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Effects of Targeted Assistance and Perturbations on the Relationship Between Pelvis Motion and Step Width in People With Chronic Stroke

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Abstract

During walking in neurologically-intact controls, larger mediolateral pelvis displacements or velocities away from the stance foot are accompanied by wider steps. This relationship contributes to gait stabilization, as modulating step width based on pelvis motion (hereby termed a “mechanically-appropriate” step width) reduces the risk of lateral losses of balance. The relationship between pelvis displacement and step width is often weakened among people with chronic stroke (PwCS) for steps with the paretic leg. Our objective was to investigate the effects of a single exposure to a novel force-field on the modulation of paretic step width. This modulation was quantified as the partial correlation between paretic step width and pelvis displacement at the step’s start (step start paretic ρ_{disp}). Following 3-minutes of normal walking, participants were exposed to 5-minutes of either force-field assistance ($n = 10$; pushing the swing leg toward mechanically-appropriate step widths) or perturbations ($n = 10$; pushing the swing leg away from

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mechanically-appropriate step widths). This period of assistance or perturbations was followed by a 1-minute catch period to identify after-effects, a sign of altered sensorimotor control. The effects of assistance were equivocal, without a significant direct effect or after-effect on step start paretic ρ_{disp} . In contrast, perturbations directly reduced step start paretic ρ_{disp} ($p = 0.004$), but were followed by a positive after-effect ($p = 0.02$). These results suggest that PwCS can strengthen the link between pelvis motion and paretic step width if exposed to a novel mechanical environment. Future work is needed to determine whether this effect is extended with repeated perturbation exposure.

Index Terms—

Biomechanics; legged locomotion; rehabilitation robotics

I. Introduction

Community-dwelling people with chronic stroke (PwCS) have an elevated fall-risk, with falls most commonly occurring during walking [1]. Many falls are not due to external perturbations (e.g. slips or trips), but are instead attributed to “intrinsic factors” such as impaired balance [2]. Balance deficits have been assessed using metrics of varying complexity, generally finding that relative to age-matched controls, PwCS tend to walk with: shorter and wider steps; more variable step lengths, times, and widths; more variable mediolateral and anteroposterior margins of stability; and larger mediolateral and vertical local divergence exponents (measuring the response to small perturbations) [3]–[5]. Several of these metrics can prospectively predict falls among PwCS (i.e. decreased step length, increased step time and length variability, increased local divergence exponent for mediolateral sacrum motion) [6]. Mediolateral balance deficits are a particular focus of attention, as a substantial proportion of post-stroke falls (~31–38%) occur sideways toward the paretic leg in both the chronic [7] and subacute [8] phase.

Biomechanically, appropriate mediolateral foot placement is an important mechanism for ensuring walking balance [9]. Neurologically-intact controls tend to place their swing foot relatively lateral for steps in which the pelvis has a large mediolateral displacement or velocity away from the stance foot, and relatively medial when the pelvis remains close to the stance foot. This behavior reduces the risk of the center of mass (CoM) moving lateral to the base of support, and can be quantified by relating fluctuations in pelvis motion to step-by-step adjustments in step width [10]. Importantly, pelvis motion at the start of a step predicts the upcoming step width, likely due to a combination of passive body mechanics and active control evidenced by modulation of swing phase gluteus medius activity [11]. In PwCS, the relationship between pelvis motion and step width is weaker for paretic steps, quantified using the partial correlation between mediolateral pelvis displacement and step width (ρ_{disp}) [12]. This paretic side deficit is likely due in part to altered active control, as the normal link between pelvis motion and paretic swing phase gluteus medius activity is disrupted in PwCS with poor balance [13].

Given the post-stroke deficits in the foot placement gait stabilization strategy, we have developed a novel force-field to manipulate the relationship between pelvis motion and step width [14], [15]. In neurologically-intact controls, we have used this force-field to assist mechanically-appropriate mediolateral foot placement, encouraging wide steps when the pelvis is displaced far from the stance foot and narrow steps when the pelvis is close to the stance foot. This approach is based on the proposal that assisting a movement pattern can strengthen an individual's ability to perform this movement independently, due in part to enhanced sensory feedback [16], [17]. Experimentally, we found that assistance had the intended direct effect of increasing ρ_{disp} , indicating a stronger correlational link between pelvis displacement and step width [15]. Conversely, we also used the force-field to perturb appropriate foot placement (e.g. encouraging narrow steps when a wide step is warranted), based on the principle that increasing movement errors can promote motor adaptation and learning [18]. Here, we found that force-field perturbations directly decreased ρ_{disp} , weakening the link between pelvis displacement and step width [15]. As our ultimate goal is to alter gait behavior outside of the force-field, we quantified whether exposure to force-field assistance or perturbations also produced after-effects in ρ_{disp} – an indicator of altered sensorimotor control [18]. Such after-effects were observed, as assistance was followed by short-lived decreases in ρ_{disp} , while perturbations were followed by short-lived increases in ρ_{disp} [15].

While our initial results in neurologically-intact controls are promising, it is unclear whether the relationship between pelvis motion and step width can be similarly altered in PwCS. Encouragingly, prior work has found that novel mechanical environments can indeed evoke changes in gait behavior in this population. Most notably, using a split-belt treadmill to amplify step length asymmetries can cause after-effects in which these asymmetries are temporarily reduced [19]. Similarly, unilaterally resisting forward leg swing can produce after-effects with reduced step length asymmetry [20], [21]. In the frontal plane, forces pushing the pelvis toward the paretic side can cause subsequent after-effects in which the pelvis stays displaced farther away from the paretic leg [22] – an effect that may not be deemed beneficial. In each case, a novel mechanical environment produced changes in a targeted biomechanical behavior.

The purpose of this study was to investigate the effects of a single force-field exposure on the step-by-step modulation of paretic step width among PwCS. Specifically, we tested whether applying force-field assistance or perturbations had direct effects on the relationship between paretic step width and mediolateral pelvis displacement at the start of the step, as well as whether after-effects were observed once these forces ceased. Based on our prior results, we hypothesized that assistance would directly strengthen the relationship between pelvis displacement and step width (increase ρ_{disp}), but would be followed by negative after-effects as ρ_{disp} would decrease relative to baseline once the assistance ceased. Conversely, we hypothesized that perturbations would have the direct effect of decreasing ρ_{disp} , but would be followed by positive after-effects in which ρ_{disp} increased. Such results would demonstrate that PwCS have the ability to modulate the sensorimotor control underlying the foot placement stabilization strategy.

II. Methods

A. Participants

A total of twenty PwCS participated in this study. This sample size was based on preliminary results presented in Supplementary Material (Appendix A), in which twelve PwCS were exposed to various forms of force-field assistance. Here, we expand our previous investigation of assistance to also include perturbations.

Basic information regarding participant demographics and function is presented in Table I. Participants were recruited from a previous screening session used to determine whether they met the study's inclusion and exclusion criteria. Inclusion criteria were: age ≥ 21 years; experience of a stroke ≤ 6 months prior; residual paresis in a lower extremity; preferred overground gait speed of at least 0.2 m/s; ability to walk for 3-minutes without a cane or walker; a step start paretic ρ_{disp} value (described in the Introduction and detailed below) of below 0.56, the lower bound of the 95% confidence interval for this metric among neurologically-intact participants walking at a typical preferred speed [23]. Exclusion criteria were: a resting heart rate above 110 beats/min or blood pressure above 200/110 mm Hg; history of cardiac dysfunction; pre-existing neurological disorders; severe visual impairment; history of pulmonary embolism; uncontrolled diabetes; orthopedic injuries or conditions with the potential to alter foot placement. Participants were permitted to wear ankle foot orthoses (AFOs), if worn during real-world walking (see Table I). All participants provided written informed consent using a form approved by the Medical University of South Carolina Institutional Review Board and consistent with the Declaration of Helsinki.

B. Experimental Protocol

Prior to the experiment, participants were informed that in some trials the force-field would push their legs sideways while they walked, and that these forces may either help them stay balanced or challenge their balance. Participants were randomly assigned to either the Assistive ($n = 10$) Perturbing ($n = 10$) or group, but were not informed of their group assignment. Participants in both groups performed a series of 3-minute walking trials at their self-selected speed, defined as the speed used "to walk around your house or the store" and identified by iteratively increasing the treadmill speed. All participants wore a harness attached to an overhead rail that did not support body weight, but would have prevented a fall in case of a loss of balance. Participants were not permitted to hold onto a handrail, which can alter the control of walking balance [24].

For the first treadmill trial (Normal), participants were not interfaced with the force-field. For the second trial, the force-field remained in either Assistive or Perturbing mode (described below) throughout the trial, corresponding to the participant's group assignment. For the third trial, the force-field was in Assistive/Perturbing mode for the first 2-minutes, before switching to Transparent mode (described below) for the final minute. The structure of the experiment is illustrated in Figure 1. Our prior work in neurologically-intact participants found that 5-minutes of force-field exposure was sufficient to produce after-effects during the subsequent minute of walking [15], [25]. Here, trial duration was 3-minutes and breaks were provided to reduce the risk of fatigue.

C. Force-Field Design and Control

The force-field used to exert mediolateral forces on participants' legs has been described in detail previously [15], [25]. Briefly, forces are applied using steel wires running parallel with the treadmill belts and in series with extension springs. The wires pass through cuffs worn on the lateral side of the shanks, allowing free anteroposterior and vertical leg motion. Linear actuators (UltraMotion; Cutchoge, NY, USA) are used to vary the mediolateral position of the wires interfacing with the swing leg, encouraging participants to step to a targeted step width. The mediolateral leg forces are proportional to the leg's deviation from the targeted mediolateral location, with an effective mediolateral stiffness of 180 N/m. The force-field was controlled using feedback from active LED markers (PhaseSpace; San Leandro, CA, USA) placed on the participants' sacrum, heels, and leg cuffs.

While our primary focus is on altered control of steps taken with the paretic leg [12], [13], the force-field applied forces to both the paretic and non-paretic legs during their swing phases. This approach allowed a secondary analysis of the effects of the applied forces on the control of non-paretic steps, which may be more similar to that in neurologically-intact populations. Additionally, in this initial investigation, the forces applied to legs were not varied based on individual participant's baseline motor function (e.g. walking speed or Fugl-Meyer lower extremity motor score).

The Transparent mode was designed to minimize the mediolateral leg forces experienced by users, as the force-field wires were continuously repositioned to stay aligned with the corresponding leg cuff.

The Assistive mode was designed to assist participants with placing their swing foot in a mechanically-appropriate mediolateral location. For example, if the pelvis was far to the right of the stance foot at the start of a right step, the force-field would push the swing leg laterally to encourage a wide step. The targeted location was determined for each step based on the following equation, derived empirically from neurologically-intact participants [23]:

$$SW = A * x_{pelvis} + B * SW_{mean} \quad (1)$$

Here, x_{pelvis} is the mediolateral location of the sacrum relative to the stance heel at the start of the step. SW_{mean} is the participant's mean step width, as calculated from the last 50-steps of the initial Normal walking trial. A and B are coefficients that vary with participant walking speed, as illustrated in Figure 2. We chose this control equation as pilot experiments (Supplementary Material; Appendix A) found it to be sufficient to produce measurable changes in the relationship between pelvis displacement and step width.

The Perturbing mode was designed to push participants' steps away from a mechanically-appropriate location, potentially requiring an active response to prevent a loss of balance. If a wide step was mechanically warranted, the force-field would push the swing leg to take a narrow step, and vice versa. For example, if the pelvis was far to the right of the stance foot at the start of a right step, the force-field would push the swing leg medially to encourage a narrow step, increasing the risk of the center of mass moving lateral to the base of support

during the subsequent stance phase. The force-field control equation took the same form as Equation 1 above, with coefficients again illustrated in Figure 2.

D. Data Collection and Processing

The locations of LED markers placed on the sacrum, bilateral heels, and bilateral leg cuffs were sampled at 120 Hz, and low-pass filtered at 10 Hz. Each step start was defined to occur when the ipsilateral heel velocity changed from posterior to anterior [26]. Each step end was defined to occur when the contralateral heel velocity changed from posterior to anterior.

Our primary outcome measure was the partial correlation between the step width and the mediolateral displacement of the pelvis from the stance foot at the start of the paretic step, accounting for mediolateral velocity of the pelvis (hereby termed step start paretic ρ_{disp}). This metric quantifies a relationship that is important for mediolateral balance during walking [9], with a focus on potential adjustments that can occur during a step. We have previously shown that this metric is decreased for paretic steps among PwCS [12]. While mediolateral pelvis velocity plays a secondary role in influencing step width [23], this relationship is not altered for paretic steps [12].

Although our primary focus is on the link between paretic step width and pelvis displacement at the start of a step, for illustrative purposes we quantified this relationship for pelvis displacement throughout the course of both paretic and non-paretic steps. Specifically, at each normalized time point in a step (from 0–100), we calculated ρ_{disp} based on the pelvis displacement and velocity values at this time point. The value of this metric at the end of a step (step end ρ_{disp}) is of secondary interest, as it is conceptually similar to step-by-step variability in mediolateral margin of stability values calculated from extrapolated center of mass [10] – a more common metric of walking balance.

We defined step width as the mediolateral displacement between the ipsilateral heel marker at the step end and the contralateral heel marker at the step start. We defined mediolateral foot placement as the mediolateral displacement between the sacrum and the ipsilateral heel at the step end. Finally, we defined step length as the difference between the anterior position of the ipsilateral heel at the step end and the anterior position of the contralateral heel at the previous step end, accounting for treadmill speed. We calculated the mean of these metrics for both paretic and non-paretic steps.

Each of the aforementioned gait metrics was calculated for each minute of walking. Due largely to differences in walking speed, the number of steps per minute varied widely across participants (range = 25–52; mean \pm s.d. = 40 \pm 7). The focus of this initial study in PwCS was on the presence of direct effects and after-effects produced by our force-field (rather than the time course of any such effects). Therefore, for each participant we calculated the average value of each gait metric across the three 1-minute periods of the initial Normal trial, as well as across the five 1-minute periods in which assistance or perturbations were delivered.

E. Statistics

Due to the relatively small sample size, we used non-parametric statistics to investigate potential direct effects and after-effects of force-field exposure. For our primary analysis

in the Assistive group, we applied Wilcoxon signed rank tests to compare the average value of step start paretic ρ_{disp} between the Normal and Assistive periods (direct effects), and to compare this metric between the Normal and Transparent periods (after-effects). To account for performing two comparisons, the alpha value indicating significance was set to 0.025. This primary analysis was repeated for the Perturbing group to detect direct effects and after-effects on step start paretic ρ_{disp} . In secondary analyses, an identical statistical approach was applied for both the Assistive and Perturbing groups to test for direct effects and after-effects on: step end paretic ρ_{disp} ; step start non-paretic ρ_{disp} ; step end non-paretic ρ_{disp} ; mean step width; mean step length; mean mediolateral foot placement. Each of the traditional gait metrics was compared for both paretic and non-paretic steps.

III. Results

The partial correlation between pelvis displacement and step width (ρ_{disp}) increased over the course of a step, as illustrated for participants in both the Assistive (Fig. 3a–b) and Perturbing (Fig. 3c–d) groups. The magnitude of ρ_{disp} during a step was generally smaller for paretic steps than non-paretic steps, and the force-field effects differed between the Assistive and Perturbing modes.

Changes in paretic ρ_{disp} were more apparent with perturbations than assistance. Assistance did not have a significant direct effect ($p = 0.037$; Fig. 4a) on our primary metric of step start paretic ρ_{disp} . Nor were any significant after-effects ($p = 0.77$; Fig. 4b) observed once the assistance ceased. In contrast, perturbations directly caused a significant decrease ($p = 0.004$; Fig. 4c) in step start paretic ρ_{disp} , followed by a significant increase ($p = 0.020$; Fig. 4d) after the perturbations ceased. For our secondary measure of step end paretic ρ_{disp} , assistance had no significant direct ($p = 0.56$; Fig. 4e) or after effects ($p = 0.38$; Fig. 4f). Perturbations significantly decreased step end paretic ρ_{disp} while applied ($p = 0.014$; Fig. 4g), but had no significant after-effects ($p = 0.85$; Fig. 4h).

The force-field's effects on non-paretic steps differed somewhat from paretic steps. Assistance again had no significant direct effects ($p = 0.92$; Fig. 5a) or after-effects ($p = 0.11$; Fig. 5b) on step start non-paretic ρ_{disp} . While perturbations directly caused a significant decrease in step start non-paretic ρ_{disp} ($p = 0.010$; Fig. 5c), no significant after-effects ($p = 0.11$; Fig. 5d) were observed. Both assistance and perturbations appeared to directly reduce step end non-paretic ρ_{disp} (Fig. 5e, g), although neither of these reductions reached significance (Assistive $p = 0.037$; Perturbing $p = 0.028$). Neither assistance ($p = 0.084$; Fig. 5f) nor perturbations ($p = 0.13$; Fig. 5h) caused significant after-effects on step end non-paretic ρ_{disp} .

The effects of assistance and perturbations on traditional gait metrics are presented in Table II. Assistance had no significant effect on step width, step length, or mediolateral foot placement. In contrast, perturbations had the direct effect of increasing step width (due to more lateral paretic foot placement), but did not influence step length. No after-effects in these metrics were present once the perturbations ceased.

IV. Discussion

We investigated whether a single exposure to assistive or perturbing forces influenced the relationship between pelvis motion and step width in PwCS, with results partially supporting our hypotheses. Force-field assistance did not consistently strengthen the relationship between pelvis displacement at the start of a step and paretic step width, and had no notable after-effects. Conversely, force-field perturbations directly weakened this relationship, as the stepping leg was pushed away from a mechanically-appropriate location. Perturbation cessation was followed by a period of after-effects in which the relationship between pelvis displacement at the start of a step and paretic step width was strengthened relative to baseline, indicative of altered sensorimotor control.

Force-field assistance did not have a consistent effect on the relationship between pelvis displacement and paretic step width. Unlike in neurologically-intact participants [15], the direct effects of assistance on step start paretic ρ_{disp} did not reach our set level of significance ($p = 0.038$), with an observed Cohen's d effect size of 0.9. However, we note that only the two participants with the highest baseline values of step start paretic ρ_{disp} did not exhibit a clear increase with assistance (see Fig 4a). Additionally, assistance did significantly increase step start paretic ρ_{disp} for the separate population of PwCS in the pilot experiment described in the Supplementary Material. Perhaps for the participants with near-normal paretic ρ_{disp} values, assistive forces interfered with the baseline gait pattern perceived as stable, and thus were resisted. Similar counter-intuitive effects of assistance have been previously observed in PwCS, with artificial plantarflexor power reducing anterior propulsive forces [27], and knee flexion assistance for swing phase ground clearance increasing leg circumduction [28]. Achieving consistent beneficial effects may require adjustment of the force-field control paradigm, such that some participants do not perceive the assistance as perturbations that should be resisted. Beyond the equivocal direct effects, we observed no consistent after-effects on step start paretic ρ_{disp} following force-field assistance. These initial results thus provide no evidence that a brief period of assistance allows PwCS to discover and maintain the targeted gait pattern, although this general approach is common in clinical practice [29].

In contrast to force-field assistance, perturbations had significant direct effects and after-effects on the relationship between pelvis displacement at the start of a step and paretic step width. These effects were similar to those in neurologically-intact controls [15]; perturbations directly caused a decrease in step start paretic ρ_{disp} , but also caused a subsequent positive after-effect once the perturbations ceased. This after-effect demonstrates that as a group, PwCS have the ability to walk with a stronger relationship between pelvis motion and paretic step width – a relationship often weakened in this population [12]. As with assistance, visual inspection of our results (Fig. 4d) suggests a possible effect of baseline function. The only participants not to exhibit a positive after-effect were the two with the lowest baseline value of step start paretic ρ_{disp} . Previous work in sensorimotor adaptation and learning has suggested just such an effect – individuals with a low skill level may not benefit from perturbations that augment movement errors [17], [30]. Instead, task difficulty should be based on an individual's skill level, an idea formalized in the challenge point framework [31].

As with our primary metric (paretic step start ρ_{disp}), our secondary metrics were more clearly affected by perturbations than assistance. Specifically, assistance did not significantly strengthen the relationship between pelvis displacement and step width for non-paretic steps, or when calculated based on pelvis displacement at the end of the step. In fact, we observed a non-significant trend ($p = 0.037$) for assistance to reduce non-paretic step end ρ_{disp} , contrary to our expectations. This decrease may be due to the preference of many PwCS to keep their non-paretic leg close to their CoM [12], [13], [32]; assistive forces that pushed the non-paretic leg laterally may have been perceived as de-stabilizing, and resisted. Assistance also did not produce consistent after-effects, and did not influence mean step width, step length, or foot placement. On the other hand, perturbations directly reduced our secondary measures of step end paretic ρ_{disp} and step start non-paretic ρ_{disp} (although not step end non-paretic ρ_{disp}), indicating effective perturbation of the targeted stabilization strategy throughout the paretic step, and at least at the start of the non-paretic step. Following the perturbations, we did not observe significant positive after-effects for our secondary ρ_{disp} measures.

Based on our recent work in neurologically-intact participants, the sensorimotor adjustments that underlie potential after-effects may require longer than 5-minutes of perturbation exposure [25]. Alternatively, perhaps sensorimotor adjustments could be facilitated by switching between mechanical environments more often (e.g. more brief periods in Transparent mode), an approach that can accelerate relearning during split-belt walking [33]. In addition to altering the relationship between pelvis motion and step width, applying perturbations directly caused wider steps and more lateral paretic foot placement. Importantly, the equation used to control the perturbations accounted for each participant's mean step width, and thus did not directly push the legs to take wider steps. Instead, the wider steps and more lateral paretic foot placement is likely due to perceived instability, particularly when transitioning into paretic stance [11], [34].

Our primary finding is that as a group, PwCS can adjust their gait pattern so pelvis displacement at the start of a step is more closely linked to paretic step width – thus strengthening a presumably useful gait stabilization strategy. Our presumption that this strategy is useful is based on the consistent theme from model simulations [35], bipedal robot design [36], and assistive exoskeletons [37], [38] that adjusting mediolateral foot placement is an efficient method of ensuring walking balance. However, the finding that many PwCS have the ability to strengthen this strategy after a short period of perturbations raises the question of why they do not simply do so in their baseline gait pattern. The use of a gait pattern perceived by observers to be non-ideal is common post-stroke, perhaps best exemplified by step length asymmetry. Many PwCS walk with substantial step length asymmetries, but can adopt a more symmetric gait after a brief period of split-belt walking in which these asymmetries are amplified [19]. One possible explanation for the post-stroke use of “non-ideal” movement patterns is that individuals develop and strengthen these habits in the acute or sub-acute phase, when brain plasticity is heightened [39]. In the early stages after a stroke when control of the paretic leg can be quite impaired, a strategy of placing the paretic leg far laterally irrespective of pelvis motion could be beneficial by simplifying control, reducing the risk of a loss of balance toward the paretic side, and allowing gravity to redirect the CoM back toward the stronger leg [40]. This habitual movement pattern may be

retained even as paretic leg function improves. Alternatively, it is possible that walking with consistently lateral paretic foot placement (or notable step length asymmetries) has benefits in the chronic stage that are not yet known. The present study is not able to differentiate between these possibilities.

This initial investigation in PwCS focused on a single exposure to assistance or perturbations, and cannot provide insight into longer-term effects of walking in these novel mechanical environments. It is possible that participants gradually revert back to their baseline gait pattern once they return to the original mechanical environment (e.g. when perturbations cease) [18]. Indeed, while the present walking trials were brief to reduce the risk of fatigue, our prior work in neurologically-intact participants found that the positive after-effects following perturbations disappear in ~1 minute of walking [15], but become longer lasting with repeated perturbation exposure [25]. Other perturbation paradigms in patients with neurological injuries have similarly suggested the potential for sustained changes with repeated exposure to a novel mechanical environment. Step length asymmetry can be reduced with repeated periods of split-belt walking [41], step lengths can be increased with repeated swing leg resistance [42], and multiple bouts of pelvis perturbations can improve stabilizing responses [43]. Speculatively, the evoked gait changes may only be sustained if they are perceived by the participant to be superior to their baseline movement pattern in some way [18]. It is feasible that repeated experience with more mechanically-appropriate adjustments of step width would be perceived by PwCS as beneficial to their gait stability, allowing them to overcome habitual movement patterns.

Our force-field is designed to perturb one aspect of gait – the relationship between pelvis motion and step width. While this behavior is believed to be important for gait stability [9], many other methods can be used to perturb walking balance. Prior work in older adults has predominantly focused on translating the treadmill surface to elicit slip-like, trip-like, or mediolateral perturbations [44]–[48]. More recently, similar approaches have been applied among PwCS [49]–[52], with results suggesting that this population can improve their balance responses. An alternative approach applies mediolateral forces to the trunk during walking. While these forces can assist symmetric weight shift by pushing the pelvis toward the paretic leg [22], [53], [54], other work has sought to either augment pelvis motion errors by pushing the pelvis farther toward the non-paretic leg [53], or apply unpredictable mediolateral forces [43]. In the longer-term, it would be valuable to compare the effects of these various perturbation paradigms. Given the apparent specificity of perturbation responses [45], discrete perturbations requiring a reactive response (e.g. slip perturbations) may have a different effect on the sensorimotor control of balance than the present work's focus on perturbations designed to encourage the restoration of a specific gait behavior (e.g. a stronger relationship between pelvis motion and step width).

A limitation of this study is the small sample size, which likely prevented us from detecting potential effects of force-field exposure with moderate effect sizes. However, the observed direct effects and after-effects of perturbations in this small population motivate a more detailed investigation. Additionally, despite random group assignment of participants, the mean walking speed of the Assistive group trended higher than that of the Perturbing group ($p = 0.053$; Wilcoxon rank sum), while more of the Assistive group wore AFOs

(5/10 vs. 1/10). Either of these group differences could have contributed to the observed effects. The present work suggests that the baseline function of individual PwCS may indeed influence the force-field's effects (e.g. high functioning individuals did not exhibit a direct increase in step start paretic ρ_{disp} with assistance; low-functioning individuals did not exhibit a positive after-effect following perturbations). Larger or more consistent changes in gait behavior may have also been produced if the magnitude of the applied forces varied across participants based on their baseline motor function. Perhaps individuals with lower paretic motor function would be more likely to benefit from weaker perturbations, which they may have sufficient strength to effectively resist. While important effects of baseline function have previously been described [17], a substantially larger sample size would be required to investigate this topic rigorously. Beyond the potential importance of individual variability in physical capacity, recent work suggests that cognitive function can influence whether PwCS adapt their gait behavior to novel mechanical demands [55]. Future work in this area could benefit from the addition of cognitive measures to the inclusion criteria, or perhaps the use of such measures as a covariate in analysis.

The results of the present study suggest that mechanical assistance does not promote restoration of the foot placement strategy typically used to ensure walking balance, whereas mechanical perturbations do – at least in the short-term. More direct clinical application will require longer-term, larger-scale studies to determine whether the link in PwCS between a disrupted foot placement strategy and poor walking balance [13] is causal. Specifically, finding that repeated exposure to force-field perturbations improves walking balance (as assessed by clinical tests) would motivate the clinical use of this strategy. An ultimate goal is to determine whether perturbation-based interventions can reduce the high rate of post-stroke fall incidence [1], [2] that can limit mobility and quality of life. Tracking fall events outside of a laboratory setting will be particularly important, as it can be challenging to accurately assess the real-world circumstances of a fall [56]. Notably, it is unclear if our focus on mediolateral walking balance during forward walking is the most important focus of intervention for this clinical population.

In conclusion, targeted perturbations can cause people with chronic stroke to strengthen the relationship between pelvis motion and paretic step width, while assistance is generally less effective. Although this result suggests that many PwCS have the ability to successfully execute a gait stabilization strategy based on foot placement adjustments, future work is needed to achieve clinical relevance. Most notably, it is unclear whether the strengthened link between pelvis motion and paretic step width can be retained for longer periods of time (possibly with repeated exposure), whether changes in this gait behavior truly benefit walking balance in terms of clinical measures of function, and whether only a subset of participants will benefit from this approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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References

- [1]. Weerdesteyn V, Niet MD, van Duijnhoven HJR, and Geurts ACH, "Falls in individuals with stroke," *J. Rehabil. Res. Develop*, vol. 45, no. 8, pp. 1195–1214, 2008.
- [2]. Jørgensen L, Engstad T, and Jacobsen BK, "Higher incidence of falls in long-term stroke survivors than in population controls: Depressive symptoms predict falls after stroke," *Stroke*, vol. 33, no. 2, pp. 542–547, Feb. 2002. [PubMed: 11823667]
- [3]. Balasubramanian CK, Neptune RR, and Kautz SA, "Variability in spatiotemporal step characteristics and its relationship to walking performance post-stroke," *Gait Posture*, vol. 29, no. 3, pp. 408–414, Apr. 2009. [PubMed: 19056272]
- [4]. Hak L et al. , "Stepping strategies used by post-stroke individuals to maintain margins of stability during walking," *Clin. Biomech*, vol. 28, nos. 9–10, pp. 1041–1048, Nov. 2013.
- [5]. Kao P-C, Dingwell JB, Higginson JS, and Binder-Macleod S, "Dynamic instability during post-stroke hemiparetic walking," *Gait Posture*, vol. 40, no. 3, pp. 457–463, Jul. 2014. [PubMed: 24931112]
- [6]. Punt M, Bruijn S, Wittink H, Port I, and Dieën J, "Do clinical assessments, steady-state or daily-life gait characteristics predict falls in ambulatory chronic stroke survivors?" *J. Rehabil. Med*, vol. 49, no. 5, pp. 402–409, 2017. [PubMed: 28475196]
- [7]. Hyndman D, Ashburn A, and Stack E, "Fall events among people with stroke living in the community: Circumstances of falls and characteristics of fallers," *Arch. Phys. Med. Rehabil*, vol. 83, no. 2, pp. 165–170, Feb. 2002. [PubMed: 11833018]
- [8]. Mackintosh SF, Hill K, Dodd KJ, Goldie P, and Culham E, "Falls and injury prevention should be part of every stroke rehabilitation plan," *Clin. Rehabil*, vol. 19, no. 4, pp. 441–451, Jun. 2005. [PubMed: 15929514]
- [9]. Bruijn SM and van Dieën JH, "Control of human gait stability through foot placement," *J. Roy. Soc. Interface*, vol. 15, no. 143, Jun. 2018, Art. no. 20170816.
- [10]. Wang Y and Srinivasan M, "Stepping in the direction of the fall: The next foot placement can be predicted from current upper body state in steady-state walking," *Biol. Lett*, vol. 10, no. 9, Sep. 2014, Art. no. 20140405.
- [11]. Rankin BL, Buffo SK, and Dean JC, "A neuromechanical strategy for mediolateral foot placement in walking humans," *J. Neurophysiol*, vol. 112, no. 2, pp. 374–383, Jul. 2014. [PubMed: 24790168]
- [12]. Stimpson KH, Heitkamp LN, Embry AE, and Dean JC, "Post-stroke deficits in the step-by-step control of paretic step width," *Gait Posture*, vol. 70, pp. 136–140, May 2019. [PubMed: 30856525]
- [13]. Dean JC and Kautz SA, "Foot placement control and gait instability among people with stroke," *J. Rehabil. Res. Develop*, vol. 52, no. 5, pp. 577–590, 2015.
- [14]. Nyberg ET, Broadway J, Finetto C, and Dean JC, "A novel elastic force-field to influence mediolateral foot placement during walking," *IEEE Trans. Neural Syst. Rehabil. Eng*, vol. 25, no. 9, pp. 1481–1488, Sep. 2017. [PubMed: 27913354]
- [15]. Heitkamp LN, Stimpson KH, and Dean JC, "Application of a novel force-field to manipulate the relationship between pelvis motion and step width in human walking," *IEEE Trans. Neural Syst. Rehabil. Eng*, vol. 27, no. 10, pp. 2051–2058, Oct. 2019. [PubMed: 31545734]
- [16]. Takahashi CD, Der-Yeghiaian L, Le V, Motiwala RR, and Cramer SC, "Robot-based hand motor therapy after stroke," *Brain*, vol. 131, no. 2, pp. 425–437, Feb. 2008. [PubMed: 18156154]

- [17]. Milot M-H, Marchal-Crespo L, Green CS, Cramer SC, and Reinkensmeyer DJ, "Comparison of error-amplification and haptic-guidance training techniques for learning of a timing-based motor task by healthy individuals," *Exp. Brain Res*, vol. 201, no. 2, pp. 119–131, Mar. 2010. [PubMed: 19787345]
- [18]. Roemmich RT and Bastian AJ, "Closing the loop: From motor neuroscience to neurorehabilitation," *Annu. Rev. Neurosci*, vol. 41, no. 1, pp. 415–429, Jul. 2018. [PubMed: 29709206]
- [19]. Reisman DS, Wityk R, Silver K, and Bastian AJ, "Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke," *Brain*, vol. 130, no. 7, pp. 1861–1872, May 2007. [PubMed: 17405765]
- [20]. Savin DN, Morton SM, and Whittall J, "Generalization of improved step length symmetry from treadmill to overground walking in persons with stroke and hemiparesis," *Clin. Neurophysiol*, vol. 125, no. 5, pp. 1012–1020, May 2014. [PubMed: 24286858]
- [21]. Yen S-C, Schmit BD, and Wu M, "Using swing resistance and assistance to improve gait symmetry in individuals post-stroke," *Hum. Movement Sci*, vol. 42, pp. 212–224, Aug. 2015.
- [22]. Wu M, Hsu CJ, and Kim J, "Motor adaptation to lateral pelvis assistance force during treadmill walking in individuals post-stroke," in *Proc. IEEE Int Conf. Rehabil. Robot*, Jun. 2017, pp. 300–303.
- [23]. Stimpson KH, Heitkamp LN, Horne JS, and Dean JC, "Effects of walking speed on the step-by-step control of step width," *J. Biomech*, vol. 68, pp. 78–83, Feb. 2018. [PubMed: 29306549]
- [24]. Buurke TJW, Lamoth CJC, van der Woude LHV, and Otter RD, "Handrail holding during treadmill walking reduces locomotor learning in able-bodied persons," *IEEE Trans. Neural Syst. Rehabil. Eng*, vol. 27, no. 9, pp. 1753–1759, Sep. 2019. [PubMed: 31425041]
- [25]. Reimold NK, Knapp HA, Henderson RE, Wilson L, Chesnutt AN, and Dean JC, "Altered active control of step width in response to mediolateral leg perturbations while walking," *Sci. Rep*, vol. 10, no. 1, p. 12197, Dec. 2020. [PubMed: 32699328]
- [26]. Zeni JA, Richards JG, and Higginson JS, "Two simple methods for determining gait events during treadmill and overground walking using kinematic data," *Gait Posture*, vol. 27, no. 4, pp. 710–714, May 2008. [PubMed: 17723303]
- [27]. McCain EM et al. , "Mechanics and energetics of post-stroke walking aided by a powered ankle exoskeleton with speed-adaptive myoelectric control," *J. NeuroEng. Rehabil*, vol. 16, no. 1, p. 57, Dec. 2019. [PubMed: 31092269]
- [28]. Sulzer JS, Gordon KE, Dhaher YY, Peshkin MA, and Patton JL, "Preswing knee flexion assistance is coupled with hip abduction in people with stiff-knee gait after stroke," *Stroke*, vol. 41, no. 8, pp. 1709–1714, Aug. 2010. [PubMed: 20576947]
- [29]. Tyson SF, Woodward-Nutt K, and Plant S, "How are balance and mobility problems after stroke treated in England? An observational study of the content, dose and context of physiotherapy," *Clin. Rehabil*, vol. 32, no. 8, pp. 1145–1152, Aug. 2018. [PubMed: 29852758]
- [30]. Sigrist R, Rauter G, Riener R, and Wolf P, "Augmented visual, auditory, haptic, and multimodal feedback in motor learning: A review," *Psychonomic Bull. Rev*, vol. 20, no. 1, pp. 21–53, Feb. 2013.
- [31]. Guadagnoli MA and Lee TD, "Challenge point: A framework for conceptualizing the effects of various practice conditions in motor learning," *J. Motor Behav*, vol. 36, no. 2, pp. 212–224, Jul. 2004.
- [32]. Balasubramanian CK, Neptune RR, and Kautz SA, "Foot placement in a body reference frame during walking and its relationship to hemiparetic walking performance," *Clin. Biomech*, vol. 25, no. 5, pp. 483–490, Jun. 2010.
- [33]. Malone LA, Vasudevan EVL, and Bastian AJ, "Motor adaptation training for faster relearning," *J. Neurosci*, vol. 31, no. 42, pp. 15136–15143, Oct. 2011. [PubMed: 22016547]
- [34]. Hak L et al. , "Speeding up or slowing down?: Gait adaptations to preserve gait stability in response to balance perturbations," *Gait Posture*, vol. 36, no. 2, pp. 260–264, Jun. 2012. [PubMed: 22464635]
- [35]. Kuo AD, "Stabilization of lateral motion in passive dynamic walking," *Int. J. Robot. Res*, vol. 18, no. 9, pp. 917–930, Sep. 1999.

- [36]. Hobbelen DGE and Wisse M, “Active lateral foot placement for 3D stabilization of a limit cycle walker prototype,” *Int. J. Humanoid Robot*, vol. 6, no. 1, pp. 93–116, Mar. 2009.
- [37]. Wang S et al. , “Design and control of the Mindwalker exoskeleton,” *IEEE Trans. Neural Syst. Rehabil. Eng*, vol. 23, no. 2, pp. 277–286, Mar. 2015. [PubMed: 25373109]
- [38]. Zhang T, Tran M, and Huang H, “Design and experimental verification of hip exoskeleton with balance capacities for walking assistance,” *IEEE/ASME Trans. Mechatronics*, vol. 23, no. 1, pp. 274–285, Feb. 2018.
- [39]. Reinkensmeyer DJ et al. , “Computational neurorehabilitation: Modeling plasticity and learning to predict recovery,” *J. NeuroEng. Rehabil*, vol. 13, no. 1, p. 42, Dec. 2016. [PubMed: 27130577]
- [40]. MacKinnon CD and Winter DA, “Control of whole body balance in the frontal plane during human walking,” *J. Biomech*, vol. 26, no. 6, pp. 633–644, Jun. 1993. [PubMed: 8514809]
- [41]. Reisman DS, McLean H, Keller J, Danks KA, and Bastian AJ, “Repeated split-belt treadmill training improves poststroke step length asymmetry,” *Neurorehabil. Neural Repair*, vol. 27, no. 5, p. 460, 2013. [PubMed: 23392918]
- [42]. Wu M et al. , “Repeat exposure to leg swing perturbations during treadmill training induces long-term retention of increased step length in human SCI,” *Amer. J. Phys. Med. Rehabil*, vol. 95, no. 12, pp. 911–920, Dec. 2016. [PubMed: 27149587]
- [43]. Matjacic Z, Zadavec M, and Olenšek A, “Feasibility of robot-based perturbed-balance training during treadmill walking in a high-functioning chronic stroke subject: A case-control study,” *J. NeuroEng. Rehabil*, vol. 15, no. 1, p. 32, Dec. 2018. [PubMed: 29642921]
- [44]. Shapiro A and Melzer I, “Balance perturbation system to improve balance compensatory responses during walking in old persons,” *J. NeuroEng. Rehabil*, vol. 7, no. 1, p. 32, Dec. 2010. [PubMed: 20630113]
- [45]. Grabiner MD, Crenshaw JR, Hurt CP, Rosenblatt NJ, and Troy KL, “Exercise-based fall prevention: Can you be a bit more specific?” *Exerc. Sport Sci. Rev*, vol. 42, no. 4, pp. 161–168, Oct. 2014. [PubMed: 25062002]
- [46]. Pai Y-C, Bhatt T, Yang F, and Wang E, “Perturbation training can reduce community-dwelling older Adults’ annual fall risk: A randomized controlled trial,” *J. Gerontol. Ser. A, Biol. Sci. Med. Sci*, vol. 69, no. 12, pp. 1586–1594, Dec. 2014. [PubMed: 24966227]
- [47]. Afschrift M, van Deursen R, De Groote F, and Jonkers I, “Increased use of stepping strategy in response to medio-lateral perturbations in the elderly relates to altered reactive tibialis anterior activity,” *Gait Posture*, vol. 68, pp. 575–582, Feb. 2019. [PubMed: 30654320]
- [48]. McCrum C, Karamanidis K, Grevendonk L, Zijlstra W, and Meijer K, “Older adults demonstrate interlimb transfer of reactive gait adaptations to repeated unpredictable gait perturbations,” *GeroScience*, vol. 42, no. 1, pp. 39–49, Feb. 2020. [PubMed: 31776885]
- [49]. Punt M, Bruijn SM, Roeles S, van de Port IG, Wittink H, and van Dieën JH, “Responses to gait perturbations in stroke survivors who prospectively experienced falls or no falls,” *J. Biomech*, vol. 55, pp. 56–63, Apr. 2017. [PubMed: 28267989]
- [50]. Patel PJ and Bhatt T, “Fall risk during opposing stance perturbations among healthy adults and chronic stroke survivors,” *Exp. Brain Res*, vol. 236, no. 2, pp. 619–628, Feb. 2018. [PubMed: 29279981]
- [51]. Nevisipour M, Grabiner MD, and Honeycutt CF, “A single session of trip-specific training modifies trunk control following treadmill induced balance perturbations in stroke survivors,” *Gait Posture*, vol. 70, pp. 222–228, May 2019. [PubMed: 30904789]
- [52]. Punt M, Bruijn SM, van de Port IG, de Rooij IJM, Wittink H, and van Dieën JH, “Does a perturbation-based gait intervention enhance gait stability in fall-prone stroke survivors? A pilot study,” *J. Appl. Biomech*, vol. 35, no. 3, pp. 173–181, Jun. 2019. [PubMed: 30676147]
- [53]. Bishop L, Khan M, Martelli D, Quinn L, Stein J, and Agrawal S, “Exploration of two training paradigms using forced induced weight shifting with the tethered pelvic assist device to reduce asymmetry in individuals after stroke,” *Amer. J. Phys. Med. Rehabil*, vol. 96, pp. S135–S140, Oct. 2017. [PubMed: 28661914]
- [54]. Hsu C-J, Kim J, Tang R, Roth EJ, Rymer WZ, and Wu M, “Applying a pelvic corrective force induces forced use of the paretic leg and improves paretic leg EMG activities of individuals

post-stroke during treadmill walking,” *Clin. Neurophysiol.*, vol. 128, no. 10, pp. 1915–1922, Oct. 2017. [PubMed: 28826022]

- [55]. French MA, Cohen M, and Reisman DS, “Does cognition predict ability to learn a novel walking pattern in individuals post-stroke?” *Neurorehabil. Neural Repair*, vol. 32, no. 12, p. 1068, 2018.
- [56]. Robinovitch SN et al. , “Video capture of the circumstances of falls in elderly people residing in long-term care: An observational study,” *Lancet*, vol. 381, no. 9860, pp. 47–54, Jan. 2013. [PubMed: 23083889]

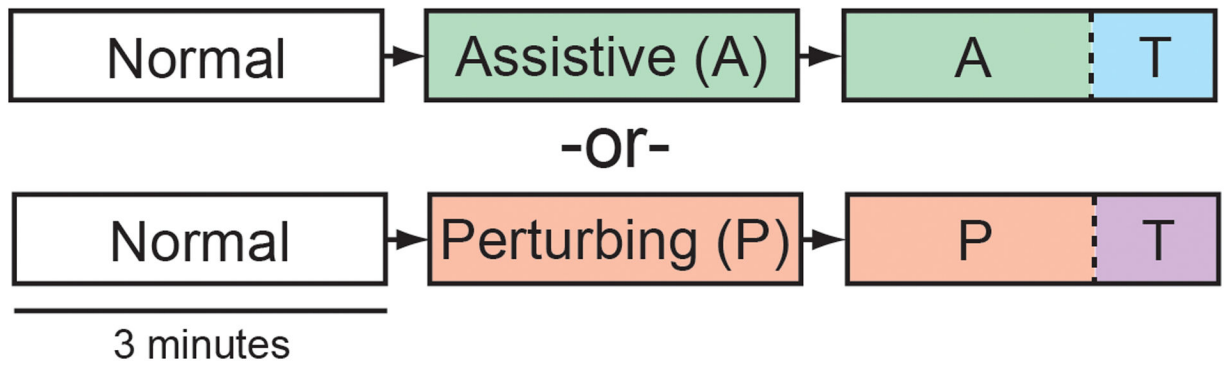


Fig. 1.

Participants performed a series of 3-minute trials after being assigned to either the Assistive group (top row) or Perturbing group (bottom row). For both groups, the force-field switched to transparent mode (T) for the final minute of the third trial.

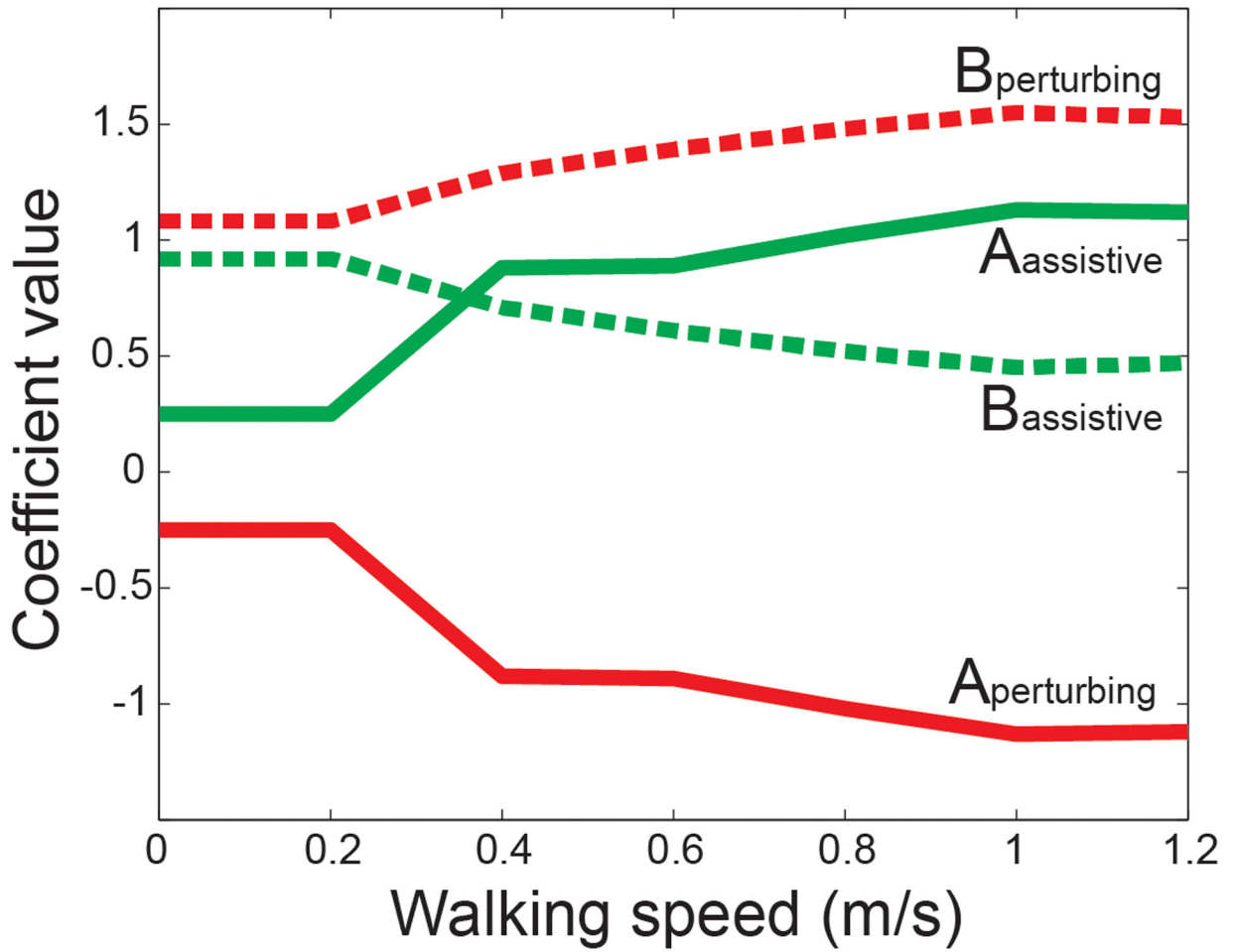


Fig. 2.

Force-field equation coefficient values (A & B) for the Assistive and Perturbing conditions, as labeled. These values vary with walking speed, based on empirically-derived best-fit coefficients from neurologically-intact control participants walking at a range of speeds (0.2, 0.4, 0.6, 0.8, 1.0, 1.2 m/s), and linearly interpolated between these values. For any speeds below 0.2 m/s, we used the 0.2 m/s coefficients.

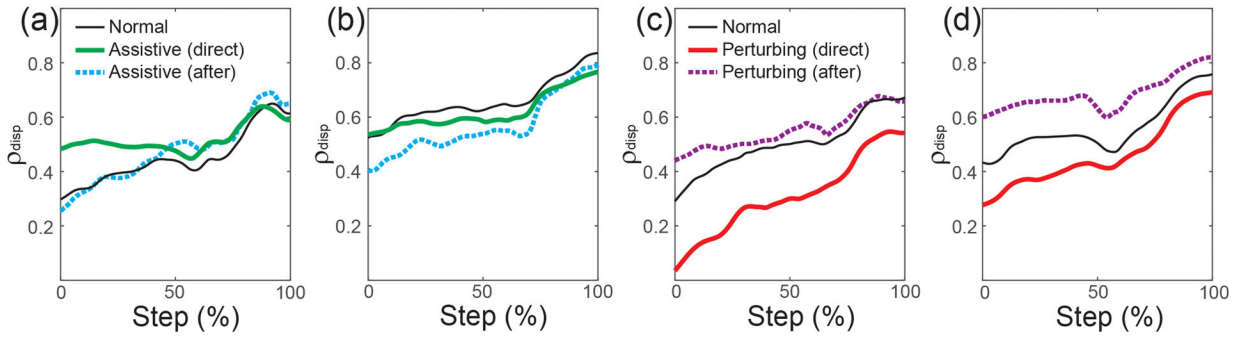


Fig. 3.

ρ_{disp} values calculated throughout the step, from step start (0%) to step end (100%). The direct effects and after-effects of assistance are illustrated for steps taken with the paretic leg (a) and the non-paretic leg (b). Similarly, the direct effects and after-effects of perturbations are illustrated for paretic steps (c) and non-paretic steps (d). Plots illustrate the mean value of these metrics across participants. Intersubject variability is not depicted due to extensive overlap, but is apparent from Figures 4–5 illustrating individual values.

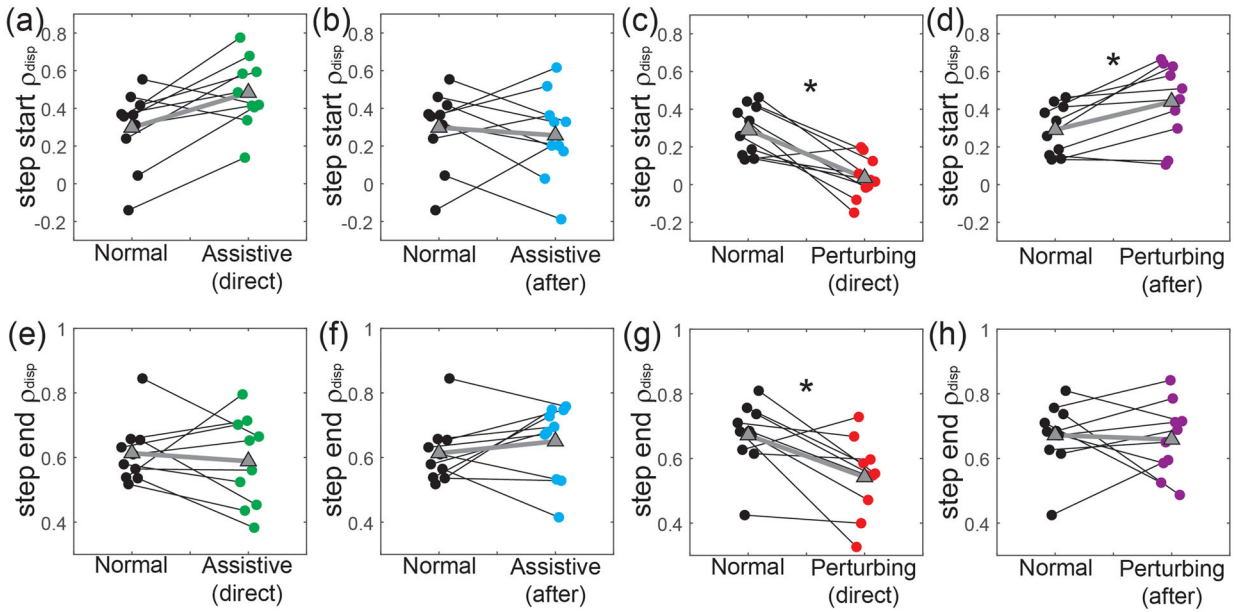


Fig. 4. Force-field effects on paretic ρ_{disp} . All panels illustrate individual participants' values for these metrics, and the change relative to Normal walking. The top row (panels a-d) illustrates step start paretic ρ_{disp} , while the bottom row (panels e-h) illustrates step end paretic ρ_{disp} . From left to right, the panels in each row illustrate the direct effects of assistance, the after-effects of assistance, the direct effects of perturbations, and the after-effects of perturbations. Small circles and thin black lines indicate individual values, outlined triangles and thick gray lines indicate group means, and statistical significance is illustrated with asterisks (*). Individual data points are slightly offset on the x-axis to reduce overlap.

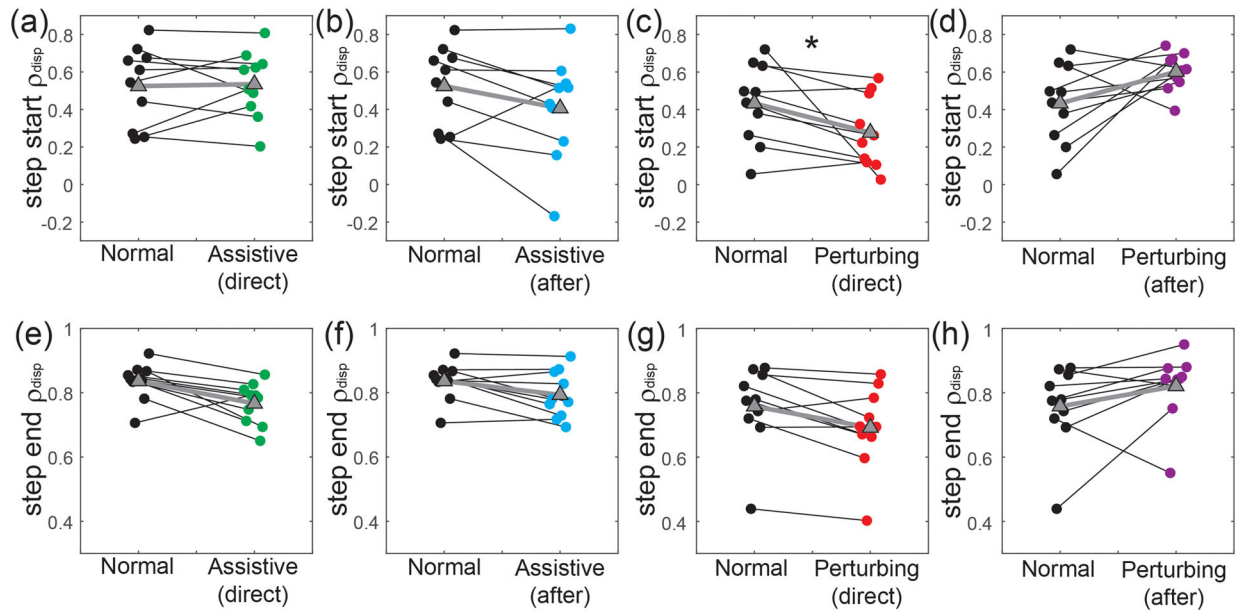


Fig. 5. Force-field effects on non-paretic ρ_{disp} . The figure structure matches that for Figure 4.

TABLE I

Participant Characteristics

#	Assistive group					Perturbing group							
	Age (yr)	Time since stroke (mo)	Paretic side	Gender	LEFM score	Walking speed (m/s)	#	Age (yr)	Time since stroke (mo)	Paretic side	Gender	LEFM score	Walking speed (m/s)
A1*	63	8	R	M	20	0.65	P1	67	73	R	M	34	0.85
A2	85	13	L	M	27	0.65	P2	55	17	L	M	22	0.25
A3	68	43	L	M	24	0.55	P3	64	16	L	M	21	0.35
A4*	61	67	R	F	21	0.55	P4	67	39	R	M	20	0.25
A5*	24	16	L	M	20	0.30	P5*	35	14	R	F	18	0.25
A6*	70	170	R	M	19	0.40	P6	55	52	L	F	28	0.30
A7*	76	10	L	M	23	0.35	P7	51	19	R	F	26	0.40
A8	46	81	R	F	27	0.45	P8	59	54	L	F	26	0.10
A9	51	16	R	M	28	0.45	P9	70	7	L	F	27	0.40
A10	53	16	R	M	26	0.20	P10	55	15	L	F	22	0.15
group	60±17	44±51	4L/6R	2F/8M	24±3	0.46±0.15	group	58±10	31±22	6L/4R	6F/4M	24±5	0.33±0.21

Participant demographic characteristics, lower extremity Fugl-Meyer (LEFM) motor scores, and treadmill walking speeds for the Assistive (A) and Perturbing (P) groups. Asterisks (*) indicate that the participant wore an AFO during testing. Numerical summary scores are presented as means ± standard deviations.

Gait Spatial Measures

TABLE II

	Assistive group			Perturbing group		
	Normal	Assistive direct effects	Assistive after-effects	Normal	Perturbing direct effects	Perturbing after-effects
Paretic step width (mm)	205±40	206±46 (p=0.92)	199±34 (p=0.084)	162±64	176±66 (p=0.014)	169±62 (p=0.49)
Paretic step length (mm)	368±134	366±121 (p=0.92)	369±123 (P=1)	245±107	239±119 (p=0.23)	241±125 (p=0.56)
Paretic foot placement (mm)	86±19	91±20 (p=0.32)	88±22 (p=0.49)	81±44	92±51 (p=0.002)	86±45 (p=0.23)
Non-paretic step width (mm)	204±40	206±46 (P=1)	199±34 (p=0.084)	162±64	176±66 (p=0.014)	169±62 (p=0.49)
Non-paretic step length (mm)	361±102	355±102 (p=0.28)	369±109 (p=0.63)	225±133	223±128 (p=0.77)	229±131 (p=0.28)
Non-paretic foot placement (mm)	55±33	50±32 (P=1)	49±30 (p=0.56)	29±41	33±44 (p=0.13)	34±47 (p=0.19)

Effects of assistance and perturbations on gait spatial measures. Values are presented as means ± standard deviations, followed by the corresponding p-value for comparisons with the baseline Normal condition. Statistically significant comparisons (p<0.025) are indicated using bolded italics.