Initial center of pressure position prior to anticipatory postural adjustments during gait initiation in people with Parkinson's disease with freezing of gait

Madli Bayot[a], Arnaud Delval[a], Caroline Moreau[a], Luc Defebvre[a], Clint Hansen[b], Walter Maetzler[b], Christian Schlenstedt[b]

[a] Univ. Lille, Inserm, CHU Lille, U1172 – LilNCog – Lille Neuroscience & Cognition, F-59000 Lille, France.

[b] Department of Neurology, University Hospital Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany.

Supplementary material

A. Kinetic and kinematic data analysis – detailed version

In order to assess preparation and execution of gait, different spatio-temporal features of the first step were extracted from the data, by using an in-house MATLAB script (The MathWorks, Natick, MA, USA) based on methodologies found in the literature to detect gait events. Data of each trial were plotted and visually checked.

- **Initial mean AP and ML COP positions**, expressed respectively as a percentage of foot length and stance width (Figure 1), were calculated and averaged over 1 s prior to APA onset. Foot length was assessed as the AP distance between points located at mean distance between both toe markers and both heel markers, whereas stance width was the ML distance between the orthogonal projections of the middle points between left/right heel and toe markers on a parallel line passing by the marker at the left/right ankle. Initial mean AP and ML COP positions over 1 s prior to APA onset were measured by reference to the middle point between both heel markers and to the orthogonal projection of the middle point between stepping-foot heel and toe markers on a parallel line passing by the ankle marker, respectively. An initial mean AP/ML COP position at 50% of the foot length/stance width thus corresponds to an averaged centered COP within the basis of support.

- **Heel off (*HO*)** was defined as the time when the heel velocity in the sagittal plane is equal to or greater than its baseline (mean velocity in the sagittal plane over 1 s after the start of recording) plus 100 mm/s [1,2]. This algorithm method has been shown to be both reliable in comparison to the visual inspection and accurate [1].

- **Toe-off event (*TO*)** was considered as the time of a local maximum in the vertical velocity component of the heel marker [3].

- Time of a local minimum in the vertical velocity component of the toe marker was detected and linked to **heel strike (*HS*)** [3].

- **APA onset** (***T₀***, see Figure A.1) was detected as the time when ML velocity of COP exceeds $mean(baseline) + 1 * standard\ deviation(baseline)$ just before exceeding

$mean(baseline) + 3 * standard\ deviation(baseline)$ [4,5]. The baseline was defined as a time interval from the start of recording until the maximum between 1 s and (TO – 2 s).

- **Duration of APA** was described as the time between T_0 and HO [6,7].
- **ML size of APA** was defined as the maximum COP displacement in the ML direction during APA, relating to the COP position at T_0 [6].
- **Lateral COP shift between T_0 and TO** that can also be described as the lateral COP shift during the unloading of the swing foot (***COP$_U$***) was also assessed, as well as the **duration of the unloading phase** (***T$_U$***).
- **AP size of APA** was described as the maximum COP excursion in the AP direction during APA, relating to the COP position at T_0 [6]. It has to be noted that a backward shift of the COP is not always observed in individuals, particularly in PD patients.
- **Length and speed of first step** as well as **swing phase duration** corresponded to the distance covered and speed of the swing leg between TO and HS, and the duration of the step execution phase.

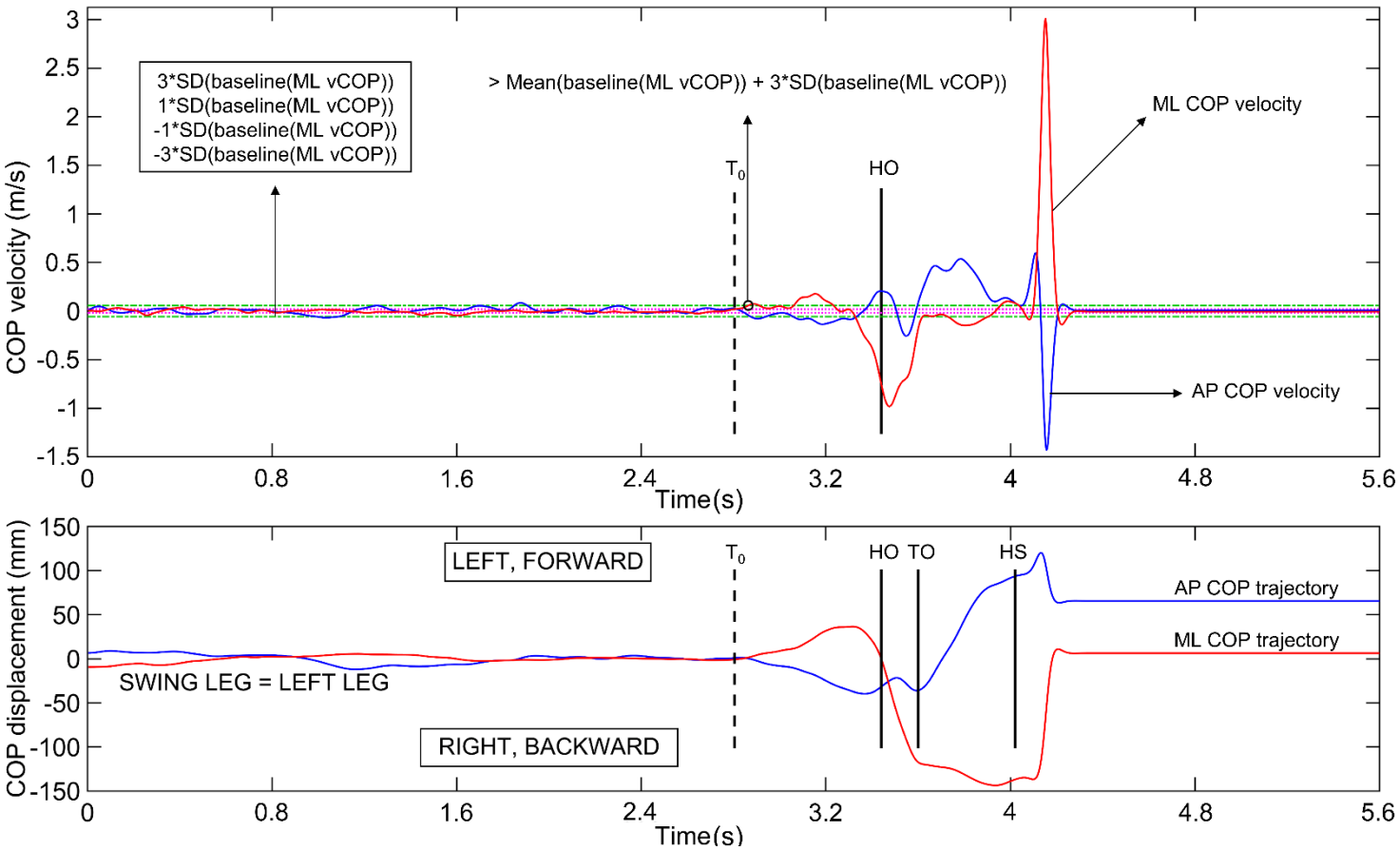

Figure A.1. Detection of APA onset based on ML COP velocity. T_0 = APA onset; HO = heel off; TO = toe off; HS = heel strike

B. Statistical analysis – detailed version

All statistical analyses were conducted in R [8], with the use of ggplot2 [9] package for producing figures. The statistical significance threshold associated with all the tests was $p < 0.05$.

Demographic and clinical data between PD+FOG, PD-FOG and HC were compared with Kruskal-Wallis test, and between PD+FOG and PD-FOG with Mann-Whitney U test. Dichotomous data were compared using Chi-Square test.

Because each participant performed a different amount of trials varying from one to five, differences between groups in terms of initial mean COP position over 1 s prior to APA onset and characteristics of the first step preparation (features of APA) and execution (the step itself) were statistically tested using a linear mixed model (LMM) with group as fixed effect, participant as random effect and stance width as covariate (except for the analysis of the initial mean ML COP position prior to APA onset). In order to control for a significantly different clinical variable between PD+FOG and PD-FOG (i.e. disease duration), a second ANCOVA related to the PD patients only was carried out, based on the same previous LMM but with disease duration as a new covariate. A Tukey correction for post-hoc tests was used to adjust for multiple comparisons. When the assumptions of normal distribution and homogeneity of variances of residuals among groups were violated (assumptions checked mainly visually with a QQ plot/a plot of residual values versus fitted values, followed by Shapiro-Wilk and Levene tests among groups), generalized linear mixed models (GLMM) were used. APA duration (and T_u), as a reaction time [10], presented a positively skewed distribution and therefore required to be tested via a GLMM with inverse gaussian distribution of the data and an inverse link function. The size of APA in AP and ML directions included some zero values while exhibiting a positively skewed distribution. The glmmTMB package was thus useful in order to fit a zero-inflated GLMM [11], with a modified Gamma distribution of the data (skipping checks for zero values and fitting therefore hurdle-Gamma models) and a log link function. In general, the use of lme4 package [12] was necessary for performing (generalized) linear mixed analyses.

Furthermore, in order to investigate the relationships between the initial mean AP/ML COP position over 1 s prior to APA onset, gait preparation and first step execution in each group, repeated measures correlation coefficients were assessed and allowed to determine the common within-individual association for paired measures evaluated in a given population [13]. Based on that, different linear mixed models including uncorrelated features of quiet stance prior to gait initiation and characteristics of APAs as potential predictors of first step length and velocity were the starting point for choosing the best regression model associated with each group by AIC (Akaike's Information Criteria) in a backward stepwise algorithm (R functions used: *lme* from nlme for building LMM, *stepAIC* from MASS for model selection, and *r.squaredGLMM* from MuMIn for obtaining marginal and conditional r-squared). Disease duration was also tested as an independent variable in the regression analysis related to each PD group. The absence of multicollinearity between predictors was confirmed by variance inflator factors that did not exceed 5 [14].

C. Execution of first step – box plots

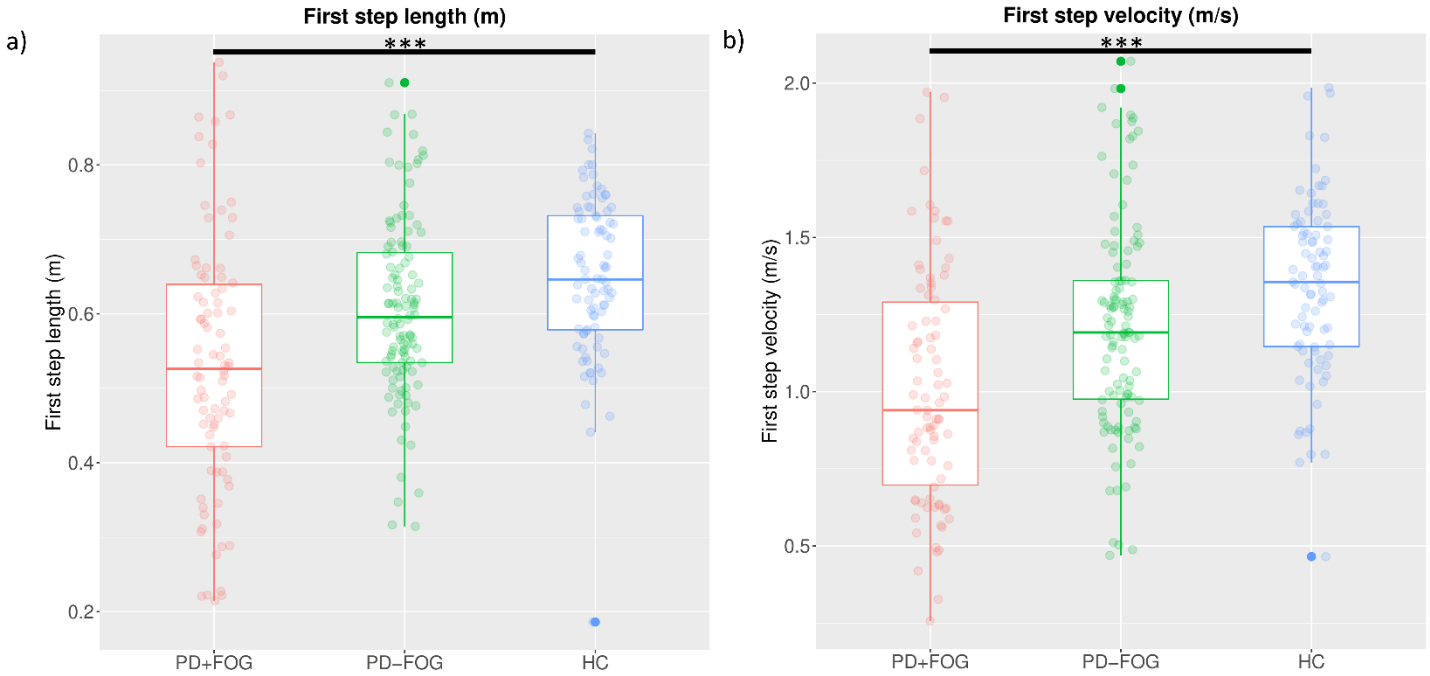

Figure C.1. Characteristics of first step execution that were significantly different between groups: first step (a) length and (b) velocity. *** for p-value < 0.001

D. Correlation analysis

Table D.1. Correlations between the initial mean COP position and characteristics of gait preparation and execution. Values represent repeated measures correlation coefficients (p-values); * p-value < 0.05; ** p-value < 0.01; *** p-value < 0.001. Cells with bold borders represent the common significant associations between two variables (different than first step length and velocity) among groups. Only statistically significant Spearman's correlation coefficients or with a trend toward significance (related p-value < 0.1) are shown

	Group	ML COP position	AP size of APA	ML size of APA	COP_U	APA duration	T_U	Stance width	Swing phase duration	First step length	First step velocity
AP COP position	PD+FOG		0.232 (0.071)							**-0.33**** (0.0099)	
	PD-FOG	**0.328**** (0.002)	**0.348**** (0.001)		-0.192 (0.078)						
	HC										
ML COP position	PD+FOG			**0.329**** (0.009)							-0.247 (0.057)
	PD-FOG				-0.202 (0.063)		**-0.296**** (0.006)				
	HC			**0.317*** (0.014)							0.217 (0.098)
AP size of APA	PD+FOG			**0.423***** (< 0.001)	**0.294*** (0.021)				-0.242 (0.061)		
	PD-FOG			**0.371***** (< 0.001)			-0.19 (0.082)		**-0.326**** (0.002)		**0.276*** (0.01)
	HC			**0.594***** (< 0.001)					-0.251 (0.055)		
ML size of APA	PD+FOG				**0.68***** (< 0.001)		**-0.289*** (0.024)	**0.274*** (0.032)			
	PD-FOG				**0.573***** (< 0.001)				**-0.291**** (0.007)	**0.308**** (0.004)	**0.401***** (< 0.001)
	HC				**0.474***** (< 0.001)			**0.289*** (0.026)			
COP_U	PD+FOG							**0.552***** (< 0.001)		0.225 (0.084)	**0.314*** (0.014)
	PD-FOG						**0.345****	**0.345****		**0.263***	**0.246***

	HC						(0.001)	(0.001)		(0.015)	(0.023)
						-0.231 (0.079)		**0.506*** (< 0.001)			
APA duration	PD+FOG										
	PD-FOG									**-0.269*** (0.039)	**-0.279*** (0.033)
	HC										
T_U	PD+FOG							-0.213 (0.099)			
	PD-FOG								**0.325**** (0.002)		-0.182 (0.096)
	HC								**0.315*** (0.015)	0.246 (0.06)	
Stance width	PD+FOG									0.216 (0.097)	
	PD-FOG										
	HC										
Swing phase duration	PD+FOG									**0.407**** (0.001)	**-0.534***** (< 0.001)
	PD-FOG										**-0.679***** (< 0.001)
	HC										**-0.596***** (< 0.001)
First step length	PD+FOG										**0.485***** (< 0.001)
	PD-FOG										**0.675***** (< 0.001)
	HC										**0.663***** (< 0.001)

E. Statistical results after having excluded trials with a FOG event

Table E.1. Significantly different parameters (initial mean COP position prior to gait initiation, and characteristics of the preparation (APAs) and execution of the first step) between groups stayed unchanged after having excluded trials with a FOG event. For each group, the mean and standard deviation of gait and balance parameters averaged through each subject's trials were reported. NS = non-significant; * for p-value < 0.05; ** for p-value < 0.01; *** for p-value < 0.001.

Classification	Variable	PD+FOG (n=25) *Mean (SD)*	PD-FOG (n=30) *Mean (SD)*	HC (n=27) *Mean (SD)*	Effect of Group *(p-values)*	Post-hoc tests	Post-hoc tests when controlling for disease duration
Prior to APA	**AP COP position (% of foot length)**	57.967 (6.153)	53.794 (10.936)	56.229 (10.457)	NS (0.179)	/	**PD+FOG > PD-FOG** (0.003**)
	ML COP position (% of stance width)	53.043 (4.412)	53.328 (9.512)	48.34 (4.208)	**0.014***	**PD+FOG > HC** (0.047*) **PD-FOG > HC** (0.019*)	NS (0.889)
	Stance width (mm)	272.936 (46.705)	248.716 (41.207)	262.572 (42.164)	NS (0.114)	/	NS (0.476)
During APA	**AP size of APA (mm)**	28.795 (22.418)	40.95 (23.805)	51.678 (23.325)	**< 0.001*****	PD+FOG < PD-FOG (0.018*) **PD+FOG < HC** (< 0.001***)	NS (0.693)
	Unloading phase duration (s)	0.522 (0.302)	0.326 (0.115)	0.317 (0.141)	**< 0.001*****	PD+FOG > PD-FOG (0.004**) **PD+FOG > HC** (0.001**)	NS (0.098)
First step	**First step length (m)**	0.532 (0.159)	0.603 (0.113)	0.643 (0.095)	**0.003****	PD+FOG < PD-FOG (0.045*) **PD+FOG < HC** (0.003**)	NS (0.487)
	First step velocity (m/s)	1.039 (0.345)	1.211 (0.335)	1.314 (0.256)	**0.006****	PD+FOG < PD-FOG (0.07) **PD+FOG < HC** (0.004**)	NS (0.611)

Table E.2. Backward stepwise multiple regressions for prediction of first step length and velocity in PD+FOG after having excluded trials with a FOG event, with (linear mixed) models selection based on AIC. * for p-value < 0.05; ** for p-value < 0.01; *** for p-value < 0.001.

Dependent variable	Group	Best model	Standardized regression coefficients	p-values	AIC	BIC	logLik	Conditional R2	Marginal R2
1ST STEP LENGTH	**PD+FOG**	**~ AP COP position** **+ ML COP position** **+ stance width**	**-0.157**** **-0.2*** **0.201***	<0.001 0.001 0.013	763.009	776.055	-375.504	0.928	0.115
1ST STEP VELOCITY	**PD+FOG**	**~ AP COP position** **+ ML COP position** **+ AP size of APA** **+ stance width**	**-0.188*** **-0.24**** **0.166**** **0.28****	0.001 0.002 0.024 0.003	874.443	889.663	-430.221	0.88	0.278

References

[1] S. Ghoussayni, C. Stevens, S. Durham, D. Ewins, Assessment and validation of a simple automated method for the detection of gait events and intervals, Gait Posture. 20 (2004) 266–272. https://doi.org/10.1016/j.gaitpost.2003.10.001.

[2] S. Lambrecht, A. Harutyunyan, K. Tanghe, M. Afschrift, J. De Schutter, I. Jonkers, Real-Time Gait Event Detection Based on Kinematic Data Coupled to a Biomechanical Model, Sensors. 17 (2017). https://doi.org/10.3390/s17040671.

[3] M. Pijnappels, M.F. Bobbert, J.H. van Dieën, Changes in walking pattern caused by the possibility of a tripping reaction, Gait Posture. 14 (2001) 11–18.

[4] R. Sun, R. Guerra, J.B. Shea, The posterior shift anticipatory postural adjustment in choice reaction step initiation, Gait Posture. 41 (2015) 894–898. https://doi.org/10.1016/j.gaitpost.2015.03.010.

[5] R. Sun, J.B. Shea, Probing attention prioritization during dual-task step initiation: a novel method, Exp. Brain Res. 234 (2016) 1047–1056. https://doi.org/10.1007/s00221-015-4534-z.

[6] J.-L. Honeine, M. Schieppati, O. Crisafulli, M.-C. Do, The Neuro-Mechanical Processes That Underlie Goal-Directed Medio-Lateral APA during Gait Initiation, Front. Hum. Neurosci. 10 (2016). https://doi.org/10.3389/fnhum.2016.00445.

[7] E. Yiou, R. Artico, C.A. Teyssedre, O. Labaune, P. Fourcade, Anticipatory Postural Control of Stability during Gait Initiation Over Obstacles of Different Height and Distance Made Under Reaction-Time and Self-Initiated Instructions, Front. Hum. Neurosci. 10 (2016). https://doi.org/10.3389/fnhum.2016.00449.

[8] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2018. https://www.R-project.org/.

[9] Hadley Wickham, ggplot2: Elegant Graphics for Data Analysis, Springer-Verlag New York, 2016. http://ggplot2.org.

[10] S. Lo, S. Andrews, To transform or not to transform: using generalized linear mixed models to analyse reaction time data, Front. Psychol. 6 (2015). https://doi.org/10.3389/fpsyg.2015.01171.

[11] M.E. Brooks, K. Kristensen, K.J. van Benthem, A. Magnusson, C.W. Berg, A. Nielsen, H.J. Skaug, M. Mächler, B.M. Bolker, glmmTMB Balances Speed and Flexibility Among Packages for Zero-inflated Generalized Linear Mixed Modeling, R J. 9 (2017) 378–400.

[12] D. Bates, M. Mächler, B. Bolker, S. Walker, Fitting Linear Mixed-Effects Models Using lme4, J. Stat. Softw. 67 (2015) 1–48. https://doi.org/10.18637/jss.v067.i01.

[13] J.Z. Bakdash, L.R. Marusich, Repeated Measures Correlation, Front. Psychol. 8 (2017). https://doi.org/10.3389/fpsyg.2017.00456.

[14] G. James, D. Witten, T. Hastie, R. Tibshirani, Linear Regression, in: G. James, D. Witten, T. Hastie, R. Tibshirani (Eds.), Introd. Stat. Learn. Appl. R, Springer, New York, NY, 2013: pp. 59–126. https://doi.org/10.1007/978-1-4614-7138-7_3.