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ORIGINAL RESEARCH ARTICLE

Title:

Inter-limb coupling in individuals with transtibial amputation during bilateral stance is direction dependent

Authors:

Peter C. Raffalt[1,2], Jenny A. Kent[2,3] and Nick Stergiou[2,4]

Affiliations:

1 Department of Physical Performance, Norwegian School of Sport Sciences, Sognsveien 220, 0806 Oslo, Norway.

2 Department of Biomechanics and Center for Research in Human Movement Variability, University of Nebraska at Omaha, 6160 University Drive, Omaha, NE 68182-0860, USA.

3 Department of Physical Therapy, University of Nevada Las Vegas, 4505 S Maryland Pkwy, Las Vegas, NV 89154 USA.

4 College of Public Health, University of Nebraska Medical Center, Omaha, NE 68198-4355, USA.

Corresponding Author:

Nick Stergiou, PhD

Department of Biomechanics and Center for Research in Human Movement Variability

University of Nebraska at Omaha

6160 University Drive

Omaha, NE 68182-0860, USA.

Email: nstergiou@unomaha.edu

Phone: 402-554-3247

Abstract

We investigated the control of upright standing in individuals with unilateral transtibial amputation (TTA) by assessing the inter-limb coupling and the coupling between the center of pressure beneath both limbs combined (COP_{NET}) and the center of pressure (COP) beneath the prosthetic limb and the intact limb. Twenty-one adults with TTA and eighteen unimpaired adults completed 90 seconds of standing on two parallel force plates. The inter-limb coupling and the coupling between the COP beneath each limb and the COP_{NET} were assessed by quantifying the synchronization of the COP signals. This included the number of epochs with synchronized signals, the total duration of signal synchronization and the relative phase and deviation phase between the signals. Additionally, magnitude and temporal characteristics of the COP displacements were quantified. Individuals with TTA exhibited less COP-coupling synchronization in the anterior-posterior direction, characterized by more shifts between epochs with synchronized signals, shorter total duration of signal synchronization, less in-phase coordination patterns and a higher deviation phase between the two limbs, compared to unimpaired individuals. This coincided with a larger and more irregular postural sway in the TTA group. No group difference was observed in the mediolateral direction. The coupling between the COP_{NET} and the COP beneath the individual limbs was similarly direction dependent, and tighter for the intact side, suggesting that an intact limb-driven strategy was utilized.

Keywords: prosthesis, phase synchronization, postural control, center of pressure dynamics

Abbreviations:

AP: anterior-posterior

COP: center of pressure

COP_I: center of pressure beneath the intact limb

COP_{NET}: combined center of pressure beneath both limbs

COP_P: center of pressure beneath the prosthetic limb

DP: deviation phase

DSYN: total duration of COP synchronization

ENT½: entropic half-life

ML: mediolateral

MRPA: mean relative phase angle

NoE: number of epochs

SaEn: sample entropy

TFA: transfemoral amputation

TTA: transtibial amputation

1. Introduction

Maintaining balance during upright standing is a fundamental task of everyday life. Solving this task requires the center of mass to be kept within the base of support whilst maintaining the flexibility needed to perform simultaneous actions and adjust to external perturbations. This involves a continuous integration of sensory inputs, i.e. information from the visual, vestibular and somatosensory systems (D. A. Winter, Patla, & Frank, 1990). Experimentally-induced manipulation of sensory feedback in healthy individuals alters postural control, illustrating the adjustability of the control system when exposed to momentary sensory disturbances (Delignieres, Torre, & Bernard, 2011; Grace Gaerlan, Alpert, Cross, Louis, & Kowalski, 2012; Nashner, Woollacott, & Tuma, 1979; Raffalt, Spedden, & Geertsen, 2019).

In individuals with permanent alterations to sensory input and to volitional control of movement due to unilateral foot or limb amputation, the intact limb is believed to function in a compensatory manner (Hlavackova, Franco, Diot, & Vuillerme, 2011; Isakov, Mizrahi, Ring, Susak, & Hakim, 1992; Rougier & Bergeau, 2009; Vrieling, et al., 2008). During upright standing, the center of pressure (COP) displacements and velocities have been shown to be greater in individuals with amputation in comparison to unimpaired individuals (Claret, et al., 2019). However, bilateral stance, both in individuals with and without amputation, is achieved using the contributions of sensory input from, and motor control of, the two limbs combined. Investigating this topic using a dual-force plate experimental setup, it has been shown that individuals with unilateral transfemoral amputation (TFA) exhibit a greater displacement and a greater velocity of the COP beneath their intact limb (COP_I) and beneath the two limbs combined (COP_{NET}) in comparison to the COP beneath their prosthetic limb (COP_P), supporting a differing role of the two limbs (Claret, et al., 2019). In addition, inter-limb comparisons of sample entropy (SaEn) and entropic half-life (ENT½) during standing have indicated, respectively, a more regular movement in the intact limb indicated by a lower SaEn value alongside more frequent COP adjustments indicated by a shorter ENT½ value (Claret, et al., 2019; Hlavackova, et al., 2011).

The aforementioned studies clearly indicate altered COP dynamics and control of the limb on the prosthetic side compared to the intact limb. However, the quantification of COP dynamics of each limb in isolation does not provide insight into the specific role of the intact limb in maintaining a flexible upright stance. It cannot be excluded that the observed differences in COP dynamics in individuals with amputation could originate from varying types of coordinated behavior of the two limbs. In several articles, Wang and colleagues investigated inter-limb coordinative patterns in healthy individuals during three different bilateral standing tasks; side-by-side, staggered and tandem stance (Wang, Jordan, & Newell, 2012; Wang & Newell, 2012a, 2012b). To assess the coupling between two COP signals, four different parameters were quantified: 1) The number of epochs (NoE) in which the COP displacements beneath the two limbs were synchronized (i.e. the COP inter-limb coupling is structurally stable (Kurz & Stergiou, 2004)). A high NoE would indicate a flexible postural control strategy with frequent shifts between structurally stable coordinative states. 2) The total duration of COP synchronization (DSYN) during each task. A long DSYN would indicate a high overall stability of the COP inter-limb coupling. 3) The mean relative phase angle (MRPA) between the COP displacements as a measure of the type of COP inter-limb coupling. Values close to 0 and 360° would indicate in-phase coordination (i.e. the COP displacements are in the same direction) and values close to 180° would indicate out-of-phase coordination (i.e. the COP displacements are in the opposite direction). 4) The deviation phase of the relative phase angle (DP) as a measure of the coordination variability (i.e. the consistency of the COP inter-limb coupling). The authors observed that when changing from side-by-side stance to tandem stance (i.e. one foot in front of the other), the NoE in the anterior-posterior (AP) direction increased and the DSYN decreased. Furthermore, the coordination shifted from in-phase with only a small amount of variability, towards less in-phase coordination with increased variability. For the mediolateral (ML) direction, the NoE and the DSYN were mostly unaltered in tandem in comparison to side-by-side stance, while there was a substantial shift in coordination from out-of-phase to in-phase with a reduction in variability (Wang, et al., 2012; Wang & Newell, 2012b). This indicates that the altered mechanical constraints induced by the change in foot position leads to a less consistent inter-limb coupling in the AP direction where, although a higher number of shifts between structurally stable coordination states are made, the overall coupling stability is reduced. In contrast for the ML direction, the change in coordination and reduction in variability leads to balance being maintained with a constant level of overall coupling stability and flexibility (Wang, et al., 2012; Wang & Newell, 2012b).

Individuals with lower limb amputation are impacted by both the mechanical constraints of the prosthesis, i.e. those related to geometry and mechanical properties and altered sensory feedback from and muscular control of the lower limb and foot muscles, and have been observed to unload the prosthetic side during standing (Hlavackova, et al., 2011; Ku, Abu Osman, & Wan Abas, 2014). Therefore, it is crucial to elucidate the coupling between the COP displacements beneath each limb, and the coupling between the COP displacements beneath each limb and the COP_{NET} displacements, when investigating the specific roles of the two limbs during upright standing in this patient population. Similar to the effect of foot position, asymmetric weight distribution in unimpaired adults during side-by-side stance was reported to change the coordination pattern away from in-phase, increase the coordination variability, and reduce the DSYN, but not to affect the NoE (Wang & Newell, 2012a). It seems reasonable to infer that the constraints of the prosthetic limb and asymmetric weight distribution in individuals with amputation alter the coupling between the COP displacements beneath the two limbs. This would lead to an altered inter-limb coupling characterized by higher coordination variability and more frequent shifts between structurally stable coordination states but less overall coupling stability, compared to unimpaired individuals. When assessing the coupling between the COP displacements in terms of coordination, compensation by the intact limb may be reflected by a COP_I displacement that dominates the COP_{NET} displacement. In such a case, a tighter coupling between COP_I and COP_{NET} displacements, compared to that between the COP_P and COP_{NET} displacements, would be expected. Therefore, it could also be expected that the coordination between the COP_I displacements and the COP_{NET} displacements would be characterized by a lower variability leading to greater overall coupling stability through fewer shifts between structurally stable states compared to that between the COP_P displacements and the COP_{NET} displacements.

Therefore, the aim of the present study was to determine how upright standing is controlled in individuals with unilateral transtibial amputation (TTA) in terms of a) the inter-limb coupling of the COP dynamics between the limb on the prosthetic side and the intact limb and b) the coupling between the limb on the prosthetic side or the intact limb and the $COP_{NET.}$ Elucidation of the role of inter-limb coupling in upright standing requires a quantification of both the behavior of the COP dynamics and the inter-limb coupling. Thus, the behavior of the COP dynamics was first assessed, using the total COP path length as a measure of the magnitude of sway, SaEn as a measure of regularity and ENT½ as a measure of the frequency of COP adjustments.

We then raised the following hypotheses:

1) Individuals with TTA would have a higher NoE, have shorter DSYN, and have greater variability in inter-limb COP coordination compared to unimpaired individuals.

2) In individuals with TTA, the coupling between the COP_P and the COP_{NET} would be characterized by a higher NoE, shorter DSYN, and greater coordination variability compared to the coupling between the COP_I and the COP_{NET}. For the unimpaired individuals, there would be no differences in the coupling characteristics.

Support of these hypotheses would infer 1) that individuals with TTA utilize looser inter-limb coupling during upright standing compared to unimpaired individuals and 2) that individuals with TTA compensate for the looser inter-limb coupling by tighten the coupling between COP_I and COP_{NET}.

2. Method and materials

2.1 Participants

Twenty-one adults with a unilateral TTA were recruited from local prosthetic clinics, plus a group of 18 unimpaired adults of a similar age from the local community (Table 1). Participants in the TTA group were pre-screened based on the following inclusion criteria: amputation more than 6 months previously, no neurological disease or impairment that may affect gait with the exception of diabetes, and no sores on the residual limb. Eligibility criteria for the unimpaired individuals included: no known neurological, vestibular or movement disorder, and no current musculoskeletal injury or pain. Pregnancy was an exclusion criterion for both groups. All participants wore their own customary prosthesis and footwear. All participants used a sleeve or pinlock suspension and had a passive energy storage-and-return type foot, with the exception of one participant who had a powered ankle, which behaved passively during standing. All participants provided written informed consent according to local university and VA Institutional Review Board approved protocols, as part of a larger study investigating a balance intervention. The specific test described in the present work was a baseline trial conducted prior to application of the interventional device, during one of two sessions at a University Biomechanics Laboratory.

2.2 Experimental setup

Participants stood on parallel floor-embedded force plates (Optima, Advanced Mechanical Technology, Inc., Watertown, MA), fixating on a wall-mounted cross. They assumed a set position with their arms folded across their torso, and with their feet as close together as possible without inducing discomfort, in order to induce a moderate challenge to balance. Participants were instructed to ‘stand in the set position’ for the duration of a 90-second trial, during which force plate data were captured at 600Hz in Cortex Software via an integrated motion capture system (Motion Analysis Corp., Santa Rosa, CA). Force data from the two force plates were combined into a single force structure in Visual 3D (C-Motion, Inc., Germantown, MD). Individual and combined plate COP time series in the anterior-posterior (AP) and medial-lateral (ML) directions were exported to MATLAB (MathWorks R2018a, Inc., Natick, MA) for further processing.

2.3 Data analysis

There was a 12/9 ratio in the right/left side amputation in the included individuals with TTA. To match this ratio, 10 of the 18 unimpaired individuals were randomly selected to have their 'matched' amputation on the right limb. Prior to further analysis, the COP time series were filtered using a Daubechies wavelet (decomposition at level 5 using 5 db), downsampled to 100Hz and the initial 15 seconds were removed.

The total path length of the COP_P, COP_I and COP_{NET} was calculated in both directions.

SaEn of the COP_P, COP_I and COP_{NET} was calculated with a vector length of m = 2 and a tolerance limit of r = 0.2 using the equation presented by Richman and Moorman (2000). Low values of SaEn indicate high regularity and high values indicate low regularity of the COP time series. To evaluate the input parameter consistency, SaEn was calculated using combinations of m = 2 and m = 3 and r = 0.1, 0.15, 0.2, 0.25 and 0.3. The results for these calculations are presented in the supplementary material and summarized in the results.

ENT½ was calculated using the procedure presented by Zandiyeh and von Tscharner (2013) and Baltich et al. (2014). In short, the original time series was reshaped into 100 new time series where the order of data points was gradually randomized more and more for each new time series (Baltich, et al., 2014; Zandiyeh & Von Tscharner, 2013). SaEn (m=2, r=0.2) was then calculated on each reshaped time series. The SaEn of each reshaped time series was normalized according to Equation 1.

Equation 1: $$Normalized\ SaEn = \frac{SaEn_{RS} - SaEn_{OR}}{SaEn_{RAN} - SaEn_{OR}}$$

Where $SaEn_{RS}$ is the SaEn of the reshaped time series, $SaEn_{OR}$ is the SaEn of the original time series, and $SaEn_{RAN}$ is the average SaEn of 50 completely randomized time series created by a random permutation of the data points in the original time series. The ENT½ corresponded to the timescale at which the normalized SaEn increased above 0.5. A short ENT½ suggests more frequent COP adjustments and a long ENT½ suggests less frequent COP adjustments.

Using the method described by Wang and colleagues (Wang & Newell, 2012a, 2012b), the characteristics of three different COP couplings was assessed: between the $\mathrm{COP_P}$ and $\mathrm{COP_I}$, between the $\mathrm{COP_P}$ and the $\mathrm{COP_{NET}}$ and between the $\mathrm{COP_I}$ and the $\mathrm{COP_{NET}}$. This method detects the NoE, DSYN, MRPA, and DP between the two signals. Due to the nonharmonic and nonstationary oscillatory nature of COP signals, we calculated a Hilbert transformed relative phase using the approach of Wang and colleagues (Wang, et al., 2012; Wang & Newell, 2012a, 2012b). The method included four calculation steps. First, the synchronization of the COP of the individual force plates and of each force plate COP and the $\mathrm{COP_{NET}}$ were quantified by the Hilbert transformed relative phase (Equation 2).

Equation 2: $$\Delta\varphi_{COP1-COP2}(t) = arctan\frac{\tilde{S}_{COP1}(t)S_{COP2}(t) - S_{COP1}(t)\tilde{S}_{COP2}(t)}{S_{COP1}(t)S_{COP2}(t) + \tilde{S}_{COP1}(t)\tilde{S}_{COP2}(t)}$$

Where $\Delta\varphi_{COP1-COP2}(t)$ represented the relative phase between the COP time series, $S_{COP1}(t)$ and $S_{COP2}(t)$ are the real parts of Hilbert transformed COP time series and $\tilde{S}_{COP1}(t)$ and $\tilde{S}_{COP2}(t)$ are the imaginary parts of the COP time series after the Hilbert transform. For the coupling between the COP time series from the individual force plates, *COP1* represented the $\mathrm{COP_P}$ and *COP2* represented $\mathrm{COP_I}$. For the couplings between the COP from each of the individual force plates and the COP_{NET}, *COP1* represented either the COP_P or COP_I and *COP2* represented the COP_{NET}. The Matlab (Math Works, R2018a) in-built unwrap function was used to unfold the $\Delta\varphi_{COP1-COP2}(t)$ time series by adding or subtracting multiples 2π when the phase angle jumps abruptly with π radians or more. Second, a moving window slope of 240 ms was applied to the unwrapped relative phase angle time series to identify epochs of phase synchronization by calculating the linear slope of the relative phase angle within each window. Third, a critical slope limit was determined as the average standard deviation of the relative phase angle across all participants for each of the three couplings and two directions (Wang & Newell, 2012b). Finally, an epoch of phase synchronization was identified when the slope of relative phase angle was below the corresponding critical limit. The NoE and the DSYN (summarized duration of synchronization of the epochs) were calculated. A high NoE between two COP signals would indicate a flexible postural control strategy with shifts between multiple structurally stable coordination states. DSYN close to the maximum of 75 seconds would indicate a postural control strategy leading to structurally stable coordination states. Furthermore, to determine the degree of in-phase/out-of-phase coordination of the coupled COP trajectories the MRPA was calculated as the circular mean vector of the relative phase angle. An MRPA close to 0 and 360° would indicate in-phase coordination in which the COPs move in the same direction relative to the laboratory coordinate system, and angles close to 180° indicate out-of-phase coordination in which the COPs move in opposite directions. This definition was consistent for both the AP and ML directions. The within-trial coordination variability of the coupled COP trajectories was determined from the DP calculated as standard deviation of relative phase angle (Batchelet, 1981).

2.4 Statistics

Group demographics of age, body height, body mass and body mass index were compared using an unpaired Student's t-test (Table 1).

To investigate the effect of group, direction and COP source (from each limb and the combined) on the total COP length, SaEn and ENT½, a three-way mixed design ANOVA with group (between-subjects), direction and COP sources (within-subjects) as independent factors and the total COP length, SaEn and ENT½ as dependent variables. In case of an overall effect of group, direction, COP sources or any interaction (group x direction, group x COP sources, direction x COP sources, group x direction x COP sources), a Holm-Sidak post hoc test was applied. Level of significance was set at 5 %.

To test the first raised hypothesis, a two-way mixed design ANOVA with group (between-subjects) and direction (within-subjects) as independent factors and the NoE, the DSYN and the DP as dependent variables. In case of an overall effect of group or direction or an interaction (group x direction), a Holm-Sidak post hoc test was applied. Because of the directional nature of the MRPA, the effect of group and direction on this variable was evaluated using a Harrison-Kanji test (equivalent to a two-way ANOVA for normally distributed linear data). In case of an overall effect of group or direction or a significant group-direction interaction, a Watson-Williams test was applied as post hoc test.

To test the second hypothesis, a two-way repeated measures ANOVA with the COP_P and COP_{NET} and the COP_I and COP_{NET} couplings and the AP and ML directions (within-subjects) as independent factors and the NoE, the DSYN and the DP as dependent variables. In case of an overall effect of coupling or direction or an interaction (coupling x direction), a Holm-Sidak post hoc test was applied. Because of the directional nature of the MRPA, the difference between the

COP_P and COP_{NET} coupling and the COP_I and COP_{NET} coupling was tested in each direction using the Watson-Williams test. Statistical analyses of the normally distributed and linear variables were performed in SPSS (IBM SPSS Statistics, Version 26, 2019, USA) and the circular variables were analyzed using the Circular Statistics Toolbox in Matlab (Math Works, R2018a, Inc., USA) (Berens, 2009).

3. Results

3.1 COP path length, sample entropy, entropic half-life

The total path length of the COP_P displacements was significantly shorter in both directions (AP: $p = 0.039$ and ML: $p = 0.014$) compared to corresponding COP displacements of the unimpaired individuals (**Figure 1A and 1B**, group-direction-COP sources interaction $F = 21.9$, $p < 0.001$). The total path length of the COP_I displacements was significantly longer in both directions (AP: $p < 0.001$ and ML: $p = 0.003$) and the COP_{NET} of the individuals with TTA in the AP direction was significantly longer ($p = 0.003$) compared to corresponding COP displacements of the unimpaired individuals.

The SaEn of the COP_I ($p < 0.001$) and COP_{NET} ($p = 0.003$) in the AP direction and of the COP_I ($p < 0.001$) in the ML direction were significantly higher for the individuals with TTA compared to the unimpaired individuals (**Figure 2A and 2B**, group-direction-COP sources interaction $F = 3.8$, $p = 0.028$). Furthermore, the SaEn of the COP_P was significantly lower ($p = 0.001$) in the ML direction for the individuals with TTA compared to the unimpaired individuals. Parameter consistency was demonstrated when using $m = 2$ and $r = 0.2$ for the SaEn analysis (see Supplementary Material for details).

There was a significant group-COP sources interaction ($F = 3.9$, $p = 0.024$) for the ENT½ (**Figure 2C and 2D)**. In both directions, the ENT½ of COP_I was significantly shorter ($p = 0.01$) for the individuals with TTA compared to the unimpaired individuals. No other effects or interactions were observed.

3.2 Inter-limb coupling

The NoE for the inter-limb COP coupling (i.e., COP_I-COP_P) in the AP direction was significantly higher ($p = 0.032$; group-direction interaction $F = 6.5$, $p = 0.015$) in the individuals with TTA compared to the unimpaired individuals but did not differ between groups in the ML direction (**Figure 3A**). While the NoE was significantly lower ($p < 0.001$) in the AP direction compared to the ML direction for the unimpaired group, no directional difference was observed for the individuals with TTA.

The DSYN for the inter-limb COP coupling in the AP direction was significantly shorter ($p = 0.004$; group-direction interaction $F = 5.1$, $p = 0.031$) in the individuals with TTA compared to the unimpaired individuals but did not differ between groups in the ML direction (**Figure 3B**). The DSYN in the AP direction was significantly longer ($p = 0.007$) compared to the ML direction for the unimpaired group, but no directional difference was observed for the individuals with TTA.

The MRPA for the inter-limb COP coupling in both directions was strongly in-phase for both groups with values close to 0°. For the AP direction, it was significantly more out-of-phase ($p < 0.001$; group-direction interaction Chi-square = 7.6, $p = 0.006$) for the individuals with TTA compared to the unimpaired individuals but did not differ between groups in the ML direction (**Figure 3C**). For both groups, there was a significant difference between directions ($p < 0.001$ for the individuals with TTA and $p = 0.012$ for unimpaired individuals).

The DP for the inter-limb COP coupling was significantly higher ($p = 0.013$; group-direction interaction $F = 6.2$, $p = 0.018$) for the individuals with TTA compared to the unimpaired individuals in the AP direction, but did not differ between groups in the ML direction (**Figure 3D**). The DP was significantly higher for the ML direction compared to the AP direction for both groups ($p < 0.001$ for both groups).

3.3 Coupling of the COP beneath individual limbs and the combined COP

In the individiuals with TTA, the NoE was significantly higher for the coupling between the COP_P and COP_{NET} in the AP direction ($p < 0.001$) and significantly lower in the ML direction ($p < 0.001$) compared to the coupling between the COP_I and COP_{NET} (**Figure 4A**, coupling-direction interaction $F = 23.6$, $p < 0.001$). While no difference in the NoE was observed between directions for the COP_P and COP_{NET} coupling, a significantly higher NoE was observed in the ML direction ($p < 0.001$) for the COP_I and COP_{NET} coupling.

The DSYN was significantly shorter for the coupling between the COP_P and COP_{NET} in the AP ($p < 0.001$) and significantly longer in the ML direction ($p < 0.001$) compared to the coupling between the COP_I and COP_{NET} in AP and ML directions, respectively (**Figure 4B**, coupling-direction interaction $F = 27.6$, $p < 0.001$). A significantly longer DSYN was observed in the AP in comparison to the ML direction for the COP_I and COP_{NET} coupling ($p < 0.001$), but no difference between directions was observed for the COP_P and COP_{NET} coupling.

The MRPA of the COP_P and COP_{NET} coupling and COP_I and COP_{NET} coupling was strongly in-phase for both directions with values close to 0°. The COP_P and COP_{NET} coupling was significantly more out-of-phase compared to the COP_I and COP_{NET} coupling in the AP direction ($F = 6.3$, $p = 0.016$) but no difference between couplings was observed in the ML direction (**Figure 4C**).

The DP of the COP_P and COP_{NET} coupling was significantly higher ($p < 0.001$) in the AP direction and significantly lower ($p = 0.002$) in the ML direction compared to the COP_I and COP_{NET} coupling (**Figure 4D**, coupling-direction interaction $F = 32.5$, $p < 0.001$). There was a significantly higher DP in the ML direction compared to the AP direction for the COP_I and

COP_{NET} coupling ($p < 0.001$) but no difference between directions for the COP_P and COP_{NET} coupling.

For the unimpaired individuals, there was no significant effect of coupling or coupling-direction interaction on the NoE, DSYN or DP (**Figure 5A, B and D**). There was significant effect of direction for all three variables. There was a significantly lower NoE ($p < 0.001$), longer DSYN ($p < 0.001$) and lower DP ($p < 0.001$) in the AP direction compared to the ML direction. There was no significant difference in the MRPA between the COP_P and COP_{NET} coupling nor between the COP_I and COP_{NET} coupling in either direction (**Figure 5C**).

4. Discussion

In order to explore the control of upright standing in individuals with TTA, we quantified the phase synchronization characteristics between COP signals originating from beneath the intact limb, the prosthetic limb and the two limbs combined. Given unilateral deficits associated with the use of a prosthesis, we hypothesized (1) that individuals with TTA would have a higher NoE, have shorter DSYN, and have greater variability in inter-limb COP coordination compared to unimpaired individuals, and (2) that for individuals with TTA, the coupling between the COP_P and the COP_{NET} would be characterized by a higher NoE, shorter DSYN, and greater coordination variability compared to the coupling between the COP_I and the COP_{NET}. Additionally, for the unimpaired individuals, there would be no differences in the coupling characteristics.

Prior to the quantification of inter-limb coupling, we quantified the total COP path sway length, SaEn and ENT½ of the COP_{NET}, COP_I and COP_P. The longer total COP path length observed beneath the intact limb compared to the prosthetic limb and longer path beneath the intact limb of individuals with TTA compared to unimpaired individuals were in agreement with previous studies (Claret, et al., 2019; Hlavackova, et al., 2011). In contrast to Hlavackova et al. (2011), we observed lower SaEn of the displacement of the COP_P of individuals with TTA compared to the COP_I. This finding suggests that the COP_P displacements were more regular compared to the COP_I displacements. Claret et al. (2019) observed a significantly shorter ENT½ of the COP_I and significantly longer ENT½ of the COP_P in individuals with TFA compared to unimpaired individuals. This suggests that the individuals with TFA made more frequent adjustments of the COP_I but less frequent adjustments of the COP_P compared to unimpaired individuals. While the results of present study support these observations for the intact limb, the group difference in ENT½ of the COP_P did not reach statistical significance as observed by Claret et al. (2019). The apparent discrepancy in comparison to previous results may be a consequence of the separation of AP and ML components of the COP in the present study as opposed to analyzing the resultant. It is also plausible that differences may be related to the sensation and volitional control of the natural knee in individuals with TTA that is not readily available for those with TFA on the affected side.

4.1 Hypothesis 1: Individuals with TTA have a tighter inter-limb coupling

The first hypothesis was supported in the AP direction but not in the ML direction, in which no group differences were observed. This implies that the mechanical constraints of the prosthesis, and the altered sensory feedback and control of the lower limb in individuals with TTA, only affect the inter-limb coupling in the AP direction. It has previously been suggested that during bilateral standing with feet positioned side-by-side, the sway in the AP direction almost exclusively originates from the plantar- and dorsiflexion of the ankle joint, placing a limit on degrees of freedom in the system and the number of 'mechanically equivalent' configurations, i.e. different mechanically stable states (Federolf, Zandiyeh, & Von Tscharner, 2015). In contrast, the two support points (the two feet) in the ML direction offer more movement options and a large number of possible mechanically stable configurations. Hence during standing with feet side-by-side, there is a potential for exploring more different structurally stable states in order to maintain upright stance in the ML direction compared to AP direction (Federolf, et al., 2015). This notion was supported by the results of the present study, as higher NoE were observed in the inter-limb coupling in the ML direction compared to the AP direction in the unimpaired individuals. However, this was not the case for the individuals with TTA, who had a significantly higher NoE in the AP direction compared to the unimpaired individuals and no difference between directions. This suggests that more shifts between structurally stable states were made in the AP direction for the individuals with TTA compared to the unimpaired individuals and could be explained by several different mechanisms. We propose the following explanations. First, due to the lack of an ankle joint, individuals with TTA could instead invoke movement about the knee and hip joint to control body sway. This will inevitably disrupt the pendulum-like motion of the affected limb as rotation will occur about two joints closely located to the center of mass instead of primarily about one distal joint in the intact limb. This is likely to generate more shifts between different structurally stable coordination states and increasing the time spent in structurally unstable transitions. As a consequence, the corresponding total duration of inter-limb COP synchronization would decrease. Second, as previously reported, individuals with unilateral lower limb amputation tend to unload their prosthetic limb (Hlavackova, et al., 2011; Ku, et al., 2014). Loading asymmetry has previously been linked to more shifts between structurally stable coordination states and lower overall coupling stability (Wang & Newell, 2012a). The latter interpretation suggests that in the AP direction, the inter-limb coupling and standing balance of individuals with TTA is achieved using an ‘intact limb-driven’ strategy. Furthermore, the sagittal plane deformation of the prosthetic foot during loading and offloading due to ML sway could plausibly result in alterations to AP COP_P fluctuations that are independent of AP motion. With clinical relevance, further exploration of the relationship between load shifts and COP coordination may reveal greater insights into the extent to which the prosthesis effectively contributes to balance regulation during standing.

Interestingly, the greater SaEn (lower regularity) and longer total path length of the COP_{NET} in the AP direction for the individuals with TTA coincided with looser inter-limb coupling in that direction. In contrast in the ML direction, the lack of group difference in the

SaEn and total path length of the COP_{NET} coincided with a lack of group difference in the inter-limb coupling. This might allude to a link between inter-limb coupling and the COP_{NET} pattern, such that the looser coupling between limbs led to more irregular and greater magnitude of sway in individuals with TTA compared to the unimpaired individuals. Although, the results of the ENT½ did not reach statistical significance a similar tendency was observed with lower ENT½ for the individuals with TTA in the AP direction but no group difference in the ML direction. This indicates that the looser inter-limb coupling in the AP direction for the individuals with TTA was also related to more frequent COP_{NET} adjustments.

4.2 Hypothesis 2: The COP_I and COP_{NET} is coupled tighter than the COP_P and COP_{NET}

The second hypothesis was supported in the AP direction but not in the ML direction, which revealed the opposite, i.e. looser coupling between COP_P and COP_{NET} than between COP_I and COP_{NET}. This direction-dependent difference between the COP_P-COP_{NET} coupling and the COP_I-COP_{NET} coupling could be related to the differences in the availability of mechanically stable states in the two directions, and to the available motor control strategies in the two directions. As previously proposed, the results for the individuals with TTA could reflect greater AP movement at the knee and hip joint altering the pendulum-like motion of the affected limb, and/or the effect on AP COP location of prosthetic foot deformation under changes in vertical load as previously described. Both of these explanations would account for the tighter coupling between the COP_I and COP_{NET} compared to the coupling between the COP_P and COP_{NET}.

COP_{NET} displacements in the ML direction may be dominated by vertical ground reaction force shifts across the two feet that result from coronal plane hip motion; independent of sway and similarly available to both groups, which may explain the lack of differences in magnitude and quality of $\mathrm{COP}_{\mathrm{NET}}$ displacement patterns in this direction. Fluctuations in vertical load, however, will have no effect on the COP beneath each foot ($\mathrm{COP}_{\mathrm{P}}$ and $\mathrm{COP}_{\mathrm{I}}$), and indeed it has been shown that there is little relationship between the $\mathrm{COP}_{\mathrm{NET}}$ displacement due to vertical load shifts and the COP beneath the individual foot (D. Winter, Prince, Stergiou, & Powell, 1993; D. A. Winter, 1995). In the ML direction, movements of the $\mathrm{COP}_{\mathrm{NET}}$ could be achieved by multiple other mechanisms, however, including whole body sway about the ankle/foot, unilateral ankle, knee and hip flexion/extension and lateral trunk lean. Therefore, consistencies between the patterns of $\mathrm{COP}_{\mathrm{NET}}$ and COP beneath an individual limb may arise via other means. In the absence of prosthetic ankle range of motion and volitional control, whole body sway about the foot of the prosthetic side effected by intact limb flexion/extension, i.e. an 'intact limb-driven' motor control strategy, will tighten the coupling between the $\mathrm{COP}_{\mathrm{NET}}$ and the $\mathrm{COP}_{\mathrm{P}}$ more than between the $\mathrm{COP}_{\mathrm{NET}}$ and the $\mathrm{COP}_{\mathrm{I}}$.

As could be expected, no differences were observed between the coupling of the $\mathrm{COP}_{\mathrm{P}}$ and $\mathrm{COP}_{\mathrm{NET}}$ and coupling of the $\mathrm{COP}_{\mathrm{I}}$ and $\mathrm{COP}_{\mathrm{NET}}$ in the unimpaired individuals.

4.3 Methodological choices and limitations

The present study adopted the method presented by Wang and Newell (2012b) to quantify the synchronization between the COP signals and used a group mean across all participants of the average standard deviation of the relative phase angle for each coupling and each direction. This approach was chosen to include a more general limit for structurally stable coordination patterns of COP synchronization. However, it does not take into account any participant-specific differences.

There was considerable group heterogeneity in the individuals with TTA making matching with unimpaired individuals difficult. In the present study participants were age-matched but significant group differences were observed in body height and body mass. Although the body mass index did not differ, it cannot be excluded that these group differences could influence the results.

The individuals with TTA wore their own prosthesis to which they had habituated. Therefore, variations in prosthetic foot geometry, structure and alignment could have influenced COP displacements and introduced greater inter-subject variability.

The individuals with TTA were active community ambulators and it is possible that less able or experience prosthesis users would display different control strategies and potentially rely more on the motion of the intact limb.

Although, several methodological choices and study limitations could have influenced the results, we believe that the present study provides valuable information about the motor control of upright standing in individuals with TTA laying the foundation for future studies focused on rehabilitation and skill acquisition.

4.4 Conclusion

The results of the present study indicate that the differences in inter-limb coupling during bilateral upright standing between individuals with TTA and unimpaired individuals are direction dependent. Thus, while inter-limb coupling appears not to differ in the ML direction, the individuals with TTA have looser coupling in the AP direction. This is likely due to a greater requirement for ankle control in the AP direction compared to the ML direction. To maintain a flexible upright standing position, the COP_I appears to dominate the COP_{NET} in individuals with TTA; likely a compensation for the constraints of the affected limb. This leads to a tighter coupling between the COP_I and the COP_{NET} compared to the coupling between the COP_P and COP_{NET} in the AP direction. Conversely, the adopted postural control strategy tightens the coupling between the COP_P and the COP_{NET} in the ML direction. Future work exploring this direction dependence in the presence of greater balance challenges and/or ecologically valid standing activities may provide further insight into the relative utilization of the prosthetic and intact limbs in individuals with amputation. Further investigation of inter-limb vertical loading effects is similarly warranted, given that bi-directional COP shifts beneath the prosthesis may occur with loading as a result of the static position and angle of orientation of the foot with respect to the residual limb.

Conflict of interest

The authors declare no conflict of interest.

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Figure legends

Figure 1: Total path length of the COP beneath the prosthetic limb, intact limb and the combined COP for the individuals with transtibial amputation (TTA) and the matched individual limbs and the combined COP for the unimpaired individuals in the anterior-posterior and mediolateral direction. Significant p-values of post hoc test from significant group-direction-COP signals interaction are presented.

Figure 2: Sample entropy (top figures) and entropic half-life (bottom figures) for the anterior-posterior and mediolateral directions of the COP beneath the prosthetic limb, intact limb and the combined COP for the individuals with transtibial amputation (TTA) and the matched individual limbs and the combined COP for the unimpaired individuals. Significant p-values of post hoc test from significant group-direction interaction are presented.

Figure 3: Number of synchronization epochs (top left), total duration of synchronization (top right), mean relative phase angle (bottom left) and deviation phase (bottom right) for the inter-limb COP coupling (Pros vs Int) in the anterior-posterior (Ant-Pos) and mediolateral (Med-Lat) directions for the individuals with transtibial amputation (TTA) and unimpaired individuals. Significant p-values of post hoc test from significant group-direction interaction are presented.

Figure 4: Number of synchronization epochs (A), total duration of synchronization (B), mean relative phase angle (C) and deviation phase (D) for the COP_P and COP_{NET} coupling and COP_I and COP_{NET} coupling in the anterior-posterior (Ant-Pos) and mediolateral (Med-Lat) for the individuals with transtibial amputation. Significant p-values of post hoc test from significant coupling-direction interaction are presented.

Figure 5: Number of synchronization epochs (A), total duration of synchronization (B), mean relative phase angle (C) and deviation phase (D) for the COP_P and COP_{NET} coupling and COP_I and COP_{NET} coupling in the anterior-posterior (Ant-Pos) and mediolateral (Med-Lat) for the unimpaired individuals. Significant p-values of post hoc test from significant coupling-direction interaction are presented.

Table 1: Demographics of the included individuals with transtibial amputation (TTA group; n = 21) and unimpaired individuals (unimpaired group; n = 18).

Group	Age (yrs)	Height (m)	Mass (kg)	BMI	Amputated side	Time since amputation	Amputation etiology
TTA 17 males / 4 females	59.7 (15.0)	1.79 (0.07)	100.3 (15.6)	31.3 (5.0)	9L 12R	9.8 (7.3)	Trauma n = 9 Vascular n = 4 Other n = 7
Unimpaired 14 males / 4 females	54.1 (16.0)	1.73 (0.10)	85.2 (18.4)	28.5 (5.3)	NA	NA	NA
P-value	0.270	0.021	0.010	0.102	NA	NA	NA

Figure 1: Total path length of the COP beneath the prosthetic limb, intact limb and the combined COP for the individuals with transtibial amputation (TTA) and the matched individual limbs and the combined COP for the unimpaired individuals in the anterior-posterior and mediolateral direction. Significant p-values of post hoc test from significant group-direction-COP signals interaction are presented.

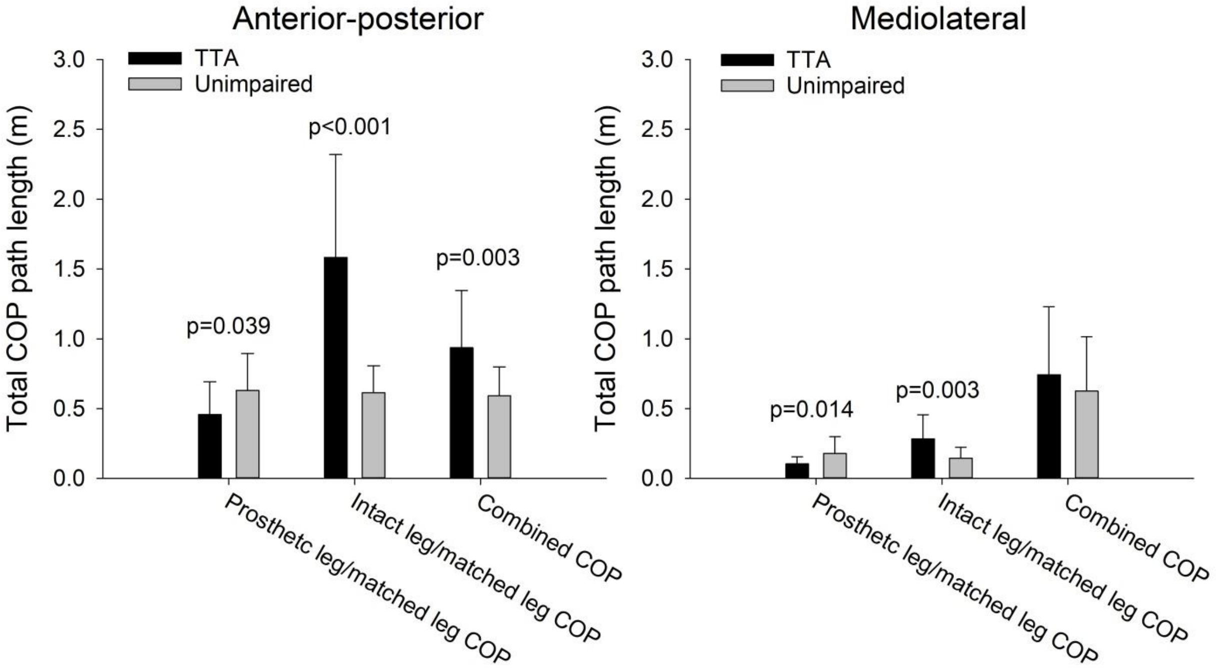


Figure 2: Sample entropy (top figures) and entropic half-life (bottom figures) for the anterior-posterior and mediolateral directions of the COP beneath the prosthetic limb, intact limb and the combined COP for the individuals with transtibial amputation (TTA) and the matched individual limbs and the combined COP for the unimpaired individuals. Significant p-values of post hoc test from significant group-direction interaction are presented.

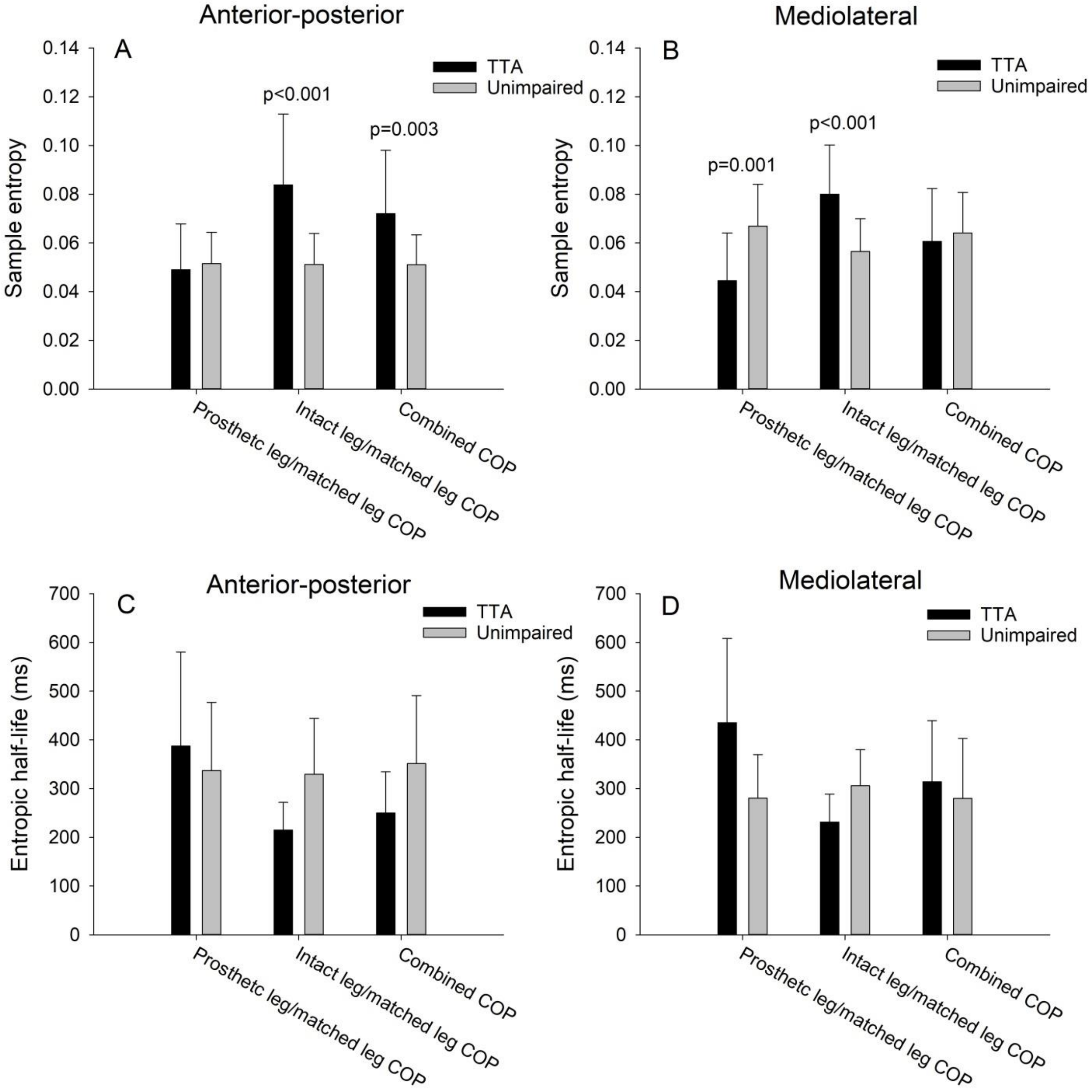
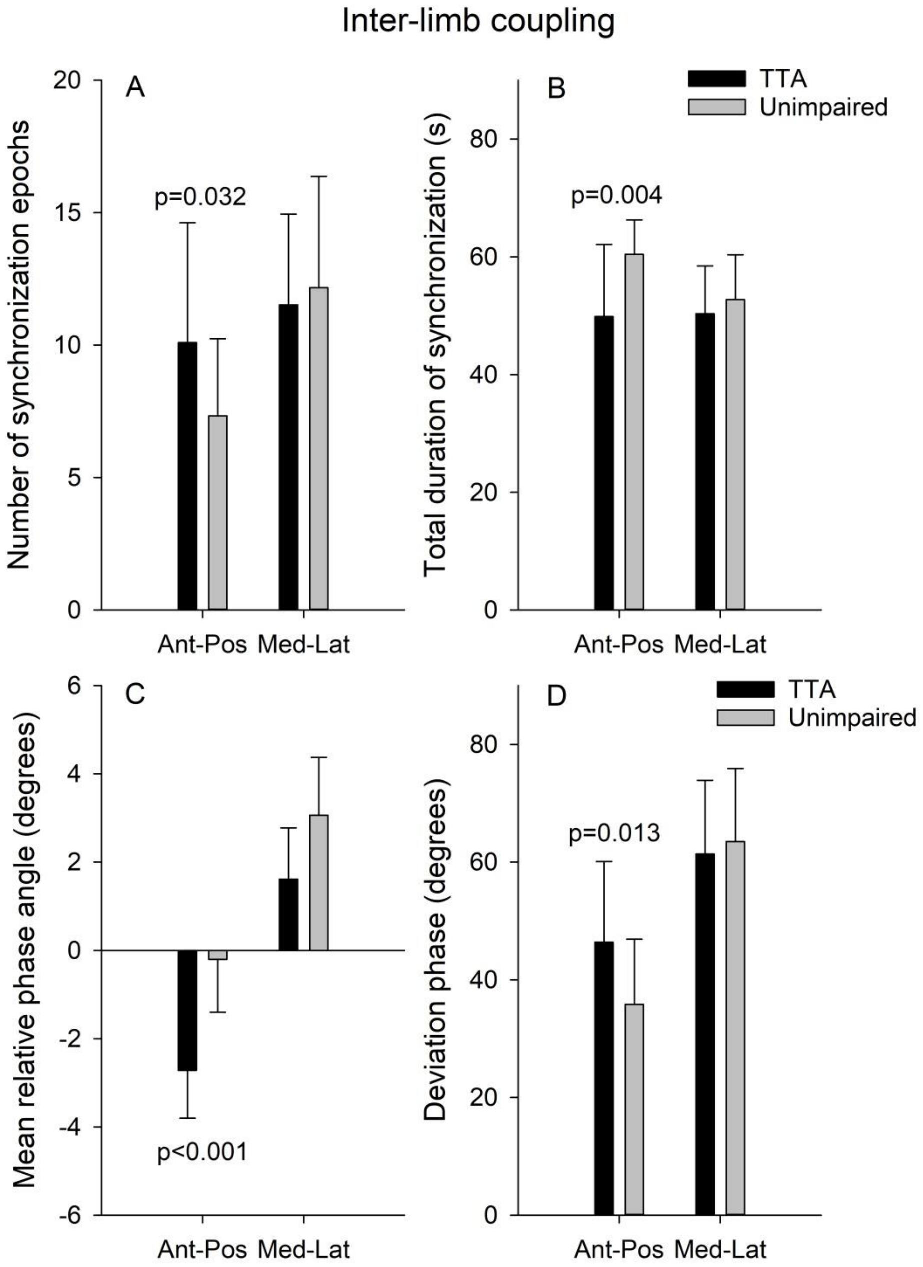


Figure 3: Number of synchronization epochs (top left), total duration of synchronization (top right), mean relative phase angle (bottom left) and deviation phase (bottom right) for the inter-limb COP coupling (Pros vs Int) in the anterior-posterior (Ant-Pos) and mediolateral (Med-Lat) directions for the individuals with transtibial amputation (TTA) and unimpaired individuals. Significant p-values of post hoc test from significant group-direction interaction are presented.



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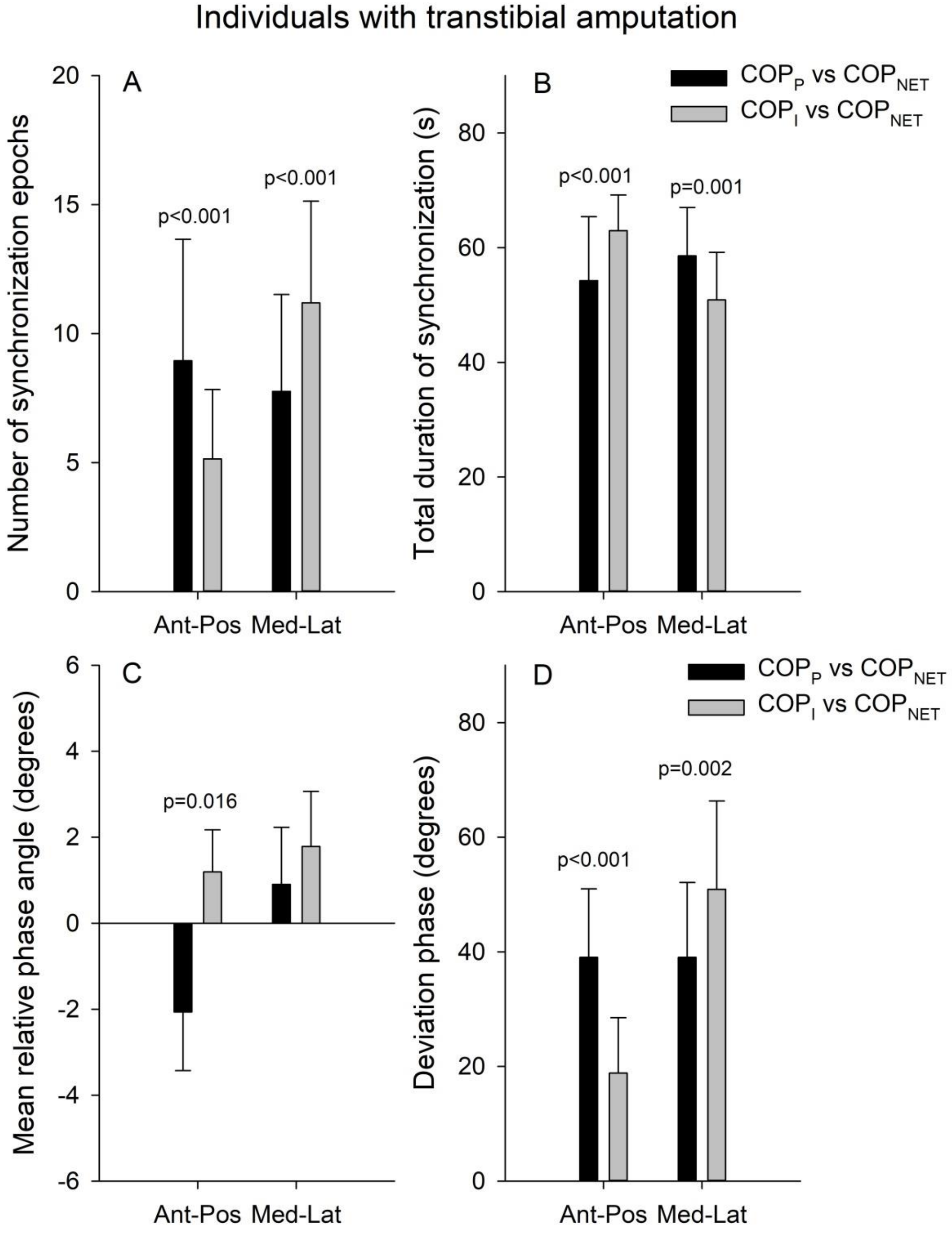

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