Clinical pharmacology studies investigating novel formulations of dopaminergic drugs

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CHAPTER 5

Touchscreen-based finger tapping: repeatability and configuration effects on tapping performance

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ABSTRACT

Background Parkinson's disease (PD) is a progressive neurodegenerative disease that affects almost 2% of the population above the age of 65. To better quantify the effects of new medications, fast and objective methods are needed. Touchscreen-based tapping tasks are simple yet effective tools for quantifying drug effects on PD-related motor symptoms, especially bradykinesia. However, there is no consensus on the optimal task set-up.

Methods The present study compares four tapping tasks in 14 healthy participants. In the alternate index and middle finger tapping task (IMFT), tapping occurred with the index and middle finger with 2.5 cm between targets. In the alternate index finger tapping task (IFT), tapping occurred with the index finger with 20 cm between targets. Both configurations were tested with or without the presence of a visual cue. Moreover, for each tapping task, within- and between-day repeatability and (potential) sensitivity of the calculated parameters were assessed.

Results Visual cueing reduced tapping speed, impaired rhythm, and improved accuracy. This effect was most pronounced for IFT. On average, IFT had a lower tapping speed with impaired accuracy and improved rhythm compared to IMFT. Of all parameters, the total number of taps and mean spatial error had the highest repeatability and sensitivity.

Conclusions The findings suggest against the use of visual cueing because it is crucial that parameters can vary freely to accurately capture medication effects. The choice for IMFT or IFT depends on the research question, as these tasks assess different aspects of movement. These results encourage further validation of non-cued IMFT and IFT in PD patients.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects roughly 1 to 2% of the population above the age of 65.[1,2] The standard treatments remain symptomatic and novel treatments are continuously being investigated.[3,4] One of the cardinal motor symptoms of PD is bradykinesia, defined as 'slowness of voluntary movement initiation, progressive reduction of speed and amplitude of repetitive movement, and difficulty of task switching'.[4] Additional motor symptoms include tremor, muscular rigidity, and postural instability.[4]

To assess the effectiveness of new (dopaminergic) medications, the Movement Disorder Society revised - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) serves as the 'gold standard' measurement.[5] This scale provides a wide range of assessments related to both motor and non-motor symptoms. Part III of the scale assesses motor symptoms, and its administration lasts approximately 15 minutes. However, the clinical rating scale is subject to varying inter-rater reliability, requires training and certification of the assessor, and is time-consuming for both the clinician and patient.[6-9] This may hamper the continuous assessment of (motor) symptoms, especially of rapid-acting agents. For instance, it will be difficult to accurately model the pharmacokinetic-pharmacodynamic relationship of a medication with an early T_{max} (e.g., of less than 15-30 minutes) when using the time-consuming MDS-UPDRS part III as a pharmacodynamic measure. Hence, there is a need for short, reliable, and objective motor symptom quantification methods that are easy to implement in clinical research.

The number and variety of technologies aimed at quantifying PD motor symptoms has increased over the last decade.[8,10] Many focus on finger tapping motions to quantify aspects of tremor, dyskinesia, and bradykinesia.[8] When quantifying bradykinesia, examples of technologies used vary from more rudimentary to increasingly sophisticated methods. For instance, arcade buttons,[11] midi-keyboards,[12] Inertial Measurement Units,[13-19] and touchscreen devices[20-28] have all been used in previous studies. Touchscreen-based

tapping tasks have been shown to not only differentiate reliably between PD patients and healthy controls[12,20,29,21-28] but also to detect medication effects.[14,20,23,29,30] Despite their potential in clinical research, there is no one standardized touchscreen based tapping task and seemingly minor configuration differences can affect the interpretation of study results.[31]

Two variations of the touchscreen based finger tapping tasks are commonly described in literature: alternate tapping with the index and middle finger of one hand between two closely placed targets (index and middle finger tapping (IMFT)),[22,25,32] and alternate tapping with the index finger between two targets placed on opposite ends of the screen (alternate index finger tapping (IFT)).[12,20] Each task assesses a different aspect of movement: whereas IMFT requires fine finger movement, IFT requires upper arm movement. Although studies report whether the IFT and/or IMFT was used, it is often unclear what the precise implementation of the tasks were (Table 1 for a brief overview of studies that used a finger tapping task). Varying target distances have been used both in IMFT and IFT. The inter target distance in IFT studies varies between 1.5 cm to 25 cm. In studies using the IMFT, most set-ups seem to place the targets under the natural position of the fingertips, yet, the precise inter-target distance is not always reported. Furthermore, both visually cued (e.g., by changing target colors)[25] and non-cued (e.g., on a keyboard),[20] versions of the test have been described. The distinction can be important as it has been shown that aiding PD patients with sensory cues can improve performance in finger tapping rhythm[33] and gait.[34] Most importantly, however, most studies do not report all design choices, often omitting details about the inter-target distance, the presence or absence of a cue, or the task duration.

To the best of our knowledge, no study has assessed the effects of cueing and task configuration in a comparative manner in healthy participants. The present study aims to compare four tapping tasks (cued/ non-cued IMFT and IFT) in healthy participants to identify the optimal design choices to be further validated in PD patients. First, the within- and between-day repeatability and (potential) sensitivity of the parameters are evaluated. Subsequently, the effect of the different configurations and cueing on tapping parameters are assessed.

METHODS

Participants

No formal sample size calculations were performed since this was an exploratory, technical validation study. A total of 16 healthy participants were planned for enrolment. The number of participants was chosen to be of similar size as an early phase clinical trial and to achieve a balanced design. Inclusion criteria were self-reported normal or corrected vision and no self-reported significant health problems. Exclusion criteria included the presence of self-reported physical hand/arm impairment, any movement disorder (e.g., PD, essential tremor, dystonia, akinesia) and/or any other neurological condition. Participants were instructed to abstain from caffeine, smoking, and intensive physical exercise starting 12 hours prior to the tasks until the last measurement was completed. Participants gave consent prior to participation and did not receive any form of compensation. All data was collected anonymously (i.e., only age, gender, and handedness were collected). All procedures were approved by the internal Research Committee. The Research Committee considered the study a technical validation study that does not fall under the Dutch Medical Research Involving Human Subjects Act (WMO). Therefore, medical ethical approval from an independent medical-ethics committee was not required.

Study design

All participants visited the Centre for Human Drug Research (CHDR), Leiden, the Netherlands, twice, with a week between visits. To achieve a balanced design, the order of the blocks was counterbalanced using a Latin square method. Tapping tasks were conducted in the morning and their order was identical on both visits. Each task was performed four consecutive times, with 10-minute breaks between sessions. Participants were given a 20-minute break between two tapping tasks (for a schematic overview, see Figure 1). One visit lasted approximately 4 hours.

Finger tapping tasks

All finger tapping tasks were performed with a touchscreen laptop (HP Pavilion x360; resolution=1920 x 1080 pixels; screen width=31 cm; screen height=17.4 cm). The tasks were developed in-house using the Python programming language (version 3.4).[36] The PsychoPy library was used for stimulus presentation.[37] The visual stimuli were two white circles (radius=1 cm) placed horizontally on the screen on a black background. The two circles were either 2.5 or 20 cm apart, corresponding to the IMFT and IFT task, respectively. Depending on the configuration, targets were presented with or without a visual cue. With visual cueing, one target is visible at a time and only when tapped correctly does this target disappear while the other appears. Hence, a total of four tapping tasks were tested: cued and non-cued IMFT, as well as cued and non-cued IFT (see Figure 2).

Tapping position (X and Y coordinates) and tapping time for each tap were registered. Parameters related to speed, accuracy, fatigue and rhythm were quantified for each of the four tapping tasks.[28] We calculated the total number of taps (TNT) as a proxy for tapping speed; the number of tapping errors (NTE), mean spatial error (SEA), and bivariate contour ellipse area (BCA), as variables of accuracy; the inter-tap interval standard deviation (ITS) representing rhythm; and the change in velocity (VEC) to capture fatigue (see Table 2 for an overview of the tapping task parameters and Figure 3 for a visual representation of the data output).

During all tapping tasks, participants were instructed to tap as accurately and fast as possible for 30 seconds. Participants used the index finger of their dominant hand during the IFT tasks, whereas they used the index and middle finger alternately during the IMFT tasks. Additionally, during the IFT tasks, participants were asked to keep their elbow fixed in place on the table to prevent additional movement compensation.

Statistical analysis

All data processing was performed via custom scripts in Python (version 3.8).[36] Statistical modeling was performed using custom scripts as well as the 'lme4'[39] and 'emmeans' packages[40] in the R software package.[41]

Repeatability

To assess the repeatability of the parameters, the available dataset was split into two subsets to separately assess the within- and between-day repeatability. For within-day repeatability, only measurements from the first visit were considered. For between-day repeatability, data from both visits was used, but from each visit the four measurements were averaged.

For each parameter and subset, a random intercept Linear Mixed Model (LMM) was fit. For within-day repeatability, both the intercept and measurement number (i.e., 1 to 4) were included as fixed effects. For between-day repeatability, both the intercept and visit number (i.e., 1 and 2) were included as fixed effects. Based on the models, the intraclass correlation coefficient (ICC) was calculated by dividing the between-subject variance by the total variance (i.e., the sum of the between-subject variance and the within-subject error variance).[42] Excellent degree of repeatability was considered for ICC values above 0.90, good for ICC values between 0.75-0.90, moderate for ICC values between 0.50-0.75, and poor for ICC values below 0.50.[42]

Minimum detectable effect

To assess potential sensitivity, minimum detectable effect (MDE) values were calculated. First, a random intercept model including measurement number (i.e., 1 to 4) as fixed effect was fitted for each parameter. For each fitted model, fixed intercept, random intercept variance and residual variance were extracted. The MDE was then calculated by multiplying the effect size by the pooled standard deviation (i.e., the square root of the sum of the within- and between-subject variance) and expressed in terms of percentage change relative to the intercept value. The effect size used to calculate the MDE was based on a paired sample t-test with a power of 0.80, a significance level of 5% (α=0.05), and a sample size of 20 (a typical sample size for a clinical trial).

Effect of task configuration on performance

To assess the effect of configuration, cueing, measurement number, and visit number, a LMM was fitted for each parameter. For each model, the intercept, configuration (i.e., IMFT or IFT), cueing (i.e., cued or non-cued), measurement number (i.e., 1 to 4), and visit (i.e., 1 or 2) were included as fixed effects. Additionally, a two-way interaction between cueing and configuration was included as fixed effect. Between-subject random effects were included for the intercept. A more elaborate random structure was not possible without running into convergence issues. Type-III F-statistics were used to assess statistical significance of the fixed effects (α=0.05). Where the interaction effect between the fixed effects was found to be significant, post-hoc pairwise comparisons with Tukey p-value correction were evaluated using the 'emmeans' package. Degrees of freedom for F-statistic denominators as well as pairwise comparisons were estimated via the Kenward-Roger method.[43] For pairwise comparisons, the effect size was estimated by calculating Cohen's d. Effect sizes were considered small, medium, or large for values of d smaller than 0.20, between 0.20 and 0.50, or larger than 0.80, respectively.[44]

RESULTS

Two participants could not be measured due to emerging COVID restrictions, hence data from 14 participants were collected (mean age: 25.6 ± SD: 3.1; 6 females, 13 right-handed). All but one of the participants successfully completed all measurements. For one participant, the first four measurements were not performed due to technical difficulties. A total of 444 tapping experiments were performed, resulting in 61103 recorded taps.

Repeatability

The within-day repeatability of the six parameters in cued/ non-cued IMFT and IFT tasks are presented in Table 3. Excellent to good repeatability was observed in the speed parameter (i.e., total number of taps) across all tasks (ICCs>0.86). The number of tapping errors showed good to moderate repeatability in IMFT (ICC_{cued}=0.81, $ICC_{non\text{-}cued}$=0.69), but poor repeatability in IFT (ICC_{cued}=0.41, $ICC_{non\text{-}cued}$=0.08). The mean spatial error showed good repeatability in IMFT (ICC_{cued}=0.79, $ICC_{non\text{-}cued}$=0.75), and good to moderate repeatability in IFT (ICC_{cued}=0.67, $ICC_{non\text{-}cued}$=0.84). Good to poor repeatability was observed in the bivariate contour ellipse area in IMFT (ICC_{cued}=0.77, $ICC_{non\text{-}cued}$=0.05), and good to moderate repeatability in IFT (ICC_{cued}=0.67, $ICC_{non\text{-}cued}$=0.84). The rhythm parameter, inter-tap interval SD, showed good repeatability in both IMFT tasks (ICC_{cued}=0.86, $ICC_{non\text{-}cued}$=0.84), while it showed moderate to poor repeatability in IFT (ICC_{cued}=0.20, $ICC_{non\text{-}cued}$=0.51). The change in velocity parameter showed moderate repeatability in IMFT (ICC_{cued}=0.56, $ICC_{non\text{-}cued}$=0.58) and moderate to poor in IFT (ICC_{cued}=0.25, $ICC_{non\text{-}cued}$=0.55).

The between-day repeatability values for the six parameters are presented in Table 4. An excellent to good repeatability was observed in the total number of taps across all tapping tasks (ICCs: 0.78-0.97). The number of tapping errors showed excellent to good repeatability in IMFT (ICC_{cued}=0.96, $ICC_{non\text{-}cued}$=0.81) and moderate to poor repeatability in IFT (ICC_{cued}=0.54, $ICC_{non\text{-}cued}$=0.06). Of the accuracy parameters, mean spatial error showed moderate to good repeatability in IMFT (ICC_{cued}=0.80, $ICC_{non\text{-}cued}$=0.70), and moderate in IFT (ICC_{cued}=0.53, $ICC_{non\text{-}cued}$=0.56). The bivariate contour ellipse area showed moderate to poor repeatability in IMFT (ICC_{cued}=0.60, $ICC_{non\text{-}cued}$=0.29), and moderate in IFT (ICC_{cued}=0.73, $ICC_{non\text{-}cued}$=0.63). The rhythm parameter, inter-tap interval SD, showed good to moderate repeatability in IMFT (ICC_{cued}=0.85, $ICC_{non\text{-}cued}$=0.52), and good to poor repeatability in IFT (ICC_{cued}=0.40, $ICC_{non\text{-}cued}$=0.75). The change in velocity showed good to moderate repeatability in IMFT (ICC_{cued}=0.79, $ICC_{non\text{-}cued}$=0.66) and good repeatability in non-cued IFT ($ICC_{non\text{-}cued}$=0.85). For cued IFT, an ICC could not be estimated due to the model not converging.

Minimum detectable effect

The calculated MDE values, expressed in percentages as well as in absolute values, can be found in Table 5. Generally, the MDE values for the IFT configuration were lower than for IMFT. The parameters having the lowest MDE values were the total number of taps, the mean spatial error, and the rhythm parameter (MDE values ranging from 9.5%-23% in IFT, and 19%-71% in IMFT).

Effect of task configuration and cueing on tapping performance

The results of all LMM models are presented in Table 6. The configuration (i.e., IMFT vs IFT) had a significant effect on all parameters. Cueing affected all parameters except the mean spatial error. Lastly, a significant interaction effect between configuration and cueing was found for all parameters except the total number of taps and change in tapping velocity. None of the parameters were affected by the measurement number, see Table 6. However, the total number of taps, mean spatial error, and the inter-tap interval SD were affected by visit. For the pairwise comparisons between testing visits, see Table 7. On the second visit, participants tapped more often than on the first visit ($p<0.01$). Moreover, the mean spatial error on the second visit was higher than on the first visit ($p<0.05$). Finally, the inter-tap interval SD was lower on the second visit than on the first visit ($p<0.01$).

All estimated mean values for the tapping tasks, as well as all pairwise comparisons are presented in Table 8 and Figure 4. Participants tapped more often during IMFT than IFT, and during a non-cued versus a cued task. In addition, more tapping errors were made in IMFT than IFT. In the absence of the visual cue, participants made more tapping errors in the IMFT task and fewer in the IFT task. The mean spatial error was larger in IFT than IMFT. The non-cued task reduced and increased the mean spatial error in the IMFT and IFT configurations, respectively. The bivariate contour ellipse area was significantly larger in IFT than IMFT. The non-cued task increased the bivariate contour ellipse area only in the IFT configuration. The SD of the inter-tap interval was lower in the IFT configuration than in the IMFT configuration. The absence of the visual cue reduced the SD of the inter-tap interval only in the IFT configuration. The tapping velocity reduced throughout a measurement in both IMFT tasks, with a steeper reduction in the non-cued tapping task. The tapping velocity increased throughout a measurement in cued IFT, but reduced in the non-cued IFT.

DISCUSSION

The current technical validation study provides several key contributions to the growing body of literature on touchscreen-based tapping devices. To the best of our knowledge, this study is the first to assess the effects of cueing and task configuration on tapping performance in a comparative manner. It is also the first study that explicitly assesses the repeatability and MDE of tapping parameters in healthy participants. Based on the results of the current study, recommendations for subsequent studies are discussed.

Repeatability and minimal detectable effect

The first research question assessed the repeatability of tapping parameters across the four tapping tasks. Establishing good within-day repeatability is important as in clinical trials medication effects are often repeatedly assessed in a relatively short period of time.[29] Moreover, studies determining the acute pharmacodynamic effects of medication on a symptom, that may vary greatly between patients, (ideally) have a crossover design. Hence, the optimal tapping task must provide repeatable parameters for the same subject both within and between testing visits. The within- and between-day repeatability were comparable for all reported parameters (see Tables 3 and 4). None of the parameters in any task showed significant changes between the four measurements within a day. This indicates the lack of significant learning effects when the measurements are repeated in a relatively short period of time. However, there was a significant effect of testing visit (the second visit occurred one week after the

first) on the total number of taps, spatial error, and the standard deviation of the inter-tap interval. With the increase in number of taps at the second visit, the mean spatial error also increased. One explanation could be that as participants were already familiar with the task on the second visit, their priority might have shifted to speed rather than accuracy. To summarize, the within-day repeatability of the tapping parameters was good, but additional care should be taken when comparing repeated measures between testing visits.

The best repeatability was found in the speed related parameters, followed by accuracy, rhythm, and fatigue parameter. There were two parameters where lower repeatability was observed in IFT compared to IMFT, i.e., the number of tapping errors and the standard deviation of the inter-tap interval (i.e., rhythm parameter). The number of tapping errors showed lower repeatability values, especially in non-cued IFT compared to the other tasks. Since most participants tapped correctly, there was little to no between-subject variation in tapping errors, lowering its ICC value. Additionally, the between-subject variance of the rhythm parameter was lower for IFT compared to IMFT. This finding suggests that it was easier for most people to tap with a steady rhythm during forearm muscle/ elbow joint driven motion than during IMFT. Taken together, the IMFT parameters generally resulted in better within-day repeatability than the IFT ones, mainly driven by the increased between-subject variability in IMFT.

The second research question assessed the parameters' sensitivity to change in all four tapping tasks. Overall, the IFT parameters were more sensitive compared to IMFT parameters. The total number of taps showed moderate sensitivity in IMFT and higher sensitivity in IFT (i.e., MDE values ranging between 9.5%-28%). Previous research indicates that the effect sizes observed on this parameter when comparing PD patients in an *ON* versus an *OFF* state, and when comparing PD patients with healthy controls, range within comparable boundaries.[20,21,23,25-27] Although less frequently reported in literature, similar effect sizes were found in the mean spatial error and rhythm parameters.[20,25] Given that PD patients tend to tap more arrhythmically,[11,14] slowly,[20,21,28,45] and less accurately,[20,28] the total number of taps, spatial error and the standard deviation of the inter-tap interval could be valuable parameters in subsequent clinical trials with patients.

The effects of task configuration and cueing on tapping performance

In the IMFT configuration, we found faster tapping, higher accuracy, worse rhythm, and more fatigue than in the IFT configuration. The inter-target distance was 8 times smaller in IMFT than IFT, thereby reducing the travel time between two consecutive taps. IMFT rhythm and fatigue effects, however, could primarily be explained by the increased muscle fatigue during fine, alternating finger movement as opposed to the upper-arm driven IFT motion.[25,45,46] Why the increased speed was not associated with lower accuracy in IMFT, could be explained by the position of the circles. The targets were placed under the natural position of the fingertips, making deviations from the center of the targets and tapping outside the target areas inherently less likely. Despite these two tasks being interchangeably used in the literature, researchers should be aware that IMFT and IFT are two different tasks, and they assess distinct motor functions.

Understanding the effects of cueing in finger tapping is crucial as cues can significantly improve motor performance in PD.[34,47] In healthy participants, cueing reduced speed and fatigue for both IMFT and IFT, improved accuracy, and worsened rhythm for IFT. In general, cueing had a larger effect on IFT and seemed to be less relevant for IMFT. The effects of cueing on tapping performance might be explained by the participant hesitating after each tap while waiting for the next circle to appear. More importantly, however, when participants tapped outside the target area, the next circle did not appear. Participants halted their hand movement, returned to correct the erroneous tap, resulting in higher inter-tap intervals, increased variability, lower fatigue, and fewer total taps. Hence cueing, rather than signaling the next target, provided immediate visual feedback. Considering a time-accuracy tradeoff, the immediate feedback and overall lower tapping speed can also account for the improved tapping accuracy in cued conditions. To summarize, cueing seemed to impair speed, rhythm, reduce fatigue, and improve accuracy of healthy participants, and it probably acted as visual feedback as opposed to a visual cue.

Limitations and future research

The most important caveat of the current paper is that we did not assess a PD patient group. Hence, a natural continuation of this work would validate the IMFT and IFT against gold standard clinical scales in a patient population (i.e., the MDS-UPDRS). Whether PD patients perform better on IFT compared to IMFT, and whether IMFT or IFT is more sensitive to detect medication effects will be assessed in a currently ongoing clinical study. Moreover, the current study did not assess the pharmacological sensitivity of the task. The optimal tapping task(s) must also be able to detect medication changes, otherwise, the task(s)' usefulness in clinical studies will be limited. In addition, even though we observed an increase in tapping speed on the second visit, we did not assess the exact nature of this effect. Future research should address the timescale and magnitude of testing visit effects on the tapping performance with respect to tapping style and/or motivation. Lastly, we did not vary the duration of the finger tapping tasks. Previous literature suggests that 30 seconds can be sufficient to detect fatigue effects,[20] without overburdening the participants. Hence, the 30 second task length makes the set-up suitable for repeated testing, even when conducting studies with rapid-acting (dopaminergic) agents.

The findings, while preliminary, caution against the use of cueing in studies involving PD patients. Previous literature suggests that tapping speed, fatigue and rhythm are clinically relevant predictors of both PD related bradykinesia, as well as medication effects.[11,14,48] In healthy participants, cueing appears to impair the speed and rhythm of tapping, while reducing detectable fatigue. Hence, we argue that the tapping task set-up should be kept as simple as possible, to accurately detect potential differences in speed, rhythm, and change parameters, without inducing experimental noise. Additionally, exact comparisons with other studies remains difficult as technical specification on the implementation are not always reported (see Table 1). We encourage researchers to report on the technical implementation details of their tapping tasks (e.g., target distance, cueing, and duration).

Taken together, it seems preferable to use non-cued IFT and IMFT versions for further (validation) studies involving a PD population. The choice for IMFT or IFT should depend on the research question, as these tasks assess different aspects of movement. IMFT appears to be more difficult for most healthy participants, and one could speculate that IMFT would also be more difficult to perform for PD patients. For instance, Agostino showed that it is significantly more difficult for PD patients to perform alternating finger tapping, as opposed to pronation-supination (i.e., forearm, elbow and shoulder driven movement),[25,45,46] and Lalvay showed that patients with severe parkinsonism have difficulties performing alternate finger tapping as opposed to one finger tapping.[25] In addition, bradykinesia appears to worsen increasingly during isolated, sequential finger movements, as opposed to gross hand movements.[45]

CONCLUSION

The current study provides evidence that the custom developed IMFT and IFT tasks are well-functioning and repeatable measurement tools. From a technical point-of-view, they can be used in clinical trials assessing medication effects on bradykinesia. Recommended parameters are total number of taps, mean spatial error, and rhythm as they showed high repeatability and sensitivity. Moreover, the use of cueing in finger tapping tasks is unwarranted as visually cueing the tapping tasks can, in healthy participants, worsen tapping speed and rhythm, while improving accuracy. The choice for IMFT or IFT, should depend on the research question, as these tasks assess different aspects of movement. Concluding the technical validation step with encouraging results, the IMFT and IFT should be further investigated in subsequent studies with PD patients and in response to dopaminergic medication.

TABLE 1 **Summary of the various finger tapping tasks found in the literature.**

Study	Device	Target distance (cm)	Cueing	Duration	Parameters
Alternate index and middle finger tapping tasks					
Arora[30,32]	Phone application	N.A.	N.A.	N.A.	Numerous. e.g. speed, rhythm, accuracy, fatigue
Lalvay[25]	Smartphone application ('Mementum')	N.A.	Alternating colors (red vs green)	20s	Regularity, rhythm, and changes in the number of taps
Tian[22]	Phone application	N.A.	N.A.	30s	Average number of buttons pressed between both hands
Alternate index finger tapping tasks					
Giancardo[27]	Arcade buttons	25	N.A.	Not clear (possibly 60s)	Average number taps between hands
Lipp[29]; Nutt[35]	Arcade buttons	20	N.A.	60s	Total number of taps
Hasan[20]	Keyboard	20	No	30s	Total number of taps, time spent on keyboards, rhythm, and dysmetria score
	iPhone application ('TapPD')	N.A.	Not clear: changing colors	30s	
	Tablet ('TapPD')	N.A.	Not clear: changing colors	30s	
Arroyo-Gallego[26]	Keyboard	25	N.A.	N.A.	Not clear (possibly the total number of taps)
Mitsi[24]; Wissel[23]	Phone app	N.A.	N.A.	30s	Total number of taps, tap interval, tap duration, and tap accuracy
Young-Lee[21]	Tablet	1.5	N.A.	10s	Numerous. E.g. inter-tap distance, inter-tap interval time, total distance of a finger movement, and tapping speed
Memedi[28]	Touch-pad with a pointer	2.7	N.A. (different target colors)	Not clear (possibly 20s)	Numerous. E.g. speed, accuracy, rhythm, and fatigue

N.A., not available.

TABLE 2 **Tapping task parameters.**

Category	Parameter		Definition
Speed	Total number of taps (#)	TNT	Sum of all taps on the screen
Accuracy	Number of tapping errors (#)	NTE	The number of two (or more) consecutive taps on the same target
	Mean spatial error (mm)	SEA	Average absolute Euclidean distance from the target's center point
	Bivariate contour ellipse area (mm^2)	BCA	Based on Castet & Crossland[38]: A bivariate contour ellipse encompassing a proportion of the highest density of finger taps: $BCA = 2X^2 \pi \sigma_H \sigma_V \sqrt{1-\rho^2}$ where, X^2 is a chi-square variable with 2 degrees of freedom; σ_H *and* σ_V is the SD of the horizontal (X) and vertical (Y) coordinates, respectively; ρ is the product-moment correlation of the two position components
Rhythm	Inter-tap interval SD (ms)	ITS	The SD of the time between two consecutive taps
Fatigue	Velocity: change (cm/min^2)	VEC	A linear slope fitted on all inter-tap velocity values. Velocity was calculated by dividing the inter-tap distance value by the inter-tap interval

SD, standard deviation.

TABLE 3 **Within-day repeatability.**

		IMFT	IFT
Parameter		**ICC (95% CI)**	**ICC (95% CI)**
TNT (#)	Cued	0.94 (0.89, 0.97)	0.86 (0.76, 0.94)
	Non-cued	0.90 (0.82, 0.96)	0.94 (0.89, 0.98)
NTE (#)	Cued	0.81 (0.67, 0.91)	0.41 (0.19, 0.66)
	Non-cued	0.69 (0.5, 0.86)	0.08 (-0.08, 0.37)
SEA (mm)	Cued	0.79 (0.64, 0.90)	0.63 (0.43, 0.82)
	Non-cued	0.75 (0.57, 0.88)	0.76 (0.60, 0.89)
BCA (mm^2)	Cued	0.77 (0.61, 0.89)	0.67 (0.47, 0.83)
	Non-cued	0.05 (-0.12, 0.32)	0.84 (0.71, 0.92)
ITS (ms)	Cued	0.86 (0.76, 0.94)	0.20 (0.00, 0.48)
	Non-cued	0.84 (0.72, 0.93)	0.51 (0.30, 0.74)
VEC (cm/min^2)	Cued	0.56 (0.34, 0.77)	0.25 (0.04, 0.53)
	Non-cued	0.58 (0.34, 0.78)	0.55 (0.34, 0.77)

TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change; IMFT, alternate index and middle finger tapping; ICC, intraclass correlation coefficient; CI, confidence interval; IFT, alternate index finger tapping.

TABLE 4 Between-day repeatability.

		IMFT	IFT
Parameter		**ICC (95% CI)**	**ICC (95% CI)**
TNT (#)	Cued	0.97 (0.93, 0.99)	0.78 (0.51, 0.91)
	Non-cued	0.86 (0.68, 0.94)	0.88 (0.71, 0.95)
NTE (#)	Cued	0.96 (0.89, 0.98)	0.54 (0.13, 0.79)
	Non-cued	0.81 (0.58, 0.92)	0.06 (-0.39, 0.49)
SEA (mm)	Cued	0.80 (0.55, 0.92)	0.53 (0.11, 0.78)
	Non-cued	0.70 (0.38, 0.87)	0.56 (0.15, 0.80)
BCA (mm^2)	Cued	0.60 (0.21, 0.82)	0.73 (0.43, 0.89)
	Non-cued	0.29 (-0.17, 0.65)	0.63 (0.26, 0.84)
ITS (ms)	Cued	0.85 (0.65, 0.94)	0.40 (-0.06, 0.71)
	Non-cued	0.52 (0.01, 0.78)	0.75 (0.47, 0.90)
VEC (cm/min^2)	Cued	0.79 (0.53, 0.91)	-
	Non-cued	0.66 (0.30, 0.85)	0.85 (0.65, 0.94)

TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change; IMFT, alternate index and middle finger tapping; ICC, intraclass correlation coefficient; CI, confidence interval; IFT, alternate index finger tapping; -, value could not be estimated due to the model not converging.

TABLE 5 Sensitivity (MDE) estimates in percentage (%) and absolute values (Abs).

		IMFT	IFT
Parameter		**MDE (Abs)**	**MDE (Abs)**
TNT (#)	Cued	28% (45)	9.5% (6.2)
	Non-cued	19% (37)	11% (9.5)
NTE (#)	Cued	98% (6.1)	57% (1.5)
	Non-cued	49% (6.7)	150% (0.54)
SEA (mm)	Cued	24% (0.73)	12% (0.54)
	Non-cued	20% (0.54)	12% (0.56)
BCA (mm^2)	Cued	48% (22)	35% (55)
	Non-cued	88% (29)	26% (55)
ITS (ms)	Cued	32% (31)	23% (19)
	Non-cued	71% (68)	20% (8.4)
VEC (cm/min^2)	Cued	-	90% (400)
	Non-cued	43% (-370)	170% (-460)

MDE, minimum detectable effect; Abs, absolute value; TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change; IMFT, alternate index and middle finger tapping; -, value could not be estimated due to the model not converging; IFT, alternate index finger tapping.

TABLE 6 F-Test results of fixed effects for each parameter.

Category	Speed	Accuracy			Rhythm	Fatigue
Parameter	TNT $F_{(1, 423.05)}$	NTE $F_{(1, 423.07)}$	SEA $F_{(1, 423.07)}$	BCA $F_{(1, 423.08)}$	ITS $F_{(1, 423.14)}$	VEC $F_{(1, 423.16)}$
Configuration	1412.11 ***	281.97 ***	593.15 ***	965.02 ***	80.14 ***	98.70 ***
Cueing	36.82 ***	5.61 *	0.01	4.77 *	5.87 *	37.03 ***
Measurement	0.95	0.83	0.13	0.76	0.47	0.21
Visit	10.61 **	0.30	7.08 **	0.72	8.51 **	0.67
Configuration × Cueing	0.33	37.24 ***	16.28 ***	10.15 **	12.78 ***	1.64

** p <0.05, ** p <0.01, *** p <0.001*
TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change.

TABLE 7 Occasion effects on tapping performance.

Category	Speed	Accuracy			Rhythm	Fatigue
Parameter (unit)	**TNT (#)**	**NTE (#)**	**SEA (mm)**	**BCA (mm^2)**	**ITS (ms)**	**VEC (cm/min^2)**
Visit 1- Visit 2	-9.86 **	0.29	-0.19 **	-3.99	12.1 **	-46.1
(SE)	(3.03)	(0.53)	(0.07)	(4.7)	(4.14)	(56.4)

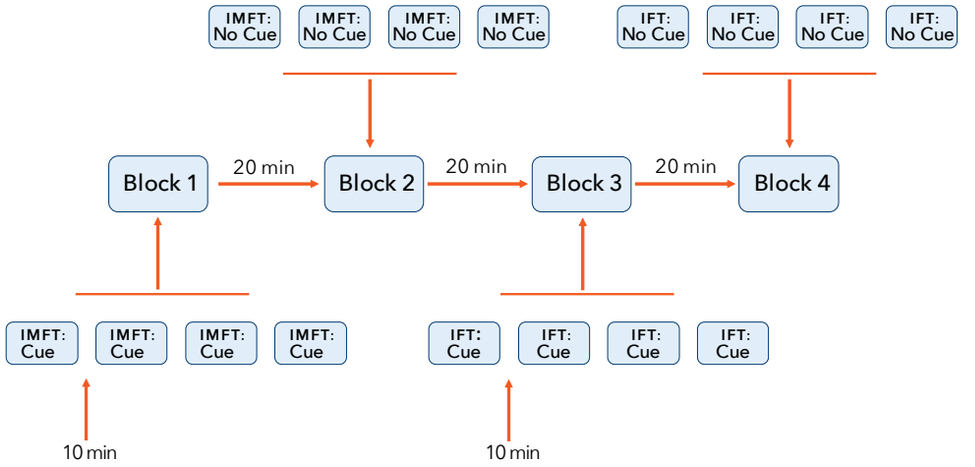
** p <0.05, ** p <0.01, *** p <0.001*
SE, standard error; TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change.

TABLE 8 Effect of task configuration and cueing on tapping performance.

		IMFT		IFT		Difference	
Parameter		EMMean (SE)	ES	EMMean (SE)	ES	IMFT– IFT (SE)	ES
TNT	Cued	185.0 (8.31)		73.0 (8.30)		112 (4.25)***	3.52
	Non-cued	205.1 (8.34)		89.70 (8.31)		115 (4.31)***	3.62
	Diff (C-NC)	-20.01 (4.31)***	-0.63	-16.70 (4.26)***	-0.52		
NTE	Cued	8.21 (1.19)		2.52 (1.19)		5.7 (0.75)***	1.02
	Non-cued	12.73 (1.20)		0.53 (1.19)		12.2 (0.76)***	2.18
	Diff (C-NC)	-4.52 (0.76)***	-0.81	1.99 (0.75)**	0.36		
SEA	Cued	3.03 (0.16)		4.47 (0.16)		-1.44 (0.1)***	-1.93
	Non-cued	2.74 (0.16)		4.75 (0.16)		-2.01 (0.1)***	-2.70
	Diff (C-NC)	0.29 (0.1)**	0.39	-0.28 (0.01)**	-0.37		
BCA	Cued	41.9 (10.3)		172.9 (10.3)		-131 (6.6)***	-2.65
	Non-cued	37.2 (10.4)		198.2 (10.3)		-161 (6.7)***	-3.25
	Diff (C-NC)	4.71 (6.7)	0.09	25.25 (6.6)***	-0.51		
ITS	Cued	84.5 (7.10)		62.2 (7.09)		22.3 (5.81)***	0.51
	Non-cued	89.2 (7.16)		37.4 (7.10)		51.9 (5.90)***	1.19
	Diff (C-NC)	-4.77 (5.90)	-0.11	24.85 (5.81)***	0.57		
VEC	Cued	-336 (91)		152 (90.9)		-488 (79.2)***	-0.82
	Non-cued	-751 (91.9)		-119 (91)		-633 (40.4)***	-1.07
	Diff (C-NC)	416 (91.0)***	0.70	271 (79.2)***	0.46		

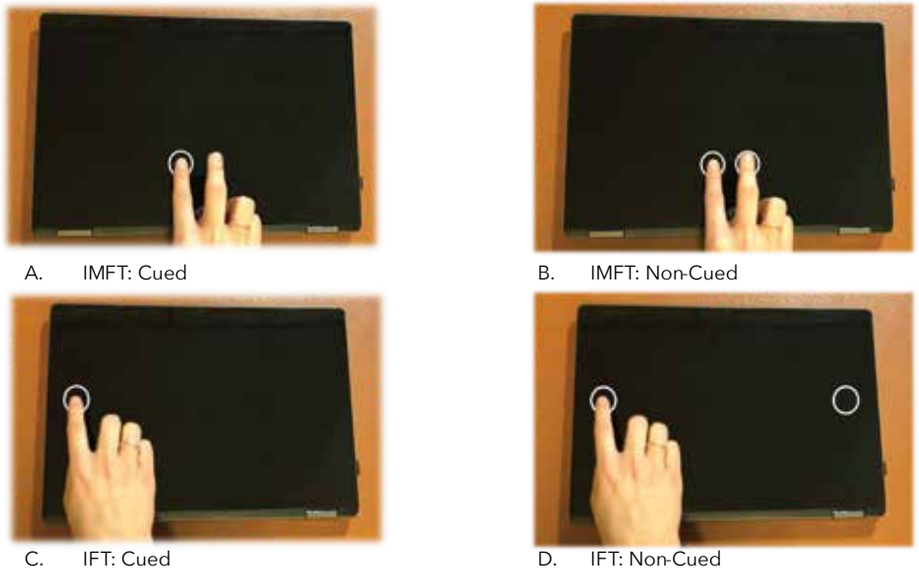
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$
TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change; IMFT, alternate index and middle finger tapping; EMMean, estimated marginal mean; SE, standard error; ES, effect size Cohen's d; IFT, alternate index finger tapping; Diff, difference; C, cued; NC, non-cued.

FIGURE 1 Timing and sequence of tapping tasks during both visits. The order of the experiments was counterbalanced using the Latin square method.



IMFT, alternate index and middle finger tapping; IFT, alternate index finger tapping.

FIGURE 2 Finger tapping tasks. Figures A and B represent alternate index and middle finger tapping (IMFT). Figures C and D represent alternate index finger tapping (IFT). In the cued configurations (A and C), the second circle only appears when a tap inside the target was successfully performed. B and D represent the non-cued tapping tasks.



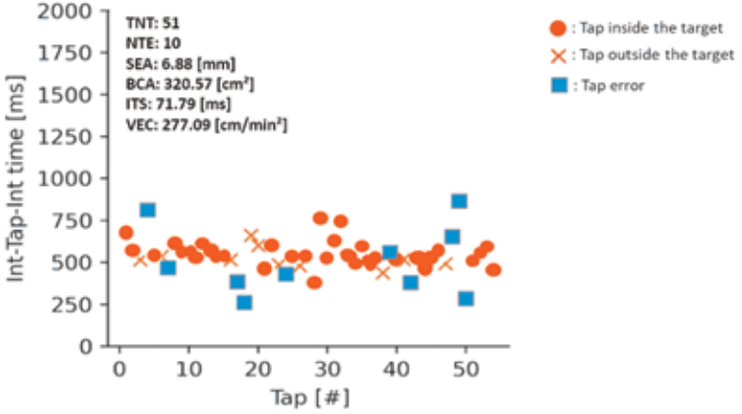
A. IMFT: Cued

B. IMFT: Non-Cued

C. IFT: Cued

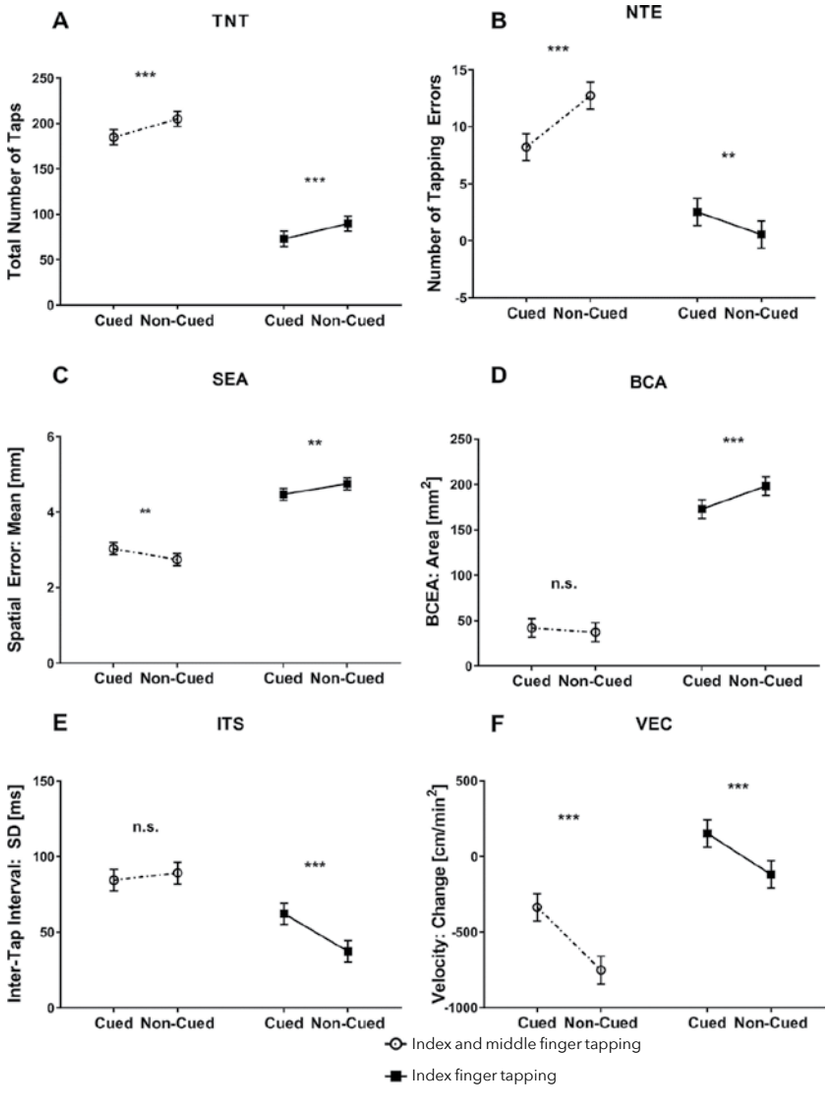
D. IFT: Non-Cued

FIGURE 3 Data output example.



TNT, total number of taps; NTE, number of tapping errors; SEA, mean spatial error; BCA, bivariate contour ellipse area; ITS, inter-tap interval standard deviation; VEC, velocity: change.

FIGURE 4 The effects of configuration and cueing on tapping performance. Effects on total number of taps (TNT) (A), number of tapping errors (NTE) (B), mean spatial error (SEA) (C), bivariate contour ellipse area (BCA) (D), inter tap interval standard deviation (ITS) (E), and change in velocity (VEC) (F).



Values are based on estimated marginal means; error bars represent standard error of the marginal mean.
** p <0.05, ** p <0.01, *** p <0.001, ns=not significant.*

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