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Biological motion during inflammation in humans

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Abstract

Biological motion is a powerful perceptual cue that can reveal important information about the inner state of an individual. Activation of inflammatory processes likely leads to changes in gait, posture, and mobility patterns, but the specific characteristics of inflammation-related biological motion have not been characterized. The aim of this study was to determine the effect of inflammation on gait and motion in humans. Systemic inflammation was induced in 19 healthy volunteers with an intravenous injection of lipopolysaccharide (2 ng/kg body weight). Biological motion parameters (walking speed, stride length and time, arm, leg, head, and shoulder angles) were assessed during a walking paradigm and the timed-up-and-go test. Cytokine concentrations, body temperature, and sickness symptoms were measured. During inflammation, compared to placebo, participants exhibited shorter, slower, and wider strides, less arm extension, less knee flexion, and a more downward-tilting head while walking. They were also slower and took shorter

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first steps in the timed-up-and-go test. Higher interleukin-6 concentrations, stronger sickness symptoms, and lower body temperature predicted the inflammation-related alterations in biological motion. These findings show that biological motion contains clear information about the inflammatory status of an individual, and may be used by peers or artificial intelligence to recognize that someone is sick or contagious.

Keywords

biological motion; gait; Kinect; inflammation; sickness; body temperature

1. Introduction

Biological motion is a powerful communication cue (1) which can provide important information about the inner state of others. For example, a mere moving point-light display is sufficient for people to correctly identify the mover's species and actions (2), recognize humans' gender (3), and detect emotions (4). It is thus likely that someone's health status could also be determined by such biological motion cues (5). Importantly, movement is detectable from a long distance (6), which indicates a strong adaptive advantage to detect sickness from someone's movement, as compared to facial cues and body odours. Biological motion is indeed altered in various medical conditions, with e.g. gait pattern indicating physical limitation due to injury or Parkinson's disease (7). Furthermore, disorders that do not directly affect motor functions, such as depression and chronic fatigue syndrome, are also characterized by slower walking speed and altered gait pattern (8, 9). Even when subjectively reported, slower walking speed is a strong predictor of mortality, surpassing smoking and other lifestyle measurements (10). Taken together, biological motion seems to be a reliable indicator of ill health. However, very little research has focused on the objective characterization and underlying mechanisms of such health-related motion.

One mechanism that likely underlies gait alterations during ill health is inflammation. It is well-known that inflammatory cytokines produced in the periphery modulate many central nervous system functions (11). The fact that inflammatory cytokines affect dopamine functioning and target the basal ganglia, a group of structures central for motor movements (12), suggests that inflammation can alter motion patterns. This proposition is supported by behavioural studies showing that increased levels of inflammatory markers are associated with slower gait amongst the elderly (13). Experimentally controlled inflammatory activation has also been shown to reduce walking speed in a small study of otherwise healthy subjects, resulting in the perception of poorer health (5). Furthermore, signs of low-grade activation of inflammatory processes have been found in patients suffering from depression and chronic fatigue syndrome (11, 14), which may contribute to the observed gait alterations in these conditions (8, 9). However, this has never before been investigated, let alone in an experimental design. Therefore, the effect of inflammation on specific gait characteristics other than a slower walking speed remains unknown. Specifying such characteristics would help determine whether, and how, inflammatory status could be detected in biological motion. This would provide important information on biological motion as a social cue for determining health status in others. It would also indicate that

biological motion could be used for the detection and diagnosis of inflammation (15), and for evaluating the efficacy of treatments.

The main aim with the current study was to characterize inflammation-related biological motion during a walking paradigm and a mobility test, using an experimentally induced inflammatory condition. A secondary aim was to determine to what degree plasma concentrations of pro-inflammatory cytokines (interleukin (IL)-6 and tumor necrosis factor (TNF)- α), body temperature, sickness symptoms, fatigue, and pain predicted such motion alterations, as all these factors increase acutely during experimental inflammation (16) (see Fig. S1).

2. Materials and Methods

2.1. Experimental design

This study was part of a larger study aimed at assessing overt sickness behaviour and its predictors, approved by the Regional Ethical Committee of Stockholm (Dnr 2014/1946-31/1 and 2015/1415-32; [ClinicalTrials.gov](https://www.clinicaltrials.gov) identifier:). Twenty-two subjects participated in the larger study, but biological motion data was unusable for three of them (see below, “missing data”). Nineteen participants (seven women, average age: 23 ± 3 years; body mass index: 23.2 ± 2.5 kg/m²) were therefore included in the current study. The sample size was determined according to previous research, which has shown significant immunological and behavioural changes after LPS administration with a sample size of 10-20 (17). A sample size of $n=18-19$, with a within-subject design, a correlation between repeated measures of 0.6, and a power of 0.80, allowed for detection of a difference between LPS and placebo conditions with an effect size of 0.3.

Participants were recruited through advertisements at university campuses, and had to fulfil the following inclusion criteria: 18-50 years old, fully healthy (i.e., no known physiological or psychiatric disease, no medical condition detected during medical examination before inclusion, no abnormal clinical blood analyses), non-smoker, and non-excessive alcohol user. Before inclusion, participants underwent a complete medical examination, including an electrocardiogram and clinical laboratory analyses of level of sodium, potassium, creatinine, transaminases, white blood cell count, and hemoglobin. Smoking, alcohol use, use of other drugs and known diagnosis of physiological or psychiatric diseases were assessed by the responsible physician during the pre-inclusion medical examination. Excessive alcohol use was defined as >14 glasses of wine/9 glasses of strong beer per week for men and >9 glasses of wine/6 glasses of strong beer per week for women. The absence of major depressive disorder was verified using the M.I.N.I. International Neuropsychiatric Interview (18). Participants were informed of the procedures both orally and in writing before participation, gave their written informed consent before inclusion, and received 3,500SEK for participating.

The procedure followed a double blind, placebo-controlled, crossover design, and was conducted at the Center for Clinical Research at Danderyd Hospital, Stockholm, Sweden from February to April 2015. All participants were injected twice, once with LPS (2.0 ng/kg body weight) and once with saline (0.9% NaCl), in a counter-balanced order (simple

randomization using sealed envelopes), with 3–4 weeks of washout in between. More experimental details have been reported previously (16). Participants and research staff, except for the safety-responsible physician, were blind to the condition of treatment and to the hypothesis of the current study. Note, however, that sickness symptoms induced by this dose of LPS manifested in a noticeable manner for both the experimenters and the participant in the majority of participants.

2.2. Walking paradigm and mobility test

For objective three-dimensional (3-D) recordings of biological motion, transportation of participants to an external facility is normally required. Here, we instead used a reliable (19), sensorless, mobile alternative that has previously been used to objectively assess posture and movement parameters (Microsoft® Kinect® for Windows, system v.1, Microsoft, USA) (20).

Participants performed the walking paradigm and mobility (timed-up-and-go, TUG) tests on both study days, 2–2.5h after the LPS/placebo injection, corresponding to the peak of cytokine systemic concentrations and sickness symptoms (see (16)). Participants wore socks without shoes, and were informed that they could sit down at any time if they did not feel well. Since some participants experienced strong nausea and dizziness, the session did not start until the participant felt well enough to walk (range 2h05min – 2h30min after injection). The Kinect® camera was placed facing the participants, 75cm above the ground. The location of the camera was fixed throughout the study period.

The procedure adhered to a standardized protocol, with each study day consisting of two walking trials, two TUG trials, and one additional walking trial, in that order. Participants were reminded that they could decline or interrupt any trial.

Each walking trial included 4–5 series, with each series composed of one back-and-forth walk following a 5.5m long walking path, starting and ending outside of the limit of detection of the Kinect® (practical range of detection: 1.2–3.5m). Participants were instructed to walk as naturally as possible, while looking straight ahead. The first walking trial was at a self-selected pace; the following two were performed following the rhythm of a metronome with 76 steps/minute (a comfortable slow pace, based on pilot data) in order to make sure that potential biological motion changes were not only due to change in pace. The walking procedure can thus be summarized as follows: two study days (LPS/saline conditions in randomized order); three walking trials on each study day (one at own pace, two at metronome pace); 4–5 walking series (= 4–5 back-and-forth walk) for each walking trial.

For each of the two TUG trials, participants sat on a chair placed 3.4m from the Kinect®. They were instructed to stand up (without using armrests), walk at a natural pace to a point outside of the limit of detection (40cm from the camera), then walk back to the chair and sit down.

2.3. Biological motion outcomes

The Kinect® detects the location of 20 body joints at ~30 Hz without the need of physical sensors. 3-D coordinates from the 20 body joints of the tracked skeleton (see Fig. 1) were obtained using the Microsoft® Software Development Kit (v1.8) and Microsoft® Visual Studio Express 2013 (Microsoft, USA). The outcomes were calculated using visual basic macros from the X, Y, and Z coordinates of the tracked skeleton.

Walking and TUG outcomes are described in Fig. 1 and Table S1. The TUG outcomes were calculated separately for each TUG trial. Walking outcomes were calculated for each series separately (“series outcomes”) or for each stride separately (“stride outcomes”) in each walking trial (see Table S1). The first series (i.e., the first back-and-forth walk) of each walking trial was removed from the analyses to obtain outcomes from a gait that was as natural as possible. Due to unreliability of data when participants walked away from the camera, only walking data from when participants faced the camera and the Z-coordinate of the hip was situated in the practical range of detection (minus 0.1m margin error) were selected. The ankle coordinate was used as foot coordinate, as the original foot coordinate was not as reliable. A step was defined as when the distance (on the Z-axis) between the two feet was maximal. A stride was composed of two steps.

The data obtained from the Kinect® system in the current study were found to be highly reliable (see Table S2 for details).

2.4. Inflammation-related factors

The following inflammation-related factors were measured before and after LPS/placebo administration, as indicated in previous reports (16) (see caption of Fig. S1 for detailed time points): plasma concentrations of pro-inflammatory cytokines IL-6 and TNF- α (using high-sensitivity multiplex, RnD Systems, MN, USA), body temperature (using a tympanic thermometer), sickness symptoms (using the SicknessQ), fatigue (using one item from the SicknessQ that specifically assessed fatigue, i.e. “I feel tired”), and back pain (using a verbal response scale ranging from 0 (no pain) to 10 (very intense pain)).

Cytokine concentrations, body temperature, and sickness symptoms increased during experimental inflammation, compared to placebo (16). Just before the walking paradigm and TUG test, cytokine concentrations and sickness symptoms peaked, while body temperature was increasing (peaking approximately 3h post-injection) (16). To assess the predictive effect of sickness-related factors on LPS-induced gait alterations, we used the data obtained most recently before the walking paradigm and TUG test for body temperature, sickness symptoms, fatigue, and pain (i.e., 1.5h after the LPS injection for sickness symptoms and fatigue, 2h after the LPS injection for body temperature and pain). For cytokines, we used the area under the curve (AUC) from 1h to 2h post-LPS injection, as the central effect of cytokines may be delayed from their peripheral measurement. To note, IL-8 was analyzed in addition to IL-6 and TNF- α for another purpose. However, only IL-6 and TNF- α were included in the current analyses in order to reduce the risk for type-I errors, and because these cytokines are the ones most often found to correlate with behavioral changes during experimental inflammation in humans.

2.5. Missing data

Twenty-two participants (nine females, average age: 23 ± 4 years) took part in the study. Data from two participants were excluded because of technical issues, and data from one participant were excluded because of clothing obscuring the joints. One additional participant had missing data from the TUG test because of a technical issue.

All participants except four performed all walking trials. Three abstained from the third walking trial in the LPS condition due to feeling sick. The fourth participant had data missing for the third walking trial in the placebo condition because of a technical issue. Four participants (three in the LPS condition, one in the placebo condition) had only one TUG trial due to technical issues or issues during the test (e.g. stretched mid-through testing).

2.6. Statistical analyses

All analyses were performed using IBM SPSS Statistics, version 22, with a significant p-value set at $p < .05$ (two-sided).

Mixed linear models were used to assess the effect of LPS administration (*versus* placebo) on the walking ($N = 19$) and TUG ($N = 18$) outcomes. Random variables were participant ID and order of repeated measures, i.e. session (1st/2nd session), trial, series, and stride number. An autoregressive (AR-1) covariance structure was chosen, and the Benjamini-Hochberg procedure was used to control for multiple analyses (false discovery rate: 5%).

In order to characterize a general inflammation-related movement pattern, and determine which symptoms predicted this pattern, we created a factor combining all gait variables that were significantly altered during experimental inflammation, using principal component analysis (PCA). First, the average of each gait variable that was significantly different in the LPS *versus* placebo condition, over all strides, series, and trials was calculated for each participant in each condition (LPS/placebo). The difference between the LPS and the placebo conditions was then calculated for each variable to obtain an estimation of the LPS-induced alteration. A forced one-factor PCA was performed on these variables to obtain a factor representing LPS-induced motion alteration. Following this, a stepwise backward multiple linear regression was performed to assess which inflammation-related factors predicted LPS-induced motion alteration, with the PCA factor as the dependent variable, and IL-6 concentration, TNF- α concentration, body temperature, sickness symptoms, fatigue, and pain as independent variables ($N = 18$). The Variance Inflation Factor (VIF) was assessed for potential multicollinearity.

2.7. Availability of data and materials

The datasets are available in the OSF repository [https://osf.io/ewkmb/?view_only=2f15c09ff96c4337a02e05e059fe6ba4] (21). The developed application software and macros used for the calculations of the Kinect® outcomes are freely available in the OSF repository [https://osf.io/esnbw/?view_only=af74018a25ec4750afa81d1a1bbb3b9b] (22).

3. Results

3.1. Walking and mobility changes during experimental inflammation

As shown in Table 1 and Fig. 2, administration of LPS induced several changes in the walking and TUG outcomes. In the walking paradigm, participants walked slower in the LPS condition than in the placebo condition (reduction of 0.19 m/sec), due to shorter and slower strides. In addition, participants exhibited a lower head angle (head tilted downwards), less arm extension, less knee flexion, and a larger stride width after LPS administration compared to placebo. In the TUG test, participants were slower to stand up and to perform the full test after having received LPS administration. They also took a shorter first step. No significant effect was found regarding shoulder angle or trunk angle, neither during the walking test nor while standing up in the TUG test.

3.2. Predictors of gait alterations during experimental inflammation

The LPS-induced motion alteration factor, obtained from PCA analysis, was positively loaded by TUG time (.849), time to stand (.795), knee flexion angle (.397), stride width (.372), and stride time (.268), and negatively loaded by TUG first step length (−.858), walking speed (−.792), stride length (−.635), arm extension angle (−.316), and to a lesser extent by head angle (−.072). A higher factor value indicates more LPS-induced biological motion alteration.

A stepwise backward multiple linear regression analysis was performed to determine to what degree inflammation-related variables could predict LPS-induced motion alterations. The best-fitted model included body temperature, sickness symptoms, back pain, and IL-6 concentration as predictors, together explaining 60% ($p=.013$) of the variance in the LPS-induced motion alteration factor. A higher value of the LPS-induced motion alteration factor was significantly predicted by stronger sickness symptoms ($\alpha=0.446$, 95% CI=[0.063 to 0.829], $p=.026$) and higher IL-6 concentration ($\beta=0.436$, 95% CI=[0.049 to 0.823], $p=.030$) (Fig. 3A–B). In addition, lower body temperature was associated with an increased LPS-induced motion alteration factor ($\beta=-0.462$, 95% CI=[−0.858 to −0.066], $p=.026$) (Fig. 3C). Back pain was also included in the model but did not significantly predict the motion alteration factor, although a trend for a positive association was observed ($\beta=0.343$, 95% CI=[−0.045 to 0.731], $p=.078$) (Fig. 3D). All VIF were around 1, indicating absence of multicollinearity.

4. Discussion

The present study demonstrates clear objective alterations in biological motion during experimental inflammation in otherwise healthy subjects. Inflammation-related gait was not only characterized by slower walking speed, but also by shorter strides, reduced extension of the arms (i.e. less swinging), less bending of the knees, a slightly wider distance between the feet, as well as the head tilted more downwards. Experimental inflammation also affected mobility, with participants being slower at standing up from a chair and taking smaller steps. Similar reductions in walking speed and stride/step length have been described in depression and chronic fatigue syndrome compared to healthy controls (8, 9), and alterations in arm

swings, head angle, and knee bending have also been documented in these patients (8, 23). The levels of inflammatory markers found in these conditions are much lower than the ones observed after LPS administration in this study. However, the behavioural effects of inflammatory cytokines are likely to occur also at low-grade inflammatory states, in particular if this state is chronic (11, 24, 25), and we thus propose that some of the motion alterations found in depression and chronic fatigue syndrome may be inflammatory-driven. Changes in the functions of brain structures involved in gait and posture control, such as the basal ganglia (12), and modifications of the peripheral connective tissue structure (26), could underlie these effects of inflammatory cytokines on biological motion. Furthermore, a drop in blood pressure was observed after the injection of lipopolysaccharide (27), and orthostatic hypotension might contribute to the alteration of some motion parameters (in particular TUG parameters).

During sickness, it has been suggested that individuals exhibit adaptive behavioural changes in order to favour preservation of energy and its redirection towards fighting the infection (11). Changes in biological motion during inflammation-induced sickness should arguably be integrated into this “sickness behaviour” profile. Given the amount of energy required to walk – about 30% of maximal aerobic capacity (28) – adapting movements during sickness, as seen here, would adjust the balance between energy preservation and performance. In other words, walking more slowly, with less arm swinging and leg lifting, may require less energy while still allowing the sick person to fulfil locomotive purposes. The finding that a higher level of inflammation-related gait alteration was connected with lower rather than higher body temperature could also reflect a need for the body to preserve energy for heating mechanisms (e.g. shivering) and reduce the heat loss caused by movement. The need for energy conservation may thus be one factor contributing to the gait patterns displayed during inflammation. This is in line with observations of reduced movements in infected animals (29). The more rigid walking pattern during inflammation may, on the other hand, increase the risk of falling (30), as many of the inflammation-associated changes in motion observed here have been associated with an increased risk for falling in older adults (31). The tilted head (facing more downward) could indicate a compensatory mechanism of keeping the balance.

In both diagnosis and infection prevention, an important question is the extent to which ill-health status can be signalled to, and detected by, others (32). In addition to other biological signals, such as body odours and facial changes (33, 34), alterations in biological motion might function as a social cue used by conspecifics to recognize that someone is sick and contagious. This is in line with previous research indicating that humans and other animals show avoidance to cues indicating disease (35). Although the observed differences in biological motion during inflammation are relatively small, a combination of these changes could provide an impression of ill health. This is supported by a previous study showing that individuals walking during an inflammatory state are perceived by others as less healthy (5). Given that biological motion, compared to odour and face cues, can be detected from a distance (6), it would provide a strong advantage from a disease-avoidance perspective.

The findings of the current study also indicate that intra-individual changes in biological motion could be used to aid in the diagnosis of conditions characterized by inflammation, as

has been suggested previously (15). It may furthermore be used to evaluate the efficacy of treatments (i.e., by assessing the improvement in gait characteristics over time). This could potentially even be automatized by the use of artificial intelligence. The Kinect® or similar portable systems could serve as reliable, inexpensive, and portable tools to objectively measure movement.

A limitation of this study is that blinding was hard to ensure since most participants became noticeably sick after LPS. Although participants were not informed of the reason for the walking paradigm and mobility test, nor any hypotheses, it is possible that they inferred these from the repeated design, which could have affected the results. Using lower LPS doses may help prevent this issue in future studies. The fact that participants were being watched while moving is also a limitation, as this may have influenced their gait. In addition, the participants were young (19-30 years old) and healthy, and findings might differ in older populations or in patients suffering from certain medical conditions. Another important point is the specificity of the effect of inflammation compared to other sickness symptoms. Indeed, inflammation did not only induce alterations in biological motion, but also sickness symptoms, including nausea, some dizziness, pain, and fatigue, which could themselves affect biological motion. It is thus difficult to fully isolate the effect of the inflammatory signal from its symptomatic and behavioural consequences. In an attempt to elucidate the influence of the different factors, we carried out a stepwise backward multivariable linear regression. Although the results of the analysis indicate that sickness symptoms indeed relate to more motion alterations during inflammation, it also reveals a significant and independent relationship with IL-6 concentrations. Importantly, the experimental procedure permits unambiguous conclusions about the specificity of the observed gait patterns, compared to naturalistic studies in patients. Nevertheless, the specificity of gait patterns for detecting different kinds of inflammation, ill-health states, and pain should be further investigated. Comparing the current results with gait pattern and mobility during conditions of ill health without an acute inflammatory response (e.g., motion sickness) would be of high interest. Furthermore, it is possible that the increase in negative mood that is induced by the activation of inflammatory processes after administration of LPS (36) also contributes to the observed changes in biological motion, since inducing sadness has been shown to bring about similar motion changes as in the current study (8, 37). Interestingly, previous studies also indicate that an individual's posture can affect emotional state (38, 39). The relationship between inflammation, negative mood and gait changes thus merits further investigation.

Another important point that could not be investigated here is the inter-individual variability and whether some individuals might be more sensitive to the effects of inflammation than others. Various factors, for instance sex (17), adiposity and baseline inflammation (40), might provide a vulnerability to the effects of an inflammatory challenge. However, the data from the current study are too limited, and larger sample size would be needed to explore this notion.

In conclusion, we show distinct changes in biological motion during experimental inflammation. These changes might reflect the need for conservation of body energy, and indicate that inflammation might be one of the underlying mechanisms of biological motion

alterations observed in certain medical conditions. Furthermore, the findings also suggest that movement pattern contains clear information about an individual's health status, which likely provides an advantage from a disease-avoidance perspective, and could be useful to identify people in need of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The effect of experimental inflammation on gait and motion in humans was determined
- Experimental inflammation resulted in an overall slower and more rigid walking pattern
- These alterations were predicted by cytokine levels and self-reported sickness symptoms
- Biological motion contains clear information about an individual's inflammatory status

Fig. 1. The Kinect® skeleton.

The dots represent the 20 joints tracked by the Kinect®. The numbers represent some of the calculated outcomes (see Table S1 for description).

Fig. 2. Effect of LPS versus placebo administration on gait outcomes.

Outcomes (average $\pm$ SEM and individual data) in the walking paradigm (a) and in the mobility TUG test (b). $n = 19$. n.s. $p > .05$, ** $p < .01$, *** $p < .001$ LPS versus placebo administration (see Table 1 for detailed statistics). Abbreviations: LPS: lipopolysaccharide; TUG: Time-up-and-go.

Fig. 3. Predictors of LPS-induced motion alteration.

Sickness symptoms (1.5h after LPS injection), IL-6 concentrations (area under the curve from 1h to 2h after the LPS injection), body temperature (2h after LPS injection) and back pain (2h after LPS injection) were included in the best-fitted model explaining 60% ($p = .013$) of the variance in the LPS-induced motion alteration factor. Abbreviations: LPS: lipopolysaccharide; IL-6: interleukin-6.

Table 1.Effect of LPS *versus* placebo administration on gait outcomes

<i>Dependent variables</i>	B	95% CI	P value
Walking paradigm			
<i>Trial outcomes</i>			
Walking speed (m/sec) ^a	−0.185 ^{***}	−0.243; −0.126	<.001
Head angle (°)	−2.499 ^{**}	−4.077; −0.922	.002
Trunk angle (°)	0.628	−0.167; 1.422	.12
<i>Stride outcomes</i>			
Stride length (m)	−0.093 ^{***}	−0.117; −0.070	<.001
Stride time (msec)	27.900 ^{***}	13.102; 42.698	<.001
Stride width (m)	0.005 ^{**}	0.002; 0.008	.002
Shoulder angle (°)	0.201	−0.130; 0.532	.23
Arm extension angle (°)	−1.500 ^{***}	−2.154; −0.845	<.001
Arm flexion angle (°)	0.306	−0.720; 1.332	.56
Knee flexion angle (°)	1.863 ^{***}	1.040; 2.686	<.001
TUG test			
Time to stand (sec)	0.260 ^{***}	0.128; 0.393	<.001
Trunk flexion angle (°)	0.583	−1.789; 2.955	.62
First step length (m)	−0.088 ^{***}	−0.117; −0.058	<.001
TUG time (sec)	2.172 ^{***}	1.230; 3.113	<.001

Results of the mixed linear model. B is the effect of LPS for each outcome, 95% CI is the 95% confidence interval (lowest; highest). All significant p-values remained significant after the Benjamini-Hochberg procedure, with false discovery rate set to 5%.

^a the effect on walking speed was assessed using uniquely data from the first walking trial (i.e., at a self-selected pace, without the metronome).

p<.001

**
p<.01

Abbreviations: LPS: lipopolysaccharide; TUG: time-up-and-go.