP) to measure brain activity and performance of subjects who had undergone adaptive computerized cognitive training of working memory function ($n = 17$) 5 days per week for 40 minutes per day for 5 weeks compared to subjects who received active control non-adaptive training. While results revealed differences between the adaptive training group and the control group for brain activity associated with attention and categorization, there was no apparent association between training and performance improvement for the task. However, the sample did not clearly show impaired performance on any of the cognitive measures before training, underscoring the importance of matching training to existing deficits.

4.2. Optimizing training duration

Optimizing training is key to efficient and effective neurorehabilitation interventions, and several important factors have been identified. First, we showed that training is most effective when the cognitive domain of the intervention is matched to the specific deficits of the trainee (Disbrow et al., 2012). Our results also suggest that training is more effective in patients with moderate (H&Y 2.5), as opposed to mild (H&Y 1.0) disease severity. In addition, Walton and colleagues (2017) reviewed cognitive training in PD and suggested that training at the PDD stage may not be effective. Furthermore, we identified the optimal number of training sessions for movement initiation in people with PD. The CUSUM chart has been used previously to monitor proficiency levels for trained skills (Song et al., 2018; Cho et al., 2014; Waller and Connor 2009). For example, Song and colleagues (2014) used CUSUM charts to measure surgical skills proficiency by determining the number of surgical procedures a surgeon needed to perform in order to overcome the learning curve hurdle for that procedure (Song et al., 2018). Similarly, Cho and colleagues (2014) used CUSUM analyses to measure competence and trainee proficiency in retrograde intrarenal stone surgery.

Our findings regarding training duration are consistent with existing research. For example, In an animal model Tennant and colleagues (2012) investigated training duration and cortical representation reorganization in the motor cortex in mice. Mice were randomly assigned to one of three training conditions: reach training, pasta handling, or untrained control. For each of these training conditions, there were two training durations: short (daily for 2–4 weeks) and long (daily for 8 weeks). Intracortical microstimulation mapping was used to identify hand representation reorganization in the motor cortex.

Eight-week training resulted in greater change than 2–4 week training, however, as in our study, performance improvement was rapid in the first 10 days and changed at a more gradual rate thereafter. Similarly, Lampit and colleagues (2014) found that 36 cognitive training session over 3 months resulted in improved performance on measures of processing speed and memory compared to active control training in elderly with multiple dementia risk factors. They found that the therapeutic effect of processing speed training peaked at 9 sessions, as in our study, and then declined after 36 sessions. In contrast, memory performance continued to improve over the 36 sessions. The authors suggest that training may work differently across cognitive domains, however it is also possible that memory training results were related to the study population which was at elevated risk for dementia. Lampit and colleagues (2014) describe a 3 phases dose response based on therapeutic effect. First, an initial 10 training session period of rapid improvement is termed a "loading dose," followed by "titration" including diminished returns and a period during which additional training becomes ineffective, and third, the post training maintenance phase. Thus, multiple lines of training data, including animal models of cortical reorganization and therapeutic outcome in people at risk for dementia are in agreement with our finding of 8–10 days optimal training duration for movement initiation in people with PD. In addition, Lampit and colleagues (2014) report durable improvement in cognitive function for 3 months following cessation of training. However, questions still remain about the timing and effectiveness of interval training. Additional study is needed to identify the optimal interval between training sessions to maximize output and minimize training demands.

4.3. Limitations

Our study has several limitations. First, our training program was not a classic cognitive training paradigm. Other investigators (e.g. Lampit et al., 2014; Walton et al., 2018) based their training on commercially available tasks that included processing speed and executive function elements. Our task was designed to specifically target movement initiation; therefore our results may not generalize to more traditional cognitive training paradigms. Second, our task had a working memory component. Because we were measuring reaction time, we used an uninformative cue and the participant was required to produce the number sequence from memory. Thus, it is possible that the improvements that we saw in performance were based on improved working memory, though we did designate a working memory deficit as an exclusion criteria. Third, while the impaired PD group did show significant improvement in task performance, they did not reach control performance levels. Future research is needed to determine if nine days of training results in a performance ceiling or if additional sessions can drive further improvement. Furthermore, optimal session interval remains to be determined. Finally, we did not show that training on our movement initiation task improved real world function. However, in our previous work (Disbrow et al. 2019) we did evaluate timed instrumental activities of daily living and motor performance. We found that training on a similar task was not associated with improved performance of instrumental activities of daily living. We found a trend for improvement on the Timed Up and Go ($F(2,48) = 3.24$, $p = 0.048$ uncorrected). Thus, real world application of this training should be interpreted with caution.

Conflict of interest

The authors have no affiliation with any organization with a financial interest, direct or indirect, in the subject matter or materials discussed in the manuscript. Funding for this work was provided by a grant from the Veterans Administration office of Research and Development (1I01 RX000181) to ED.

References

Acaröz Candan, S., & Özcan, T. Ş. (2019). Dual-task interference during hand dexterity is a predictor for activities of daily living performance in Parkinson's disease. *Parkinsonism and Related Disorders*, (December 2018), 0–1. https://doi.org/10.1016/j.parkreldis.2019.07.017

Alzahrani, H., & Venneri, A. (2018). Cognitive Rehabilitation in Parkinson's Disease: A Systematic Review. *Journal of Parkinson's Disease*, *8*(2), 233–245. https://doi.org/10.3233/JPD-171250

Amano, S., Hong, S. L., Sage, J. I., & Torres, E. B. (2015). Behavioral inflexibility and motor dedifferentiation in persons with Parkinson's disease: bilateral coordination deficits during a unimanual reaching task. *Neuroscience Letters*, *585*, 82–87. https://doi.org/10.1016/j.neulet.2014.10.007

Blair, J. R., & Spreen, O. (1989). Predicting premorbid IQ: A revision of the national adult reading test. *Clinical Neuropsychologist*, *3*(2), 129–136. https://doi.org/10.1080/13854048908403285

Burki, C. N., Ludwig, C., Chicherio, C., & de Ribaupierre, A. (2014). Individual differences in cognitive plasticity: an investigation of training curves in younger and older adults. *Psychological Research*, *78*(6), 821–835. https://doi.org/10.1007/s00426-014-0559-3

Castiello, U., Bennett, K. M., Bonfiglioli, C., & Peppard, R. F. (2000). The reach-to-grasp movement in Parkinson's disease before and after dopaminergic medication. *Neuropsychologia*, *38*(1), 46–59. https://doi.org/10.1016/s0028-3932(99)00049-4

Chatterjee, S., & Qiu, P. (2009). Distribution-free cumulative sum control charts using bootstrap-based control limits. *Annals of Applied Statistics*, *3*(1), 349–369. https://doi.org/10.1214/08-AOAS197

Cho, S. Y., Choo, M. S., Jung, J. H., Jeong, C. W., Oh, S., Lee, S. B., & Jeong, H. (2014). Cumulative sum analysis for experiences of a single-session retrograde intrarenal stone surgery and analysis of predictors for stone-free status. *PloS One*, *9*(1), e84878. https://doi.org/10.1371/journal.pone.0084878

Disbrow, E. A., Russo, K. A., Higginson, C. I., Yund, E. W., Ventura, M. I., Zhang, L., & Sigvardt, K. A. (2012). Efficacy of tailored computer-based neurorehabilitation for improvement of movement initiation in Parkinson's disease. *Brain Research*, *1452*, 151–164. https://doi.org/10.1016/j.brainres.2012.02.073

Favre, E., Ballanger, B., Thobois, S., Broussolle, E., & Boulinguez, P. (2013). Deep brain stimulation of the subthalamic nucleus, but not dopaminergic medication, improves proactive inhibitory control of movement initiation in Parkinson's disease. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *10*(1), 154–167. https://doi.org/10.1007/s13311-012-0166-1

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fox, S. H. (2013). Non-dopaminergic treatments for motor control in Parkinson's disease. *Drugs*, *73*(13), 1405–1415. https://doi.org/10.1007/s40265-013-0105-4

Glickstein, M., & Stein, J. (1991). Paradoxical movement in Parkinson's disease. *Trends in Neurosciences*, *14*(11), 480–482. https://doi.org/10.1016/0166-2236(91)90055-y

Haith, A. M., Pakpoor, J., & Krakauer, J. W. (2016). Independence of movement preparation and movement initiation. *Journal of Neuroscience*, *36*(10), 3007–3015. https://doi.org/10.1523/JNEUROSCI.3245-15.2016

Hallett, M. (1990). Clinical neurophysiology of akinesia. *Revue Neurologique*, *146*(10), 585–590.

Heremans, E., Nieuwboer, A., Spildooren, J., Vandenbossche, J., Deroost, N., Soetens, E., & Vercruysse, S. (2013). Cognitive aspects of freezing of gait in Parkinson's disease: A challenge for rehabilitation. *Journal of Neural Transmission*, *120*(4), 543–557. https://doi.org/10.1007/s00702-012-0964-y

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology*, *17*(5), 427–442. https://doi.org/10.1212/wnl.17.5.427

Jahanshahi, M., Jenkins, I. H., Brown, R. G., Marsden, C. D., Passingham, R. E., & Brooks, D. J. (1995). Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain: A Journal of Neurology*, *118 (Pt 4*, 913–933. https://doi.org/10.1093/brain/118.4.913

Klusmann, V., Evers, A., Schwarzer, R., Schlattmann, P., Reischies, F. M., Heuser, I., & Dimeo, F. C. (2010). Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *65*(6), 680–688. https://doi.org/10.1093/gerona/glq053

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized Cognitive Training in Cognitively Healthy Older Adults: A Systematic Review and Meta-Analysis of Effect Modifiers. *PLoS Medicine*, *11*(11). https://doi.org/10.1371/journal.pmed.1001756

Lana, R. de C., de Araujo, L. N., Cardoso, F., & Rodrigues-de-Paula, F. (2016). Fatores determinantes do nível de atividade física de indivíduos com doença de Parkinson. *Arquivos de Neuro-Psiquiatria*, *74*(2), 112–116. https://doi.org/10.1590/0004-282X20160009

Leung, I. H. K., Walton, C. C., Hallock, H., Lewis, S. J. G., Valenzuela, M., & Lampit, A. (2015). Cognitive training in Parkinson disease: A systematic review and meta-analysis. *Neurology*, *85*(21), 1843–1851. https://doi.org/10.1212/WNL.0000000000002145

Martin, K. E., Phillips, J. G., Iansek, R., & Bradshaw, J. L. (1994). Inaccuracy and instability of sequential movements in Parkinson's disease. *Experimental Brain Research*, *102*(1), 131–140. https://doi.org/10.1007/bf00232445

Morris, M. E., Iansek, R., Matyas, T. A., & Summers, J. J. (1994). The pathogenesis of gait hypokinesia in parkinson's disease. *Brain*, *117*(5), 1169–1181. https://doi.org/10.1093/brain/117.5.1169

Noyez, L. (2009). Control charts, Cusum techniques and funnel plots. A review of methods for monitoring performance in healthcare. *Interactive Cardiovascular and Thoracic Surgery*, *9*(3), 494–499. https://doi.org/10.1510/icvts.2009.204768

Shah, T. M., Weinborn, M., Verdile, G., Sohrabi, H. R., & Martins, R. N. (2017). Enhancing Cognitive Functioning in Healthly Older Adults: a Systematic Review of the Clinical Significance of Commercially Available Computerized Cognitive Training in Preventing Cognitive Decline. *Neuropsychology Review*, *27*(1), 62–80. https://doi.org/10.1007/s11065-016-9338-9

Spay, C., Meyer, G., Welter, M. L., Lau, B., Boulinguez, P., & Ballanger, B. (2019). Functional imaging correlates of akinesia in Parkinson's disease: Still open issues. *NeuroImage: Clinical*, *21*(December 2018). https://doi.org/10.1016/j.nicl.2018.101644

Walton, C. C., Mowszowski, L., Gilat, M., Hall, J. M., O'Callaghan, C., Muller, A. J., & Lewis, S. J. G. (2018). Cognitive training for freezing of gait in Parkinson's disease: a randomized controlled trial. *Npj Parkinson's Disease*, *4*(1), 1–9. https://doi.org/10.1038/s41531-018-0052-6

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, *17*(1), 37–49. https://doi.org/10.1016/0022-3956(82)90033-4