Clinical pharmacology studies investigating novel formulations of dopaminergic drugs

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CHAPTER 6

A placebo-controlled study to assess the sensitivity of finger tapping to medication effects in Parkinson's disease

Mov Disord Clin Pract. 2022;9(8):1074-1084. doi: 10.1002/mdc3.13563

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ABSTRACT

Background Movement Disorder Society–Unified Parkinson's Rating Scale part III (MDS-UPDRS III) is the gold standard for assessing medication effects in patients with Parkinson's disease (PD). However, short and rater-independent measurements would be ideal for future trials.

Objectives To assess the ability of three different finger tapping tasks to detect levodopa/carbidopa-induced changes over time, and to determine their correlation and compare their discriminatory power with MDS-UPDRS III.

Methods Randomized, double-blind, crossover study in 20 PD patients receiving levodopa/carbidopa and placebo capsules after overnight medication withdrawal. Pre- and up to 3.5 hours post-dose, MDS-UPDRS III and tapping tasks were performed. Tasks included two touchscreen-based alternate finger tapping tasks (index finger versus index-middle finger tapping) and a thumb-index finger task using a goniometer.

Results In the alternate index finger tapping task, levodopa/carbidopa compared with placebo resulted in significantly faster (total taps: 12.5 (95% confidence interval (CI), 6.7-18.2)) and less accurate tapping (total spatial error: 240 mm (123-357 mm)) with improved rhythm (inter-tap interval standard deviation (SD): -16.3% (-29.9%-0.0%)). In the thumb-index finger task, tapping was significantly faster ((mean opening velocity: 151 degree/s (64-237 degree/s)), with higher mean amplitude ((8.4 degrees (3.7-13.0 degrees)) and improved rhythm ((inter-tap interval SD: -46.4% (-63.7% to -20.9%)). The speed-related endpoints showed a moderate-to-strong correlation with the MDS-UPDRS III (r=0.45-0.70). The effect sizes of total taps and spatial error in the alternate index finger tapping task, and opening velocity in the thumb-index finger task were comparable to MDS-UPDRS III. In contrast, the MDS-UPDRS III performed better than the alternate index-middle finger task.

Conclusion The alternate index finger and the thumb-index finger tapping tasks provide short, rater-independent measurements that are sensitive to levodopa/carbidopa effects with a similar effect size as the MDS-UPDRS III.

INTRODUCTION

The Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is considered the gold standard for assessing (dopaminergic) medication effects.[1] Part III of the scale is often used in clinical trials to show motor improvements after medication intake. However, part III requires a trained rater who preferably assesses a patient throughout the entire trial to avoid inter-rater variability. Additionally, the assessment takes relatively long (i.e., approximately 15 minutes, but depends on the patient's clinical state). This makes accurate time-response assessment of fast-acting agents challenging, especially when safety and pharmacokinetic measurements also need to be performed. Hence, a short, rater-independent measurement would be ideal for use in clinical trials.
Literature has shown that finger tapping can be used to show differences between healthy controls and PD patients,[2-7] and between medication states (*ON*/*OFF*).[3,5,6,8,9] Moreover, various finger tapping configurations have shown correlation with the MDS-UPDRS part III.[3-6,8,10] However, the set-up and devices used for these tapping tasks vary among studies and it is unclear which is best suitable for determination of medication effects in randomized placebo-controlled trials.

In this randomized, double-blind, placebo-controlled trial, we assessed the response to dopaminergic medication during an induced *OFF* state in PD patients by using the gold standard MDS-UPDRS III as well as three different tapping tasks. For this, two touchscreen-based alternate finger tapping tasks (with 2.5 or 20 cm between targets) and a task using a goniometer that assesses angular movement during thumb-index finger tapping, were developed in-house. The aim was to validate these tapping tasks by demonstrating their ability to detect and quantify acute pharmacodynamic effects over time. Moreover, we evaluated whether the finger tapping endpoints correlated with MDS-UPDRS III.

METHODS

This study is registered in the Netherlands Trial Register (Trial NL8617), and was conducted at the Centre for Human Drug Research (Leiden, the Netherlands) between July and November 2020.

Study design

This was a randomized, double-blind, placebo-controlled, two-way crossover study in 20 PD patients. A sample size of 18 was considered sufficient to show a treatment effect based on a paired t-test with 80% power and a two-sided alpha level of 5%, assuming an expected difference on the best response of 8 total taps (SD=7) between placebo and treatment.[11] To be conservative, it was decided to include 20 patients. The study consisted of a screening visit followed by two treatment periods of two days each, with a 1-week washout between periods. Patients were randomized 1:1 to one of two treatment sequences (levodopa/carbidopa - placebo, or vice versa). The randomization code was generated using SAS v9.4 by a study-independent statistician. Patients were instructed to withhold their own anti-Parkinson medication in the evening prior to treatment in both treatment periods. Patients were dosed the next morning when in an *OFF* state, as assessed by the physician. Patients were allowed to resume their own medication 110 minutes after dosing, or, if feasible for the patient, after the last efficacy assessments 210 minutes post-dose.

Participants

PD patients with self-described motor fluctuations and recognizable *OFF* periods aged between 20-85 years with Hoehn and Yahr stage I-III were eligible for participation. In addition, patients had to be levodopa responsive as evidenced by current or historical use of levodopa. Reasons to exclude a patient were a previous intolerance, a potentially relevant interaction of co-medication with or a contra-indication to levodopa and/or carbidopa. Patients were ineligible when the levodopa equivalent dose (LED) of their morning medication exceeded 500 mg.

Investigational drugs

To ensure blinding, levodopa/carbidopa 100/25 mg (Sinemet) tablets were over-encapsulated in 00 gelatin (Swedish orange) capsules. Similarly, placebo tablets were over-encapsulated. Patients received a semi-individualized dose based on the LED of their morning medication. To calculate the LED, conversion factors as described by Tomlinson et al were used.[12] For long-acting dopamine agonists, only 25% of their LED was included, since only their acute effect was of importance for calculation of the morning LED. Finally, the LED was multiplied by 1.25 to ensure a supramaximal dose was given that was at least 25% higher than the usually administered morning dose (to ensure *OFF-ON* transition). This supramaximal LED was rounded up to a whole number of levodopa/carbidopa 100/25 mg (or placebo) capsules that was required for that patient. Since food, and especially proteins can affect the absorption of levodopa, study drug administration occurred at least 1 hour after finishing a protein-restricted breakfast and food was not allowed until 1 hour after dosing.

Safety

Patients enrolled in this study were already using levodopa or had used it in the past. Therefore, they were expected to tolerate the study treatment well. Nonetheless, subject safety was evaluated by monitoring of adverse events throughout the study, and by examining the patient's vital signs, ECG and physical/neurological examination before discharge. As no notable changes were observed, these data are not shown.

Outcome measures

MDS-UPDRS

MDS-UPDRS part III was used to assess motor function. Physicians administering the scale were trained in its use. To the degree feasible, the same physician evaluated a patient during both treatment periods at Day -1 (day before dosing) and at Day 1 pre-dose and 10, 30, 60, 90 and 210 minutes post-dose. The last measurement was

only performed when the patient had not yet resumed their own medication.

TOUCHSCREEN-BASED TAPPING TASKS[13]

1 Alternate index and middle finger tapping: task in which the patient was instructed to alternately tap with the index and middle finger on two circles (radius 1.2 cm) spaced 2.5 cm apart (Figure 1A).
2 Alternate index finger tapping: task in which the patient was instructed to alternately tap with the index finger on two circles (radius 1.7 cm) spaced 20 cm apart (Figure 1B).

For both tasks, the instructions were to tap as accurately and as fast as possible for 30 seconds with the hand most affected by PD (or the dominant hand if both sides were equally affected). Calculated endpoints were: total number of taps, total taps inside the target, ratio good: total taps, number of halts, mean inter-tap interval, SD of inter-tap intervals, inter-tap interval change, mean spatial error, SD of spatial error, spatial error change, and total spatial error. Refer to Supplemental Table 1 for a description of each endpoint.

THUMB-INDEX FINGER TAPPING

A goniometer (Biometrics Ltd, UK) placed on the proximal phalanx and metacarpal of the index finger of the most affected (or dominant if both sides were equally affected) hand measured the angle of the index finger (Figure 1C). Patients were instructed to tap the index finger on the thumb as quickly and as wide as possible for 15 seconds. Calculated endpoints included: total number of taps, mean inter-tap interval, SD of inter-tap intervals, inter-tap interval change, mean tapping amplitude, tapping amplitude change, peak frequency area under the curve (AUC), angle frequency change, and mean opening and closing velocity (Supplemental Table 1).

Patients were trained on all three tapping tasks twice on Day -1 and once on Day 1 pre-dose. These measurements were not used in the analysis. Finger tapping tasks included in the analyses were performed on Day 1 pre-dose (double baseline) and approximately 10, 25, 45, 60, 75, 90, 105, and 210 minutes post-dose (if time points coincided with MDS-UPDRS III, then finger tapping tasks were performed first, followed by MDS-UPDRS III). The last measurement was only performed when the patient had not yet resumed their own medication.

Data exclusion

In case the ratio good: total taps was <0.3 in the alternate index and middle finger tapping task, inter-tap interval parameters (mean, SD, change) and number of halts could not be reliably calculated, so were excluded from analysis. One patient seemed unable to correctly perform and/or the device did not correctly record the alternate index and middle finger tapping, so this task was completely excluded from analysis for this patient.

Statistical analysis

Analyses were performed using SAS v9.4. To detect significant treatment effects on the primary endpoints, each endpoint was analyzed using a mixed model analysis of variance with period, treatment, time, and treatment by time as fixed factors, subject and subject by time as random factors, and the average baseline measurement as covariate. Homoscedasticity assumption of the mixed modelling framework was relaxed by allowing separate variance estimates for each treatment. Within the model, the contrast levodopa/carbidopa versus placebo was calculated based on all post-dose measurements. In case of non-normality, endpoints with positive numerical results were re-analyzed after log-transformation. For ten endpoints, no models could be fitted since they violated the normality assumption, even after log-transformation.

Pearson's or Spearman's (in case of non-normal or log-normal data) correlation was used to evaluate the relationship between finger tapping endpoints and MDS-UPDRS III at a selected time point (90 min for MDS-UPDRS and 105 min (after completion of MDS-UPDRS at 90 min) for tapping). Correlation analysis was performed for placebo and levodopa/carbidopa separately. The strength of the correlation was classified as weak (r<0.40), moderate (r=0.40-0.59), strong (r=0.60-0.79) or very strong (r=0.80-1.0).

For both analyses, a p-value of ≤0.05 was used as cut-off for determining significance. No correction for multiple testing was performed due to the exploratory nature of this study.

Standardized effect sizes were calculated by dividing the Least Squares Means (LSMs) difference (levodopa/carbidopa - placebo) by the pooled SD of the treatment effect. The pooled SD was calculated with the formula described by Brown et al.[14] A Hedge's g correction was done to account for small sample size. Effect sizes were calculated for comparison of endpoints and tasks, but are not intended for future power calculations (model-based estimates to be used).

RESULTS

Baseline characteristics

The number of patients screened, randomized, completed and analyzed are summarized in the CONSORT flow diagram in Supplemental Figure 1. Table 1 outlines the demographics and baseline characteristics of the 20 PD patients that completed the study. Most (95%) patients received a levodopa-containing agent as part of their regular medication regimen. Supramaximal morning LED ranged between 47 and 391 mg. Therefore, patients received between 1-4 capsules of levodopa/carbidopa 100/25 mg and placebo in a randomized order.

Overall task performance

For 6 out of 20 PD patients, the alternate tapping task with the index and middle finger was sometimes difficult to correctly perform. Difficulty was being defined as having a ratio of good: total taps less than 0.3 on at least 4 of 22 performed tests (but this reached up to 17 of 22 tests). Difficulties were approximately equally divided over placebo and levodopa/carbidopa tests. One patient seemed unable to correctly perform and/or the device did not correctly record the alternate index and middle finger tapping. This was concluded based on taps only being recorded during the first few seconds or by gaps of >10 seconds where no taps were recorded (in the absence of freezing). With the alternate index finger tapping and thumb-index finger tapping tasks, the patients usually did not experience any difficulties. However, the goniometer devices used for the thumb-index finger tapping task turned out fragile and broke in a few instances. This led to missing data for one patient after placebo, and two patients after levodopa/carbidopa treatment.

Treatment and treatment by time effects

After placebo treatment, 14 out of 20 patients had to resume their own Parkinson's medication prior to the last assessment planned at 3.5 hours post-dose. After levodopa/carbidopa, this was 6 out of 20. Meaning that the MDS-UPDRS III and finger tapping measurements at 3.5 hours were performed in n=14 levodopa/carbidopa- and n=6 placebo-treated patients.

Table 2 shows treatment and treatment by time effects for the gold standard MDS-UPDRS III and the three tapping tasks. In Figure 2, the LSMs (geometric LSMs for back-transformed data) change from baseline data over time are depicted for MDS-UPDRS III and a subset of three endpoints of each tapping task that showed to be significant in Table 2. For graphs of the other finger tapping endpoints, refer to Supplemental Figure 2.

The MDS-UPDRS III showed a significant treatment effect and treatment by time interaction effect (Table 2), as is also visualized in Figure 2A. For the alternate index and middle finger tapping task, it was shown that levodopa/carbidopa compared to placebo resulted in significantly faster (i.e., lower mean inter-tap interval) and more accurate tapping (i.e., more total taps inside target and higher ratio good: total taps) (Table 2, Figure 2B). No significant treatment effect, but a significant treatment by time interaction effect was found for the total number of taps, indicating that at least at one time point there was a significant difference between placebo and levodopa/carbidopa. Even though a significantly lower inter-tap interval SD, i.e., improved rhythm, was found for levodopa/carbidopa compared to placebo, it did not show a clear time-related response (Figure 2B). Spatial error and number of halts were not significantly different between active and placebo treatment.

Also in the alternate index finger tapping task, significantly faster tapping (increased total number of taps, and as a result, total taps inside the target) was observed after levodopa/carbidopa compared to placebo treatment (Table 2, Figure 2C). In contrast, accuracy was significantly reduced as observed by a higher mean and total spatial error. Lastly, levodopa/carbidopa compared to placebo resulted in a better tapping rhythm as observed by a lower SD of the inter-tap intervals, which showed a clear time-related response.

In the thumb-index finger tapping task, levodopa/carbidopa did not only result in significantly faster tapping (higher mean opening and closing velocities), but also in an increased mean tapping amplitude (Table 2, Figure 2D). Another measure of amplitude, peak frequency area under the curve, was also significantly higher after levodopa/carbidopa than placebo treatment. As in the alternate index and middle finger tapping task, total number of taps did not show a significant overall treatment effect but did show a significant treatment by time interaction effect. SD of the inter-tap intervals was again lower in the levodopa/carbidopa than in the placebo group, indicating improved rhythm. No significant treatment effect on fatigue, i.e., a decrease in tapping amplitude over time, was observed.

To enable the comparison of endpoints within and between tasks, standardized mean differences (Hedge's g) between levodopa/carbidopa and placebo treatment were calculated (Supplemental Figure 3). This shows that alternate index finger tapping and thumb-index finger tapping had higher standardized effect sizes than alternate index and middle finger tapping. The endpoint in the alternate index and middle finger tapping task with the highest standardized effect size was the ratio of good: total taps. For alternate index finger tapping, these were total number of taps and total spatial error. For thumb-index finger tapping, the opening and closing velocity had the highest standardized effect sizes, followed by the amplitude endpoints and inter-tap interval SD. Four of these endpoints had a standardized effect size that was similar to that of the MDS-UPDRS III, namely the total number of taps and the total spatial error in the alternate index finger tapping task, and the opening and closing velocity in the thumb-index finger tapping task.

Correlation with MDS-UPDRS III

At 1.5 hours post-dose, none of the alternate index and middle finger tapping endpoints correlated with MDS-UPDRS III total score except for total spatial error after levodopa/carbidopa treatment (Pearson's r=0.50, p=0.0306) (Table 3).

In the alternate index finger tapping task, the total number of taps showed a significant moderate correlation with MDS-UPDRS III in both the placebo (Pearson's r=-0.45, p=0.0454) and levodopa/carbidopa (Pearson's r=-0.45, p=0.0457) group. Similarly, the mean inter-tap interval was significantly correlated with MDS-UPDRS III, but only in the placebo group (Spearman's r=0.50, p=0.0249). The accuracy parameters, total taps inside the target and ratio good: total taps, significantly correlated with MDS-UPDRS III in the levodopa/carbidopa group (Pearson's r=-0.55 and p=0.0120; Spearman's r=-0.45 and p=0.0446 respectively). For the other accuracy and rhythm parameters, no correlation was found.

In the thumb-index finger tapping task, all speed parameters had a strong correlation with MDS-UPDRS III in the placebo group (r ranging between -0.65 and 0.70). Closing velocity also showed a moderate correlation with MDS-UPDRS III in the levodopa/carbidopa group (Pearson's r=-0.50, p=0.0426). No other significant correlations were found except for a strong correlation of inter-tap interval SD with MDS-UPDRS III in the levodopa/carbidopa group (Spearman's r=0.66, p=0.0037).

DISCUSSION

In this randomized, placebo-controlled trial, we assessed the ability of three different finger tapping tasks to detect and quantify acute pharmacodynamic effects of dopaminergic medication. Moreover, we investigated whether the finger tapping endpoints correlated with the MDS-UPDRS III score. The advantage of finger tapping over the MDS-UPDRS III is its short duration and rater independence. The short duration allows for frequent assessments and thus for a better detection of the onset of pharmacodynamic effects. Since no trained

rater is required, it is logistically easier to perform the task during a clinical trial, but also allows for testing at home. To our knowledge, this is the first time these tapping tasks have been directly compared to the MDS-UPDRS III in a placebo-controlled study.

Both the alternate index finger tapping and thumb-index finger tapping tasks showed significant differences between levodopa/carbidopa and placebo treatment, with effect sizes comparable to the MDS-UPDRS III. PD patients were able to perform both tasks without difficulties. The goniometer used for the thumb-index finger tapping task was quite fragile and broke several times. In a clinical trial setting where backup devices are available this is not a major problem, but it does make the task unsuitable for at-home testing. In contrast, the alternate index finger tapping only requires a touchscreen tablet and therefore would also be suitable for testing of medication effects or disease progression over time in an at-home setting.

For the alternate index finger tapping task, endpoints relating to speed (i.e., total number of taps) and accuracy (i.e., total spatial error) performed best. An increased speed was associated with reduced accuracy. Such a trade-off between speed and accuracy has previously been described in Parkinson's disease patients,[6,15] even though not consistently.[8] Different results between studies might have been obtained due to differences in the test set-up, as well as in how accuracy was calculated (e.g., on a continuous scale vs. inside/outside target). In the alternate index finger tapping task, rhythm was also significantly improved (i.e., lower geometric mean of inter-tap interval SD) after levodopa/carbidopa compared to placebo, albeit with a lower effect size than the speed and accuracy endpoints. The total number of taps correlated moderately with the MDS-UPDRS III. In contrast, the total spatial error and the inter-tap interval SD, which showed significant treatment effects with a time-related response, did not correlate with MDS-UPDRS III. This might be because they quantify aspects of tapping performance that are not captured by (parts of) the MDS-UPDRS III. Therefore, despite the absence of a correlation, they can be valuable additional endpoints in drug efficacy trials. Particularly the total spatial error since it has an effect size comparable to that of the MDS-UPDRS III.

In the thumb-index finger tapping task, levodopa/carbidopa compared to placebo resulted in faster tapping with a bigger amplitude and improved rhythm. This is in line with previously reported results on thumb-index finger tapping when *ON* and *OFF* states were compared.[5,9] When comparing all endpoints, mean opening and closing velocity had the largest effect sizes, which were comparable to that of the MDS-UPDRS III. In addition, both endpoints showed a moderate-to-strong correlation with the MDS-UPDRS III. The SD of the inter-tap intervals also showed a significant difference between levodopa/carbidopa and placebo, but with a smaller effect size than the opening and closing velocity. Moreover, the inter-tap interval SD showed a strong correlation with the MDS-UPDRS III in the levodopa/carbidopa group and a trend towards a moderate correlation in the placebo group. The mean tapping amplitude and peak frequency AUC, both measures of amplitude, showed a significant treatment effect with a similar effect size. Since they performed equally, but the peak frequency AUC requires a more difficult formula and therefore might be harder to interpret, the mean tapping amplitude is preferred for use in future studies. Mean tapping amplitude did not correlate with MDS-UPDRS III, which was in contrast to the strong correlation (r=-0.79) reported by Ling et al. in PD patients when *OFF*.[5] No medication effects on fatigue, i.e., a change in tapping amplitude over time, were observed. This is in line with what is reported for other thumb-index finger tapping tasks.[5,9] However, the lack of an effect might be related to the relatively short task duration of 15 seconds in all of these tasks. By increasing the task duration, one might enhance fatigue, and thereby leave more room to show improvement by medication.

Of the three tapping tasks, the alternate index and middle finger tapping task performed worst, i.e., had the lowest effect sizes. Its effect sizes were also below that of the gold standard MDS-UPDRS III. Moreover, the task was sometimes difficult to perform for the PD patients, resulting in a high percentage of same-sided double taps. This is likely the result of the patients not lifting their finger from the touchscreen before tapping with the other finger, resulting in two fingers touching the screen simultaneously. With the used set-up, this was recorded as a single tap. The number of tests with more than

70% of same-sided double taps (i.e., a ratio good: total taps <0.3) was approximately balanced over placebo and levodopa/carbidopa treatment. Nevertheless, the ratio good: total taps on a continuous scale was significantly different between placebo and levodopa/carbidopa treatment and showed a time-related response. The same holds true for the total taps inside the target, albeit with a lower effect size. In contrast, the mean and SD of the inter-tap intervals showed a significant treatment effect, but no clear time-related response, making it possible that these were chance findings due to multiple testing. None of the alternate index and middle finger tapping endpoints with significant treatment or treatment by time interaction effects showed a correlation with the MDS-UPDRS III score. Overall, the problems with correctly performing/recording the alternate index and middle finger tapping task, combined with the relatively small effect sizes, make the task in its current configuration the least suitable for efficacy studies including PD patients.

In conclusion, the alternate index finger tapping and thumb-index finger tapping tasks provide short, rater-independent measurements that are sensitive to dopaminergic medication effects and have a similar effect size as the MDS-UPDRS III. When including these tasks in future trials, at least the following endpoints should be included: total number of taps and total spatial error (for alternate index finger tapping), and opening or closing velocity, mean tapping amplitude and inter-tap interval SD (for thumb-index finger tapping). Even though spatial error and amplitude did not correlate with MDS-UPDRS III, they should be included in future placebo-controlled efficacy trials, since they show a clear difference between active and placebo treatment, as well as a time-related response. Since these measurements only take 15 to 30 seconds, they can be performed repeatedly during clinical trials and are therefore expected to better detect onset of effect and time to reach maximum effect than the MDS-UPDRS III. The alternate index finger tapping task may also be suitable for testing new drugs or monitoring disease progression in an at-home setting.

TABLE 1 **Demographics.**

	All PD patients (N=20)
Age (years)	
Median (range)	61 (48-70)
Mean (SD)	60.6 (6.0)
BMI (kg/m^2)	
Median (range)	27 (23-30)
Mean (SD)	26.5 (2.5)
Sex (n/n (%/%))	
Female/Male	6/14 (30/70)
Race (n (%))	
White	20 (100)
Hoehn and Yahr stage at screening (n (%))	
Stage 1	7 (35)
Stage 2	7 (35)
Stage 3	6 (30)
MDS-UPDRS III total score on the day prior to dosing (i.e., when using regular medication)	
Median (range), placebo treatment	23 (7-52)
Mean (SD), placebo treatment	24.2 (13.1)
Median (range), active treatment	22 (5-70)
Mean (SD), active treatment	24.6 (14.7)
Concomitant PD medication (n (%))	
Levodopa-containing agents	19 (95)
Dopamine agonists	14 (70)
COMT inhibitors	4 (20)
MAO-B inhibitors	2 (10)
Amantadine	4 (20)
Deep brain stimulation (bilateral subthalamic nucleus)	2 (10)
Levodopa Equivalent Dose (mg)[a]	
Median (range)	275 (47-391)
Mean (SD)	246.9 (112.5)
Number of capsules[b]	
Median (range)	3 (1-4)
Mean (SD)	3 (1)

a. Supramaximal levodopa equivalent dose of the morning medication (for calculation, refer to the Methods). /
b. Number of levodopa/carbidopa 100/25 mg or placebo capsules administered in this study.
SD, standard deviation; BMI, body mass index; MDS-UPDRS III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III; PD, Parkinson's disease; COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase B.

TABLE 2 **Per endpoint, Least Squares Means, Least Squares Means change from baseline, p-values of the treatment and treatment x time effects, and the estimated difference for the levodopa/carbidopa-placebo contrast with its 95% CI are shown.**

Category	Parameter (unit)[a]	Least Squares Means		Treatment p-value	Treatment x Time p-value	Contrast levodopa/carbidopa vs placebo (95% CI)	Least Squares Means change from baseline	
		Placebo	Levodopa/carbidopa				Placebo	Levodopa/carbidopa
MDS-UPDRS III total score								
Gold standard	MDS-UPDRS III	34.3	27.0	**0.0014**	**<.0001**	-7.3 (-11.6, -3.0)	-0.7	-8.0
Alternate index and middle finger tapping[b]								
Speed	Total number of taps	81.3	87.5	0.2173	**0.0052**	6.3 (-3.9, 16.4)	-8.9	-2.7
	Mean inter-tap interval (ms)	389.5	317.3	**0.0198**	0.1106	-18.5% (-31.2%, -3.5%)	15.3%	-6.0%
Accuracy	Total taps inside target	75.0	86.6	**0.0308**	**0.0001**	11.6 (1.1, 22.1)	-10.3	1.4
	Ratio good: total taps	0.59	0.72	**0.0006**	**<0.0001**	0.14 (0.07, 0.21)	-0.1	0.0
	Total spatial error (mm)	470.4	428.5	0.2629	0.1974	-41.9 (-116.9, 33.0)	-6.2	-48.1
	Mean spatial error (mm)	5.6	5.0	0.0950	0.3893	-12.0% (-24.4%, 2.4%)	10.6%	-2.7%
Rhythm	Inter-tap interval SD (ms)	219.7	162.8	**0.0304**	0.2219	-25.9% (-43.4%, -3.0%)	21.6%	-9.9%
	Spatial error SD (mm)	2.2	2.0	0.4203	0.1024	-8.3% (-26.2%, 13.9%)	1.6%	-6.9%
	Number of halts	3.2	3.4	0.6975	0.2483	0.2 (-0.7, 1.1)	-0.1	0.0
Alternate index finger tapping[c]								
Speed	Total number of taps	66.1	78.6	**0.0001**	**<.0001**	12.5 (6.7, 18.2)	-2.4	10.0
Accuracy	Total taps inside target	55.5	63.2	**0.0260**	**<.0001**	7.7 (1.0, 14.4)	-2.5	5.1
	Total spatial error (mm)	719.0	959.3	**0.0002**	**<.0001**	240.3 (123.3, 357.3)	-29.7	210.6
	Mean spatial error (mm)	10.8	12.0	**0.0205**	0.6719	1.2 (0.2, 2.2)	0.0	1.2
Rhythm	Inter-tap interval SD (ms)	52.3	43.8	**0.0494**	**0.0307**	-16.3% (-29.9%, -0.0%)	8.9%	-8.8%
	Spatial error SD (mm)	4.5	4.9	0.2830	0.1083	7.6% (-6.1%, 23.3%)	3.7%	11.6%

[continuation of Table 2]

Category	Parameter (unit)[a]	Least Squares Means		Treatment p-value	Treatment x Time p-value	Contrast levodopa/carbidopa vs placebo (95% CI)	Least Squares Means change from baseline	
		Placebo	Levodopa/carbidopa				Placebo	Levodopa/carbidopa
Thumb-index finger tapping[d]								
Speed	Total number of taps	46.1	52.6	0.0633	**<.0001**	6.5 (-0.4, 13.4)	-1.5	5.0
	Mean opening velocity (degree/s)	372.2	522.7	**0.0013**	**<.0001**	150.5 (64.2, 236.8)	-62.9	87.6
	Mean closing velocity (degree/s)	479.1	659.0	**0.0028**	**<.0001**	180.0 (67.0, 292.8)	-90.4	89.5
Amplitude	Mean tapping amplitude (degree)	27.4	35.7	**0.0009**	**<.0001**	8.4 (3.7, 13.0)	-4.9	3.4
	Peak frequency AUC (degree^2)	107.4	187.8	**0.0089**	**0.0034**	80.4 (21.8, 138.9)	-44.9	35.5
Rhythm	Inter-tap interval SD (ms)	62.4	33.4	**0.0028**	**0.0004**	-46.4% (-63.7%, -20.9%)	24.8%	-33.1%
Fatigue	Tapping amplitude change (degree/s)	-0.34	-0.50	0.1781	0.9049	-0.16 (-0.40, 0.08)	0.0	-0.2

*P-values <0.05 are shown in **bold**.*
a. For log transformed parameters, Geometric Least Square Means are given, and estimates of the contrast with their 95% confidence intervals are back-transformed and therefore given in percentages. / b. The analysis results of inter-tap interval change (ms/min) and spatial error change (mm/min) have not been reported because they violated the normality assumption. / c. The analysis results of ratio of good: total taps, inter-tap interval change (ms/min), mean inter-tap interval (ms), number of halts, and spatial error change (mm/min) have not been reported because they violated the normality assumption. / d. The analysis results of angle frequency change (Hz/min), inter-tap interval change (ms/min), and mean inter-tap interval (ms) have not been reported because they violated the normality assumption.
CI, confidence interval; MDS-UPDRS III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III; SD, standard deviation; AUC, area under the curve.

TABLE 3 Correlation between each finger tapping endpoint and MDS-UPDRS III total score.

Category	Parameter	Placebo		Levodopa/carbidopa	
		r	P-value	r	P-value
Alternate index and middle finger tapping					
Speed	Total number of taps	0.08	0.7381	0.31	0.1935
	Mean inter-tap interval	-0.11	0.6599	-0.41	0.1001
Accuracy	Total taps inside target	0.06	0.8165	0.28	0.2478
	Ratio good: total taps	-0.17	0.4899	-0.23	0.3379
	Total spatial error	0.30	0.2159	0.50	**0.0306**
	Mean spatial error	0.35	0.1389	0.32	0.1769
Rhythm	Inter-tap interval SD	-0.06	0.8101	-0.10	0.6889
	Spatial error SD	-0.10	0.6931	0.02	0.9401
	Number of halts	0.22	0.4029	0.22	0.3959
Fatigue	*Inter-tap interval change*	0.14	0.5928	0.23	0.3758
	Spatial error change	-0.04	0.8635	0.37	0.1189
Alternate index finger tapping					
Speed	Total number of taps	-0.45	**0.0454**	-0.45	**0.0457**
	Mean Inter-tap interval	0.50	**0.0249**	0.21	0.3764
Accuracy	Total taps inside target	-0.39	0.0849	-0.55	**0.0120**
	Ratio good: total taps	-0.24	0.3140	-0.45	**0.0446**
	Total spatial error	-0.23	0.3365	-0.04	0.8528
	Mean spatial error	0.11	0.6482	0.29	0.2123
Rhythm	Inter-tap interval SD	0.25	0.2822	0.32	0.1733
	Spatial error SD	-0.06	0.7906	0.10	0.6784
	Number of halts	-0.16	0.5022	-0.10	0.6703
Fatigue	*Inter-tap interval change*	-0.05	0.8397	-0.26	0.2661
	Spatial error change	0.12	0.6143	0.16	0.4984
Thumb-index finger tapping					
Speed	Total number of taps	-0.65	**0.0024**	-0.21	0.4255
	Mean Inter-tap interval	0.70	**0.0013**	0.17	0.5249
	Mean opening velocity	-0.66	**0.0027**	-0.24	0.3628
	Mean closing velocity	-0.65	**0.0025**	-0.50	**0.0426**
Amplitude	Mean tapping amplitude	-0.27	0.2748	-0.41	0.1021
	Peak frequency AUC	-0.28	0.2376	-0.29	0.2553
Rhythm	Inter-tap interval SD	0.45	0.0586	0.66	**0.0037**
Fatigue	*Inter-tap interval change*	-0.09	0.7160	-0.22	0.3886
	Tapping amplitude change	-0.11	0.6577	0.11	0.6732
	Angle frequency change	0.08	0.7418	0.26	0.3201

*P-values <0.05 are shown in **bold**. Correlation coefficient r and p-value are given for both the placebo and the levodopa/carbidopa group. For parameters in italics, no model could be fitted.*
MDS-UPDRS III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III; SD, standard deviation; AUC, area under the curve.

FIGURE 1 Depiction of the 3 finger tapping tasks: alternate index and middle finger tapping (A), alternate index finger tapping (B), and thumb–index finger tapping (C).

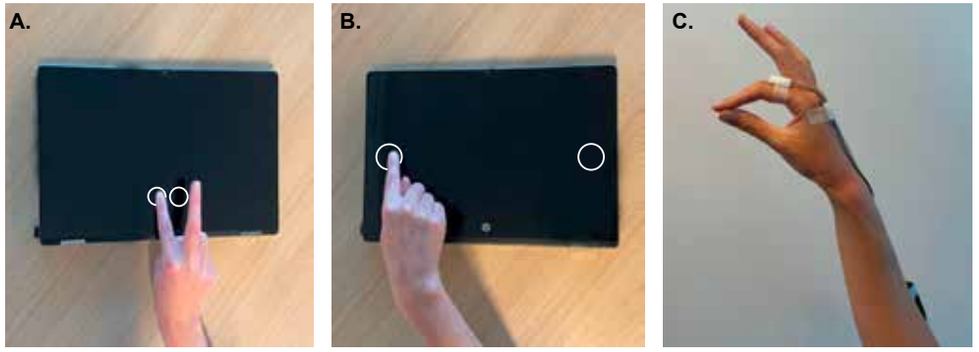
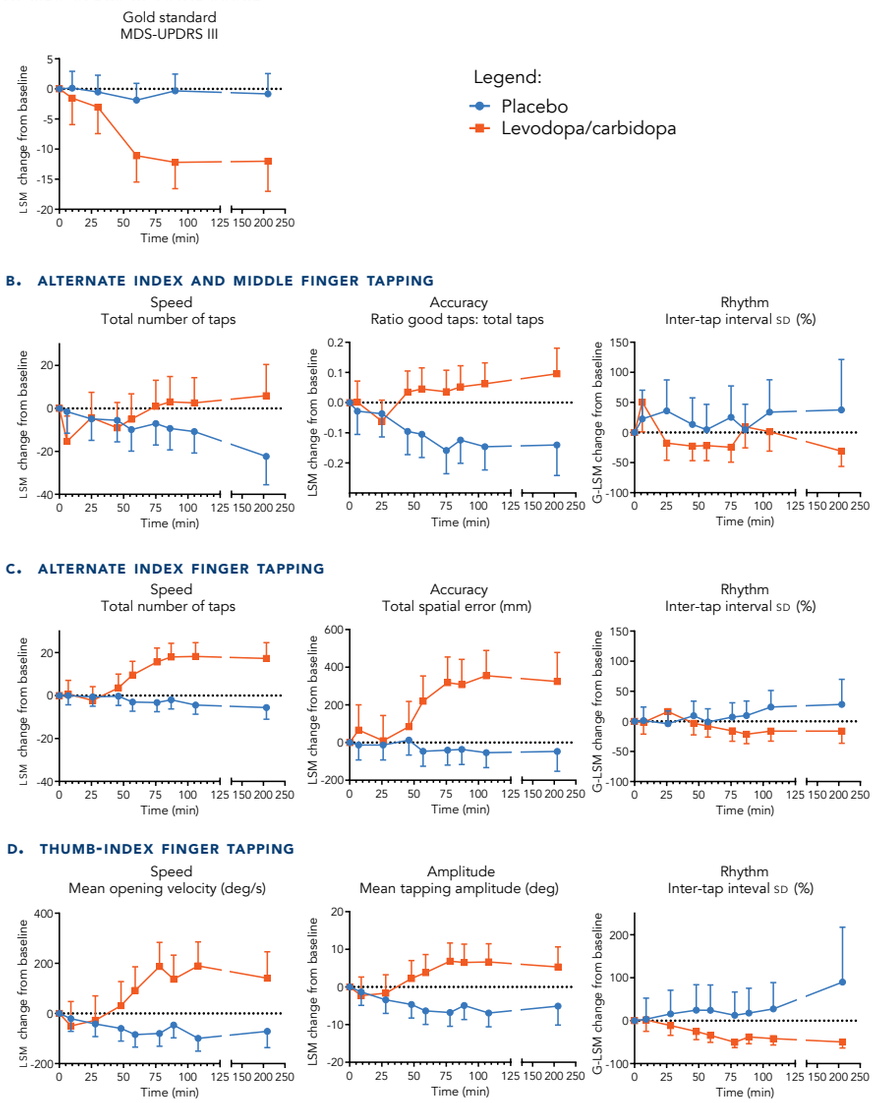


FIGURE 2 (G-)LSM change from baseline with 95% confidence intervals plotted over time for MDS-UPDRS III (A) and for 3 endpoints of the alternate index and middle finger tapping (B), alternate index finger tapping (C), and thumb-index finger task (D).



G-LSM, geometric-least square means; LSM, least square means; MDS-UPDRS III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III; SD, standard deviation.

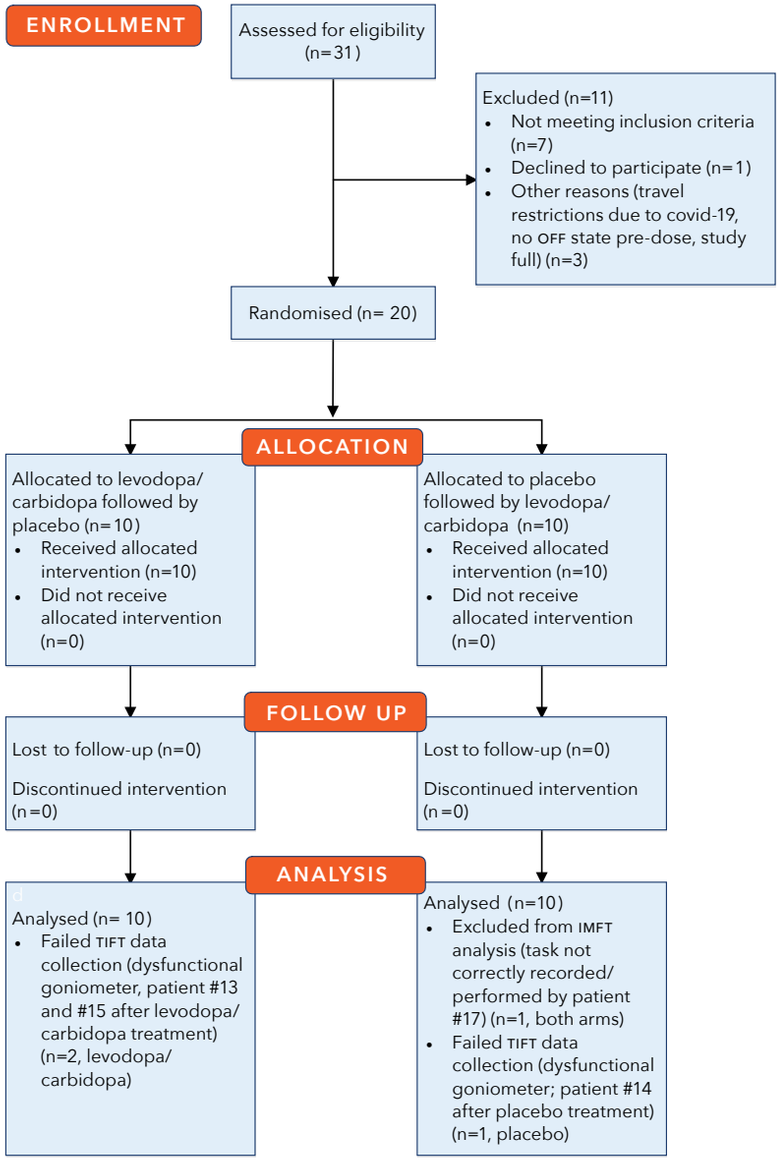
SUPPLEMENTARY MATERIAL

SUPPLEMENTAL TABLE 1 Description of finger tapping endpoints.

Endpoint (unit)	Definition	Calculated for task
Total number of taps	Sum of all taps.	IMFT, IFT, TIFT
Total taps inside target	Taps within the target circle.	IMFT, IFT
Ratio good: total taps	Taps on the correct side (left/right) of the screen divided by total number of taps.	IMFT, IFT
Mean inter-tap interval (ms)	Mean time between two consecutive taps.	IMFT, IFT, TIFT
Inter-tap interval SD (ms)	Standard deviation of all inter-tap intervals.	IMFT, IFT, TIFT
Inter-tap interval change (ms/min)	Change of the inter tap intervals over time.	IMFT, IFT, TIFT
Number of halts	Number of taps where the inter-tap interval is larger than 2 * mean inter-tap interval.	IMFT, IFT
Total spatial error (mm)	Sum of the Euclidean distances between each tap and the center of the target.	IMFT, IFT
Mean spatial error (mm)	Total spatial error divided by total number of taps.	IMFT, IFT
Spatial error SD (mm)	Standard deviation of Euclidean distances of each tap from the targets' center point.	IMFT, IFT
Spatial error change (mm/min)	Slope from linear regression of each tap's spatial error against time.	IMFT, IFT
Mean tapping amplitude (degrees)	Mean of each finger tap's maximum amplitude.	TIFT
Tapping amplitude change (degrees/s)	Change of tapping amplitude over time.	TIFT
Peak frequency area under the curve (degrees^2)	The total power around the peak frequency, i.e., the area under the curve (AUC) in the power spectrum around the peak frequency. Measure of amplitude.	TIFT
Angle frequency change (Hz/min)	Change in peak tapping frequency over time.	TIFT
Mean opening velocity (degrees/s)	Average of the amplitude (i.e., angle) travelled per second for each tap when moving the index finger away from the thumb (opening); velocity extracted from the derivative of the amplitude.	TIFT
Mean closing velocity (degrees/s)	Average of the amplitude (i.e., angle) travelled per second for each tap when moving the index finger towards the thumb (closing); velocity extracted from the derivative of the amplitude.	TIFT

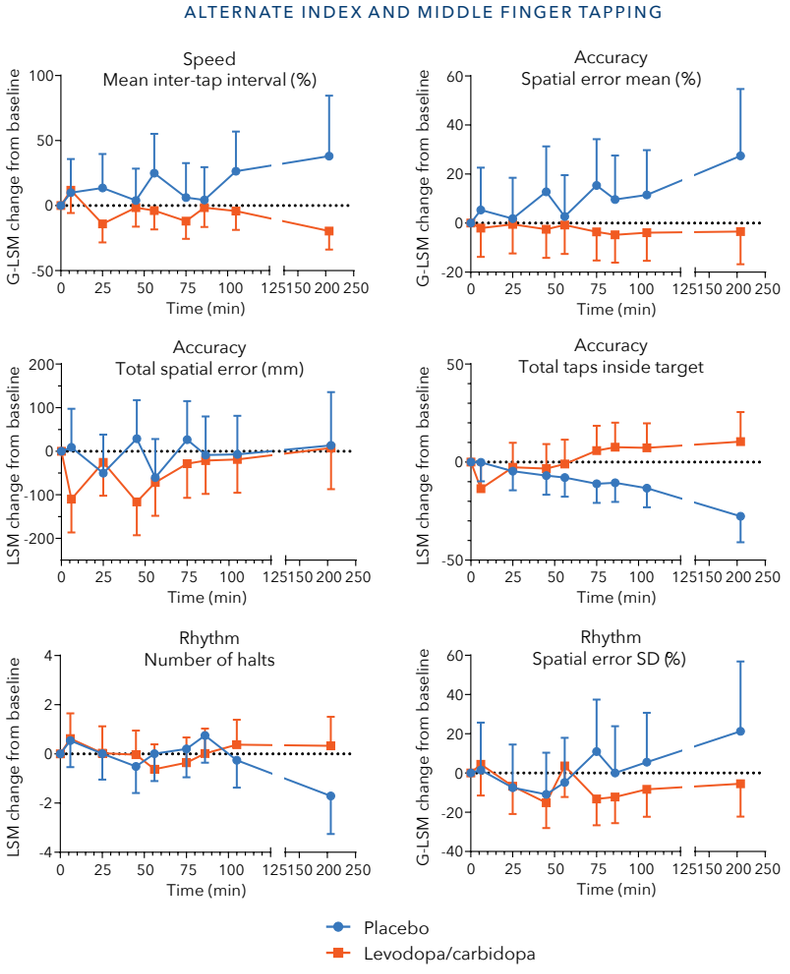
IMFT, alternate index and middle finger tapping; IFT, alternate index finger tapping; TIFT, thumb-index finger tapping.

SUPPLEMENTAL FIGURE 1 **CONSORT flow diagram.**

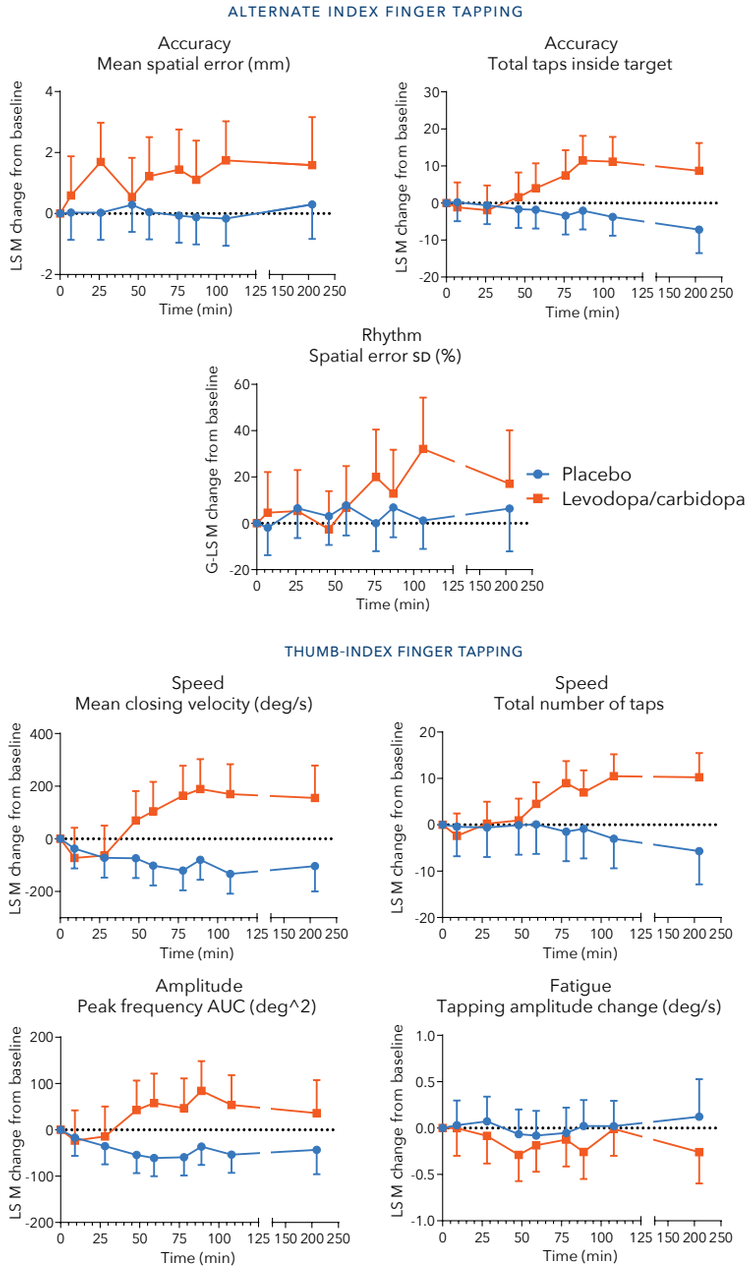


CONSORT, Consolidated Standards of Reporting Trials; TIFT, thumb-index finger tapping; IMFT, alternate index and middle finger tapping.

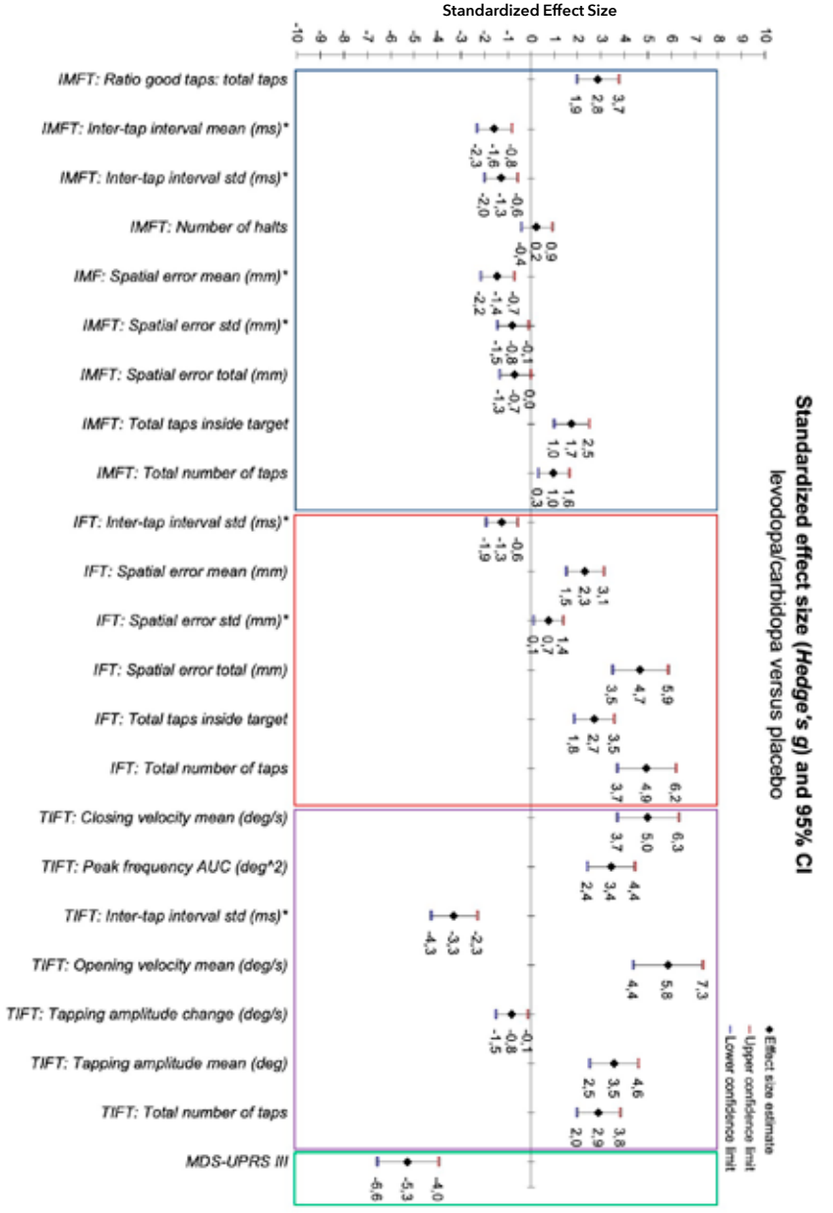
SUPPLEMENTAL FIGURE 2 **(Geometric-) Least squares means ((G-)LSM) change from baseline with 95% confidence intervals plotted over time for the endpoints of the alternate index and middle finger tapping, alternate index finger tapping, and thumb-index finger tapping that were not depicted in Figure 2.**



[continuation of Supplemental Figure 2]



SUPPLEMENTAL FIGURE 3 **Standardized effect sizes.**



CI, confidence interval; IMFT, alternate index and middle finger tapping; IFT, alternate index finger tapping; TIFT, thumb-index finger tapping.

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