Title

Opposite effects of visual cueing during writing-like movements of different amplitudes in Parkinson's disease

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Abstract

Background

Handwriting is often impaired in Parkinson's disease (PD). Several studies have shown that writing in PD benefits from the use of cues. However, this was typically studied during writing and drawing sizes that are usually not used in daily life.

Objective

This study examines the effect of visual cueing on a pre-writing task at small amplitudes (≤ 1.0 cm) in PD and healthy controls to better understand the working action of cueing for writing.

Methods

Fifteen PD patients and 15 healthy age-matched controls performed a pre-writing task at 0.6 cm and 1.0 cm in the presence and absence of visual cues (target lines). Writing amplitude, variability of amplitude and speed were chosen as dependent variables, measured using a newly developed touch-sensitive tablet.

Results

Cueing led to immediate improvements in writing size, variability of writing size and speed in both groups in the 1.0 cm condition. However, when writing at 0.6 cm with cues, a decrease in writing size was apparent in both groups ($p<.001$) and the difference in variability of amplitude between cued and uncued writing disappeared. In addition, the writing speed of controls decreased when the cue was present.

Conclusions

Visual target lines of 1.0 cm improved the writing of sequential loops in contrast to lines spaced at 0.6 cm. These results illustrate that, unlike for gait, visual cueing for fine motor tasks requires a differentiated approach, taking into account the possible increases of accuracy constraints imposed by cueing.

Keywords

- Parkinson's disease

- Cueing

- Handwriting

Introduction

The basal ganglia play an important role during self-generated and well-learned movements [1-3]. As handwriting is an internally-generated and habitual movement, basal ganglia dysfunction inevitably leads to handwriting problems. In the past, handwriting difficulties in Parkinson's disease (PD) were often referred to as micrographia, i.e. a progressive reduction in amplitude during writing [4]. However, writing problems in PD do not only include an amplitude scaling deficit, but also timing deficits, irregularities and breakdown of movement [5-8]. Initially, writing problems seem to respond well to dopaminergic medication. However, improvements due to medication are mainly found for movement speed and to a lesser extent for writing size [5, 7]. Writing faster is often associated with a decreased legibility [9]. With disease progression writing performance may further deteriorate. Therefore, complementary strategies are necessary to maintain or improve writing amplitude in PD.

One possible approach is offering external cueing. Cues provide discrete external information, serving as a reference, target or trigger for movement generation [10]. As patients with PD suffer from difficulties with automatic movement control, cueing was proposed to induce a transition from habitual behavior to a goal-directed mode of motor control [11]. In gait it was shown that cueing has beneficial effects for patients with PD (for review see [12, 13]). So far, only few studies have investigated the effects of cueing on fine motor skills, usually during more visually controlled tasks than gait (for a review see [14]). Both bimanual drawing and writing studies showed that PD patients improve their writing or drawing size in the presence of visual cues [15-18]. However, these studies included writing and drawing sizes of 1.0 cm and larger, whereas older adults generally write a self-generated text at a size of on average 2.4 mm [19]. PD is increasingly prevalent in people who are still working [20] and despite the intensive use of computers, handwriting is still necessary in many professions. Though visual cueing was

shown to be a valuable tool for writing with a larger amplitude and is recommended as a rehabilitation strategy in PD [21], techniques that improve daily life writing sizes, should be further investigated, as suggested by Bryant *et al.* [15]. Therefore, we want to study the effect of visual cues on two different sizes during a pre-writing task. We hypothesize that the therapeutic window of cueing may be smaller in PD for movements in the small amplitude range [22], as a recent study showed that patients with PD experienced more problems when writing at 0.6 cm compared to writing at 1.0 cm during dual-task writing [23]. Furthermore, we want to investigate whether cueing for different amplitudes has a different effect in PD patients and healthy controls. In line with earlier work, we hypothesize that cueing will lead to a reduction in amplitude of loops at the large compared to small amplitude in healthy controls, as they tend to overshoot when writing large in the absence of cues [16].

Materials & Methods

Participants

For this cross-sectional study 30 right-handed participants were tested, including 15 PD patients and 15 healthy age-matched controls. Patients with PD were recruited by the neurologist (W.V.) of the Movement Disorders Clinic at the University Hospital Leuven. Inclusion criteria for PD patients were: (i) diagnosis of PD according to the United Kingdom PD Society Brain Bank criteria [24]; (ii) Hoehn and Yahr (H&Y) stage I to III in the on-phase of the medication cycle [25]; (iii) experiencing writing problems, as identified by a score of 1 or more on item 2.7 (Handwriting) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II; and (iv) without cognitive impairment (Mini-Mental State Examination (MMSE) $\geq$ 24). The exclusion criteria for both patients and healthy controls were: (i) color blindness or other impairments in vision interfering with handwriting; and

(ii) upper limb problems other than those related to PD. All patients were tested in the on-phase of the medication cycle, i.e. approximately 1h after the last drug intake. For eleven patients this was in the morning, while 4 patients were tested in the afternoon. The study design and protocol were approved by the local Ethics Committee of the KU Leuven and were in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki, 1967). After complete explanation of the study protocol, written informed consent was obtained from all participants prior to participation in the study.

Experimental procedure & tasks

Before performing the pre-writing tests, all participants completed a clinical test-battery incorporating overall cognitive status (MMSE [26]), fine motor skills (Purdue Pegboard Test [27] and Manual-Ability Measure (MAM-16) [28]) and emotional behavior (Hospital Anxiety and Depression Scale (HADS) [29]). In addition, disease specific characteristics were assessed by means of the (i) MDS-UPDRS part III [30] and (ii) H&Y scale [25]. In addition, participants were asked to perform a writing test in which they had to copy a standardized text for 5 minutes on paper (Systematic Screening of Handwriting Difficulties (SOS-test) [23, 31]).

Next, participants performed a simple repetitive pre-writing task which allowed assessment of pure writing performance. The same 3-loop sequence was chosen as previously described by Broeder *et al*. [23]. This task offers the advantage that it is a fluent writing-like movement, excluding long left-to-right letter sequences which would require a shift of the hand over the surface and avoiding the involvement of language and higher cognitive demands. This approach ensured optimal experimental control, while still representing a writing-like movement. The pre-writing sequence was performed on a custom-made touch-sensitive writing tablet (**Fig. 1A**) and was performed at two different sizes, 0.6 and 1.0 cm (**Fig. 1B & 1C resp.**), in two cueing

conditions, consisting of visual target zones. The requested writing amplitude was indicated on the tablet by colored target zones (gray, yellow and blue) with a bandwidth of 2 mm. For both sizes, participants were instructed to start writing within the start circle and write the loops from the bottom of the blue target zone until the top of the yellow target zone and returning to the bottom of the blue zone. The distance between the bottom of the blue and top of the yellow target zone was 0.6 or 1.0 cm. After completion of the third loop, participants were instructed to return to the start circle via the gray target zone to avoid left-to-right sequence progression. Each loop disappeared from the screen at the end of the loop figure. This allowed continuous repetition of the same figure without hand repositioning movements during the whole trial of 27 s. In the without cue condition, the target zones were initially presented to indicate the requested amplitude but disappeared after 2 s. Before each task, participants performed one practice trial on paper and one on the writing tablet to become accustomed with writing on the tablet and sudden disappearance of the cue. In addition, participants were instructed to produce natural and fluent loops and write at a comfortable speed.

Data processing and statistical analysis

All data were filtered at 7 Hz with a 4th-order Butterworth filter [8] and further processed using Matlab R2011b. Amplitude (% of target size) and speed (cm/s) were chosen as dependent variables based on previous studies on handwriting [5, 17, 32]. The dependent variables were determined using the same process as previously described in the study by Broeder *et al*. [23]. In short, amplitudes of individual up- and downstrokes were defined by calculating local minima and maxima. To compare the different sizes, the participants' amplitude was expressed as a percentage of the target amplitude (% of target size) to make the data comparable. For each up- and downstroke, the time to complete (s) was computed and used to calculate speed (cm/s). In

addition to these variables, the within-patient coefficient of variation of writing amplitude was also analyzed (COV_{ampl}).

Data processing of the SOS-test was performed manually by a blinded researcher. The total SOS-score measures the handwriting quality and is calculated by evaluating the following criteria: (i) fluency of letter formation, (ii) fluency in connections between letters, (iii) regularity of letter height, (iv) space between words and (v) straightness of the sentences [31]. A higher total SOS-score indicates worse quality of handwriting. Mean writing size (mm) and writing velocity (number of letters written in 5 minutes) were also determined.

Statistical analysis was performed using Statistica software (version 10). All data were checked for normality and equality of variances and appropriate parametric or non-parametric analyses were performed. To compare differences in demographic characteristics between PD patients and healthy controls Mann-Withney U (MWU) tests were used. Amplitude, writing speed and COV_{ampl} were analyzed using a 2 x 2 x 2 repeated measures analysis of variance (ANOVA), with group (PD and CT) as a between-subjects factor and cue (with and without cue) and size (0.6cm and 1.0cm) as within-subjects factors. Significant interactions were further investigated using the Tukey's Honest Significance test as a post-hoc analysis method. Finally, correlations between writing on the tablet and writing on paper were calculated using Spearman Rank tests. Significance levels for all tests were set at $p < .05$.

Results

Participants

Demographics and clinical characteristics of the participants are specified in **Table 1**. Patients and healthy controls did not differ significantly, except for measures of fine motor skills (MAM-

16 and Purdue Pegboard tests, p<.001) and the depression subscale of the HADS (p=.029).

Patients also wrote smaller (p=.056) and slower (p<.001) compared to controls on the SOS-test.

Writing amplitude

A 2 x 2 x 2 ANOVA (group x size x cue) showed a significant interaction between size and cue ($F_{(1,28)}$ = 65.5, p<.001; **Figure 2A**). Post-hoc analysis revealed that writing in the 0.6 cm condition induced a relatively larger amplitude (with cue 80% ± 11%; without cue 86% ± 15%) than in the 1.0 cm condition (with cue 72% ± 11%; without cue 65% ± 11%) for both writing with and without cues (both p<.001). In the 0.6 cm condition, both groups wrote with a larger amplitude in the absence of cues compared to the presence of cues (p<.001). In the 1.0 cm condition, the opposite was true: participants wrote larger with cues compared to without (p<.001) irrespective of group. In addition, a significant main effect of group showed that patients with PD wrote overall significantly smaller than healthy controls ($F_{(1,28)}$ = 9.5, p=.005).

Variability of amplitude (COV$_{ampl}$)

For COV$_{ampl}$ the 2 x 2 x 2 ANOVA (group x size x cue) revealed two significant interactions: between cue and group ($F_{(1,28)}$ = 4.5, p=.044) and between size and cue ($F_{(1,28)}$ = 7.2, p=.012). For the first interaction (Cue x Group), the observation was made that PD patients overall had a higher variability; however this was not significantly different. Post-hoc analysis showed that only in healthy controls there was a significantly higher variability when writing without cues compared to with cues (p<.001) (**Figure 2B**). This was not the case for patients with PD (p=.384). Post-hoc analysis of the size x cue interaction showed that there was no difference in variability between both size conditions while writing with cues (p=.976) (**Figure 2B**). When writing without cues there was a higher variability in the 1.0 cm condition compared to the 0.6 cm condition (p=.001). In addition, a significantly higher variability was found when writing

without cues compared to with cues (p<.001) in the 1.0 cm condition, while there was no difference in variability between cueing conditions in the 0.6 cm condition (p=.572).

Writing speed

For writing speed a significant 2 x 2 x 2 interaction was found ($F_{(1,28)}$ = 10.8, p=.003). Post-hoc analysis showed that both groups wrote faster in the 1.0 cm condition compared to the 0.6 cm condition, both while writing with and without cues (all p<.001) (**Figure 2C**). Furthermore, analysis revealed that healthy controls wrote significantly faster without cues in the 0.6 cm condition (p<.001), while in the 1.0 cm condition they wrote faster in the presence of cues (p<.001). No significant differences were found for patients with PD.

Correlation analysis

The Spearman Rank test showed a high correlation between the total SOS-score (quality) and writing of loops at 1.0 cm without cues (R=-.514; p<.05) and weaker correlation for 0.6 cm without cue (R=-.306; p=.100). Both analyses showed that a better handwriting quality on paper was correlated with writing larger loops on the tablet. In addition, strong correlations were found between writing speed on the tablet and on paper (0.6 cm with cue: R=.584; 0.6 cm without cue: R=.650; 1.0 cm with cue: R=.613; 1.0 cm without cue: R=.675; all p<.001), indicating that writing faster on paper was associated with writing faster on the tablet.

Discussion

In this study it was investigated for the first time whether there was a different response to cueing during a pre-writing task at two sizes comparable to the ones used in daily life, i.e. 0.6 and 1.0 cm, in patients with PD and healthy controls. As anticipated and consistent with previous literature [15-18], patients displayed micrographia compared to controls in all conditions, as well

as during the SOS paper-and-pen test, confirming the validity of the experimental paradigm. The results for writing at 1.0 cm showed immediate improvements in writing size, variability of writing size and speed in the presence of cues in both groups. In contrast, the cue seemed to hinder writing performance in the 0.6 cm condition: writing was smaller and there was no difference in variability compared to uncued writing in both groups. In addition, the writing speed of healthy controls decreased when the cue was present.

Interfering effect of cueing in the small writing condition

During externally-triggered movements, the dorsolateral neural network, consisting of parietal and premotor cortices and cerebellum, has been found to be more active compared to when the same movements are internally controlled in healthy young and older adults [1, 3, 33]. This network may bypass the cortico-basal ganglia pathway which is dysfunctional in PD, as was seen for the pre-writing task at 1.0 cm. However, our results suggest that visual lines may be perceived differently during writing at the small 0.6 cm size. At 0.6 cm the target zones seemed to create an additional accuracy constraint, making the task more complex than the self-generated version. This is in line with a study on forearm movements, which demonstrated size-dependent feedback effects in PD [34]. Fast and small movements were performed better when no visual feedback was available. Conversely, slow and large movements improved in the presence of visual feedback. In addition, several studies reported that fast and small movements, both during gait and upper limb movements, make patients with PD more susceptible to additional difficulties, such as freezing episodes or hastening [16, 35-39]. Therefore, a potential explanation for the fact that negative effects of cueing are more pronounced at small amplitudes is that these conditions could have led to more disordered motor control, at least in patients with PD.

In gait it was already shown that when task demands increase, the attentional resources may become overloaded, causing gait abnormalities [40]. Gait in PD, and even more so under complex conditions, may no longer be considered as an automated activity, requiring executive functioning and attention [41, 42]. Although handwriting is very different from gait, it is not implausible that the cues added task complexity during writing at the small size. Handwriting has been proposed to require executive functioning and attention [43]. As in gait, the capacity to improve writing may thus depend on the ability to use attention for compensation [35], which in turn depends on the individual's cognitive reserve. This cognitive reserve model suggests that the brain actively recruits pre-existing cognitive or other compensatory processes to substitute for ageing or pathology (for a review see [44]). However, when cognitive reserve wears out impairments will become noticeable. Applying this knowledge to the current pre-writing paradigm, the task may have led to the activation of primarily writing specific brain regions, i.e. superior and middle frontal area, superior parietal area and cerebellum, in addition to non-writing specific motor regions [45, 46]. The additional attention drawn to the writing process by means of visual cueing probably implied less automatic performance, triggering additional activity in the parietal and premotor cortices and cerebellum, drawing on the cognitive reserve. While this led to improved performance in the 1.0 cm condition, the greater accuracy constraints imposed by the visual cues in the small pre-writing task added extra stress to these compensatory mechanisms. As a result, we speculate that limitations in neural resources were reached earlier, explaining worse performance in the 0.6 cm condition in the presence of visual cues.

It is also possible that the smaller sized-loops required more visual control regions and more motor areas in line with greater motor precision demands [47] or increased task complexity [48, 49]. The greater involvement of these regions may have precluded the efficient allocation of the

dorsolateral system, as normally the case during externally-triggered movements, thereby leading to compromised performance during writing of small loops.

Similar response of patients and healthy controls

Contrary to our hypothesis, the response of both groups to the different cueing conditions was overall similar. While other studies made strict comparisons between writing or drawing with cues compared to spontaneous movements [16, 17], in the present study every trial started with a short display of visual lines, which disappeared in the uncued condition after 2 seconds. This may have provided an internal reference of the desired amplitude and as such prevented overshooting in controls and thus reduced the relative effect of cueing. Similar to previous studies regarding handwriting and aiming movements and consistent with Fitts' law [50-52], both patients and controls in this study wrote with greater accuracy (% of desired amplitude) in the small compared to the large condition and this was accompanied by slower writing. This speed-accuracy trade-off was observed both in the presence and absence of cueing, supporting the hypothesis that an internal reference of the desired amplitude may have been formed in both groups.

Another explanation for the few between-group effects is that controls and patients were age-matched and that age-related changes in handwriting explained the similar responses in controls [19]. It has been reported that both ageing and PD can lead to executive dysfunction and reduced cognitive reserve [44, 53-55]. As intact executive functioning is important for handwriting, healthy older controls may also have responded to cueing in a similar way. In support of this hypothesis, it was shown previously that the presence of external cues led to less efficient writing movements in healthy elderly compared to young adults [56]. More recently, Vitorio *et al.* showed that in gait, PD patients and healthy controls used the same strategy to capture visual information from visual cues [57].

Although PD patients and controls showed comparable behavior during both internally- and externally-triggered movements in a computerized choice reaction time task [56], there were great differences at the neural level [57]. Results showed increased functional connectivity between the dorsolateral prefrontal cortex (PFC) and lateral premotor cortex (PMC) in patients compared to controls only in the externally-guided condition. These results provided a strong indication for a compensatory role of the PFC-PMC connection to allow patients with PD to maintain task performance at a level similar to that of healthy elderly during external cueing. Further research is warranted to know whether this also applies for a daily-life repetitive activity such as handwriting.

Implications for neurorehabilitation

The current results have important implications for neurorehabilitation aimed at designing the most optimal learning environment for people with a neurological disorder. Visual cueing was shown to be a very effective method to optimize gait (for review see [12, 13]). We found that visual cueing can be used as a strategy to improve writing of loops at sizes larger than average writing size in PD. However, we also demonstrated that cueing is not an optimal strategy for producing smaller loops, in line with daily-life writing. The current results illustrate that cueing needs to be administered with insight into how it changes the task demands of fine motor skills. Hence, cueing effects are task-dependent in PD. As novel technology is invading the field of neurorehabilitation, the development of digitized pens and tablets holds promise for writing training [58]. Such devices are able to provide cueing or feedback when writing quality starts to deteriorate. Also, intermittent cueing or performance feedback may stimulate the formation of an internal representation of the motor task and stimulate consolidation of learning. The current results contribute to the development of such technological devices as it was shown that cueing

should not be delivered in a one-fits-all-fashion, but rather be offered in a differentiated way. Our results suggest further that for letter and loop-training of larger sizes cueing has immediate advantageous effects, which could not be replicated for small sizes. However, long-term training studies should be performed to investigate whether intensive training with visual cues leads to retention and transfer to daily life performance.

Conclusion

In conclusion, we found that while effects of cueing on writing of loops at 1.0 cm were positive, this was not the case for writing at the smaller 0.6 cm amplitudes. We attributed these findings to the additional cognitive load imposed by having to write in a narrow space. These context-dependent effects of cues have an important impact on the rehabilitation of writing skills in PD and illustrate that cueing needs to be administered with care. As a cue may induce a shift from automatic to more controlled processing, requiring more (pre)frontal involvement, ultimately a cue may encourage de-automaticity. Future neuro-imaging research should focus on the underlying mechanisms of cueing during writing, both at small and large amplitudes. Our results confirm the use of visual cueing as a rehabilitation strategy when writing large-sized letters. In addition, alternative cues or feedback strategies using a sensory pen [58], may be valuable techniques for writing small-sized letters. Finally, the results of this study illustrate that further knowledge on cueing and feedback strategies in different motor effectors is needed to understand how patients with PD most optimally adapt to their loss of motor control.

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References

[1] Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Internal vs external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. NeuroImage. 2003 Jul;19(3):764-76.

[2] Francois-Brosseau FE, Martinu K, Strafella AP, Petrides M, Simard F, Monchi O. Basal ganglia and frontal involvement in self-generated and externally-triggered finger movements in the dominant and non-dominant hand. The European journal of neuroscience. 2009 Mar;29(6):1277-86.

[3] Hoffstaedter F, Grefkes C, Zilles K, Eickhoff SB. The "what" and "when" of self-initiated movements. Cerebral cortex. 2013 Mar;23(3):520-30.

[4] Wagle Shukla A, Ounpraseuth S, Okun MS, Gray V, Schwankhaus J, Metzer WS. Micrographia and related deficits in Parkinson's disease: a cross-sectional study. BMJ Open. 2012;2(3).

[5] Lange KW, Mecklinger L, Walitza S, Becker G, Gerlach M, Naumann M, et al. Brain dopamine and kinematics of graphomotor functions. Hum Mov Sci. 2006 Oct;25(4-5):492-509.

[6] Letanneux A, Danna J, Velay JL, Viallet F, Pinto S. From micrographia to Parkinson's disease dysgraphia. Movement disorders : official journal of the Movement Disorder Society. 2014 Oct;29(12):1467-75.

[7] Tucha O, Mecklinger L, Thome J, Reiter A, Alders GL, Sartor H, et al. Kinematic analysis of dopaminergic effects on skilled handwriting movements in Parkinson's disease. J Neural Transm. 2006 May;113(5):609-23.

[8] Van Gemmert AW, Adler CH, Stelmach GE. Parkinson's disease patients undershoot target size in handwriting and similar tasks. J Neurol Neurosurg Psychiatry. 2003 Nov;74(11):1502-8.

[9] Berwick DM, Winickoff DE. The truth about doctors' handwriting: a prospective study. Bmj. 1996 Dec 21-28;313(7072):1657-8.

[10]   Nieuwboer A, Kwakkel G, Rochester L, Jones D, van Wegen E, Willems AM, et al. Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. Journal of neurology, neurosurgery, and psychiatry. 2007 Feb;78(2):134-40.

[11]   Redgrave P, Rodriguez M, Smith Y, Rodriguez-Oroz MC, Lehericy S, Bergman H, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci. 2010 Nov;11(11):760-72.

[12]   Rocha PA, Porfirio GM, Ferraz HB, Trevisani VF. Effects of external cues on gait parameters of Parkinson's disease patients: a systematic review. Clin Neurol Neurosurg. 2014 Sep;124:127-34.

[13]   Spaulding SJ, Barber B, Colby M, Cormack B, Mick T, Jenkins ME. Cueing and gait improvement among people with Parkinson's disease: a meta-analysis. Archives of physical medicine and rehabilitation. 2013 Mar;94(3):562-70.

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[14]   Nackaerts E, Vervoort G, Heremans E, Smits-Engelsman BC, Swinnen SP, Nieuwboer A. Relearning of writing skills in Parkinson's disease: a literature review on influential factors and optimal strategies. Neurosci Biobehav Rev. 2013 Mar;37(3):349-57.

[15]   Bryant MS, Rintala DH, Lai EC, Protas EJ. An investigation of two interventions for micrographia in individuals with Parkinson's disease. Clin Rehabil. 2010 Nov;24(11):1021-6.

[16]   Nieuwboer A, Vercruysse S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. The European journal of neuroscience. 2009 Apr;29(7):1422-30.

[17]   Oliveira RM, Gurd JM, Nixon P, Marshall JC, Passingham RE. Micrographia in Parkinson's disease: the effect of providing external cues. J Neurol Neurosurg Psychiatry. 1997 Oct;63(4):429-33.

[18]   Ringenbach SD, van Gemmert AW, Shill HA, Stelmach GE. Auditory instructional cues benefit unimanual and bimanual drawing in Parkinson's disease patients. Hum Mov Sci. 2011 Aug;30(4):770-82.

[19]   van Drempt N, McCluskey A, Lannin NA. Handwriting in healthy people aged 65 years and over. Aust Occup Ther J. 2011 Aug;58(4):276-86.

[20]   Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Movement disorders : official journal of the Movement Disorder Society. 2014 Nov;29(13):1583-90.

[21]   Sturkenboom IHWM, Thijssen MCE, Gons-van Elsacker JJ, Jansen IJH, Maasdam A, Schulten M, et al. Guidelines for occupational therapy in Parkinson's disease rehabilitation. 2008;

[22]   Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain. 2009 Aug;132(Pt 8):2151-60.

[23]   Broeder S, Nackaerts E, Nieuwboer A, Smits-Engelsman BC, Swinnen SP, Heremans E. The effects of dual tasking on handwriting in patients with Parkinson's disease. Neuroscience. 2014 Mar 28;263:193-202.

[24]   Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of neurology, neurosurgery, and psychiatry. 1992 Mar;55(3):181-4.

[25]   Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967 May;17(5):427-42.

[26]   Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98.

[27]   Tiffin J, Asher EJ. The Purdue pegboard; norms and studies of reliability and validity. J Appl Psychol. 1948 Jun;32(3):234-47.

[28]   Chen CC, Granger CV, Peimer CA, Moy OJ, Wald S. Manual Ability Measure (MAM-16): a preliminary report on a new patient-centred and task-oriented outcome measure of hand function. J Hand Surg Br. 2005 May;30(2):207-16.

[29]   Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.

[30]   Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating

Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement disorders : official journal of the Movement Disorder Society. 2008 Nov 15;23(15):2129-70.

[31]   Van Waelvelde H, Hellinckx T, Peersman W, Smits-Engelsman BC. SOS: a screening instrument to identify children with handwriting impairments. Phys Occup Ther Pediatr. 2012 Aug;32(3):306-19.

[32]   Ponsen MM, Daffertshofer A, Wolters E, Beek PJ, Berendse HW. Impairment of complex upper limb motor function in de novo Parkinson's disease. Parkinsonism Relat Disord. 2008;14(3):199-204.

[33]   Jueptner M, Weiller C. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain. 1998 Aug;121 (Pt 8):1437-49.

[34]   Levy-Tzedek S, Krebs HI, Arle JE, Shils JL, Poizner H. Rhythmic movement in Parkinson's disease: effects of visual feedback and medication state. Experimental brain research. 2011 Jun;211(2):277-86.

[35]   Iansek R, Danoudis M, Bradfield N. Gait and cognition in Parkinson's disease: implications for rehabilitation. Rev Neurosci. 2013;24(3):293-300.

[36]   Moreau C, Defebvre L, Bleuse S, Blatt JL, Duhamel A, Bloem BR, et al. Externally provoked freezing of gait in open runways in advanced Parkinson's disease results from motor and mental collapse. Journal of neural transmission. 2008 Oct;115(10):1431-6.

[37]   Vercruysse S, Spildooren J, Heremans E, Vandenbossche J, Levin O, Wenderoth N, et al. Freezing in Parkinson's disease: a spatiotemporal motor disorder beyond gait. Movement disorders : official journal of the Movement Disorder Society. 2012 Feb;27(2):254-63.

[38]   Vercruysse S, Spildooren J, Heremans E, Vandenbossche J, Wenderoth N, Swinnen SP, et al. Abnormalities and cue dependence of rhythmical upper-limb movements in Parkinson patients with freezing of gait. Neurorehabil Neural Repair. 2012 Jul-Aug;26(6):636-45.

[39]   Williams AJ, Peterson DS, Ionno M, Pickett KA, Earhart GM. Upper extremity freezing and dyscoordination in Parkinson's disease: effects of amplitude and cadence manipulations. Parkinsons Dis. 2013;2013:595378.

[40]   Almeida QJ, Wishart LR, Lee TD. Disruptive influences of a cued voluntary shift on coordinated movement in Parkinson's disease. Neuropsychologia. 2003;41(4):442-52.

[41]   Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. Movement disorders : official journal of the Movement Disorder Society. 2013 Sep 15;28(11):1520-33.

[42]   Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. Movement disorders : official journal of the Movement Disorder Society. 2008 Feb 15;23(3):329-42; quiz 472.

[43]   Van Galen GP. Handwriting: issues for a psychomotor theory. Hum Mov Sci. 1991;10:165-91.

[44]   Stern Y. Cognitive reserve. Neuropsychologia. 2009 Aug;47(10):2015-28.

[45]   Planton S, Jucla M, Roux FE, Demonet JF. The "handwriting brain": a meta-analysis of neuroimaging studies of motor versus orthographic processes. Cortex. 2013 Nov-Dec;49(10):2772-87.

[46]   Purcell JJ, Turkeltaub PE, Eden GF, Rapp B. Examining the central and peripheral processes of written word production through meta-analysis. Frontiers in psychology. 2011;2:239.

[47]   Prodoehl J, Corcos DM, Vaillancourt DE. Basal ganglia mechanisms underlying precision grip force control. Neurosci Biobehav Rev. 2009 Jun;33(6):900-8.

[48]   Caproni S, Muti M, Principi M, Ottaviano P, Frondizi D, Capocchi G, et al. Complexity of motor sequences and cortical reorganization in Parkinson's disease: a functional MRI study. PloS one. 2013;8(6):e66834.

[49]   Wu T, Wang L, Hallett M, Li K, Chan P. Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease. Brain. 2010 Aug;133(Pt 8):2394-409.

[50]   Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psychol. 1954 Jun;47(6):381-91.

[51]   Haaland KY, Harrington DL, Grice JW. Effects of aging on planning and implementing arm movements. Psychol Aging. 1993 Dec;8(4):617-32.

[52]   Teulings HL, Contreras-Vidal JL, Stelmach GE, Adler CH. Adaptation of handwriting size under distorted visual feedback in patients with Parkinson's disease and elderly and young controls. J Neurol Neurosurg Psychiatry. 2002 Mar;72(3):315-24.

[53]   Dirnberger G, Jahanshahi M. Executive dysfunction in Parkinson's disease: a review. J Neuropsychol. 2013 Sep;7(2):193-224.

[54]   Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med. 2013 Nov;29(4):737-52.

[55]   Hindle JV, Martyr A, Clare L. Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis. Parkinsonism & related disorders. 2014 Jan;20(1):1-7.

[56]   Slavin MJ, Phillips JG, Bradshaw JL. Visual cues and the handwriting of older adults: a kinematic analysis. Psychol Aging. 1996 Sep;11(3):521-6.

[57]   Vitorio R, Lirani-Silva E, Pieruccini-Faria F, Moraes R, Gobbi LT, Almeida QJ. Visual cues and gait improvement in Parkinson's disease: which piece of information is really important? Neuroscience. 2014 Sep 26;277:273-80.

[58]   Walker RW, Zietsma R, Gray WK. Could a new sensory pen assist in the early diagnosis of Parkinson's? Expert Rev Med Devices. 2014 May;11(3):243-5.
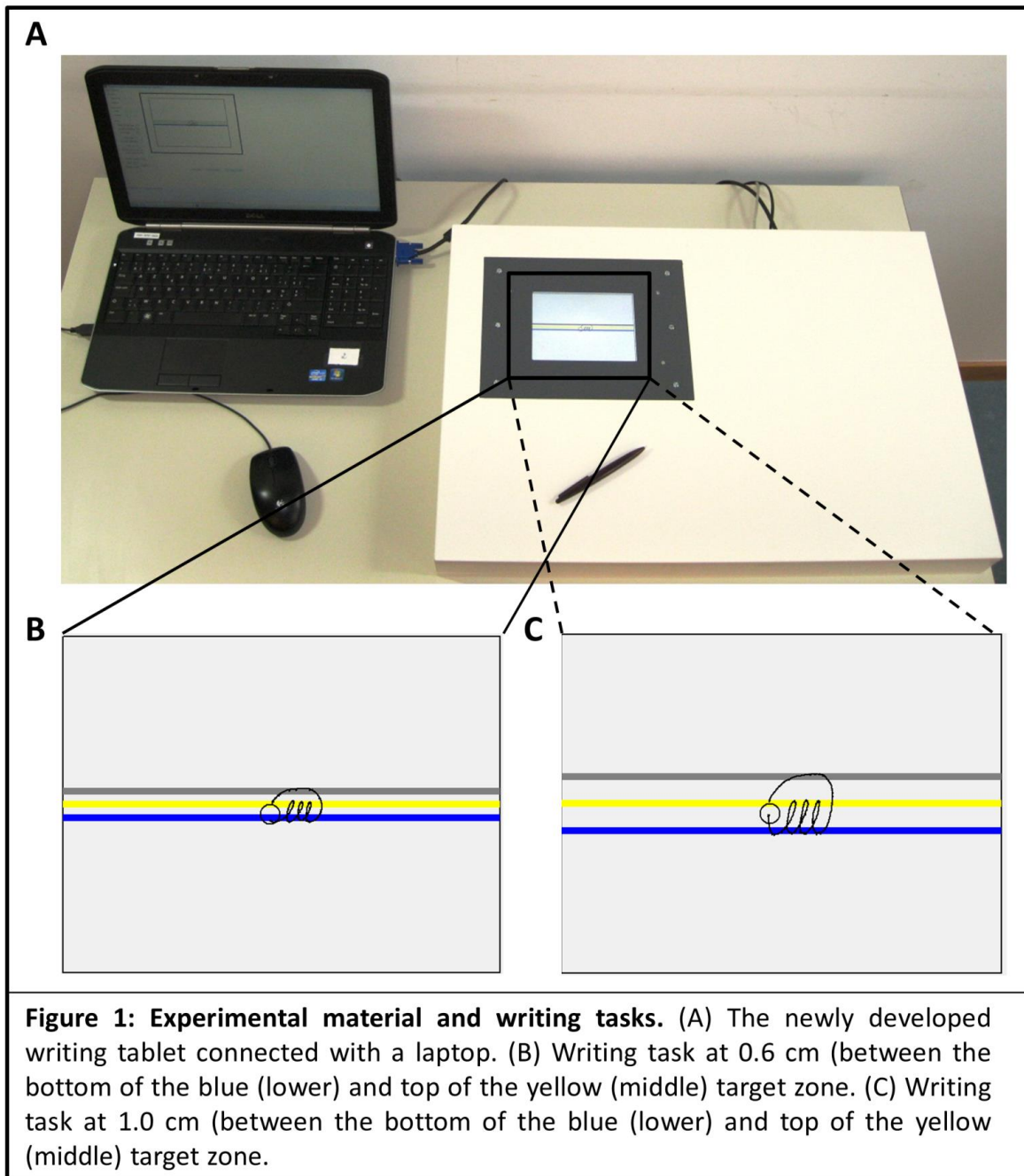
Tables

Table 1: Participant characteristics; median and interquartile range (25%-75%)

Parameter	PD Patients	Controls	P-value
Age (years)	64 (58-71)	62 (60-73)	.806
Gender	9♂ / 6♀	5♂ / 10♀	.217
MAM-16 (0-64)	58 (50-61)	64 (64-64)	<.001*
HADS			
Anxiety (0-21)	3 (1-5)	4 (2-5)	.512
Depression (0-21)	3 (1-5)	1 (0-2)	.029*
MMSE (0-30)	29 (28-30)	29 (29-30)	.174
Disease duration (years)	7 (3-10)	-	-
MDS-UPDRS-III (0-132)	32 (23-39)	-	-
H&Y (I-V)	II (II-II)	-	-
Purdue Pegboard			
Right hand	9 (7-11)	13 (12-14)	<.001*
Left hand	8 (7-11)	13 (11-13)	<.001*
Bimanual	16 (12-18)	21 (18-23)	<.001*
Combination	15 (12-19)	26 (24-30)	<.001*
SOS-test			
SOS-score (0-10)	3 (0-4)	2 (1-3)	.389
Size (mm)	2 (2-2)	2.5 (2-3)	.056(*)
Speed (letters/5minutes)	323 (236-439	509 (465-551)	<.001*

*Groups significantly different at p<0.05 (Mann-Whitney U Test); MAM, Manual Ability Measure; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental State Examination; MDS-UPDRS-III, Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III; H&Y, Hoehn and Yahr staging scale; SOS-test: Systematic Screening of Handwriting Difficulties.

Figures

Figure 1: Experimental material and writing tasks. (A) The newly developed writing tablet connected with a laptop. (B) Writing task at 0.6 cm (between the bottom of the blue (lower) and top of the yellow (middle) target zone. (C) Writing task at 1.0 cm (between the bottom of the blue (lower) and top of the yellow (middle) target zone.
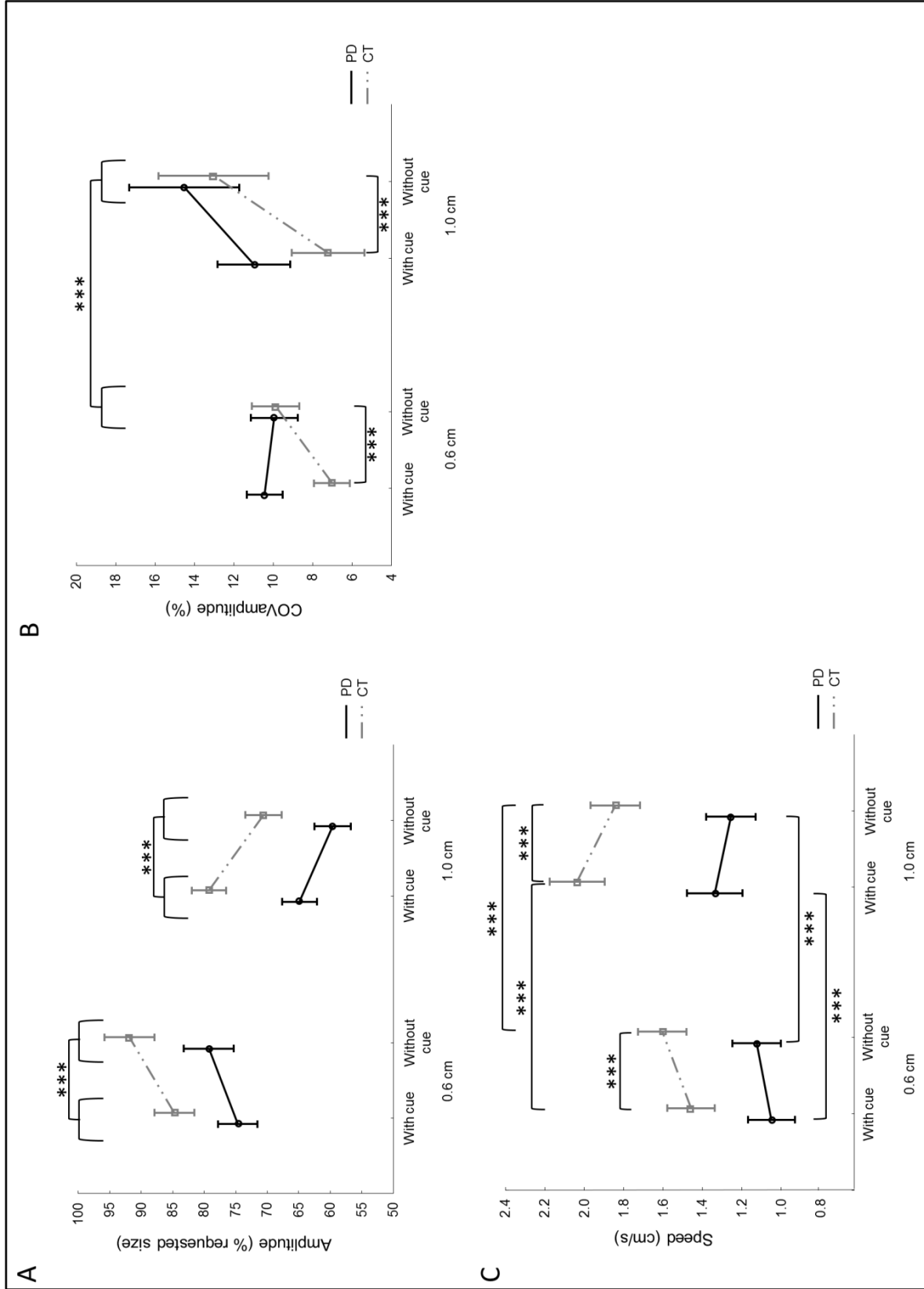
Figure 2: Performance differences between writing with and without cue. (A) For amplitude a significant interaction was found between size and cue (p<.001). Post-hoc analysis showed that both PD patients (PD) and controls (CT) wrote larger without cues in the 0.6cm-condition, while in the 1.0cm-condition this was opposite. **(B)** For COVamplitude an interaction between group and cue (p=.044) was found, showing that CTs wrote with higher variability during writing without cues in both size conditions. In addition, an interaction between size and cue was found (p=.012), indicating higher variability in the 1.0cm-condition compared to the 0.6cm-condition during writing without cue. **(C)** For speed a significant interaction was found between size, cue and group (p=.003), showing that both groups wrote faster in the 1.0cm-condition compared to 0.6cm condition, both during writing with and without cues. CTs also wrote faster without cues in the 0.6-cm condition and slower without cues in the 1.0cm-condition. Variables are displayed as mean ± 1 standard deviation. *** indicate p-values ≤ .001
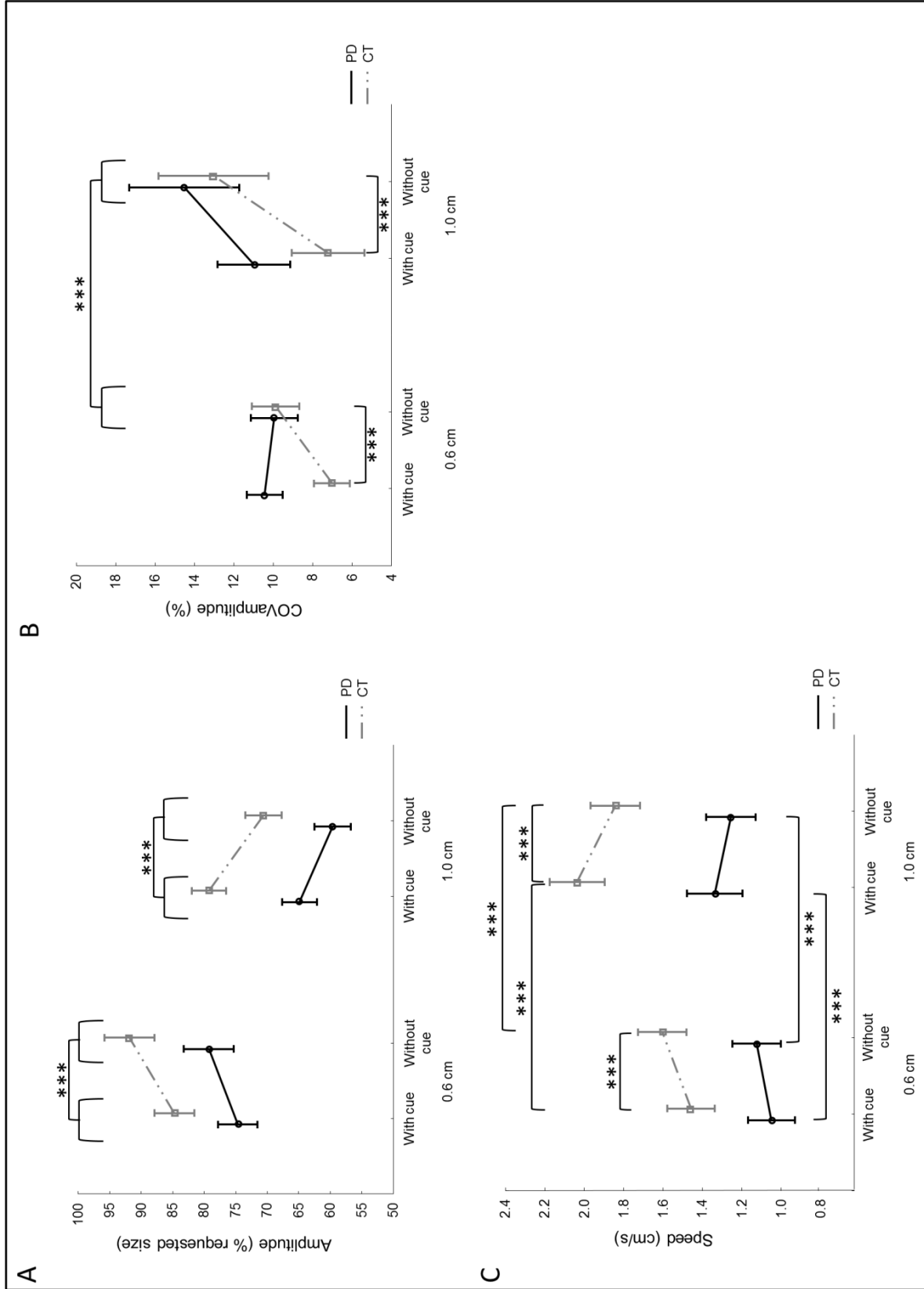
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