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Treading on the unknown increases prefrontal activity: A pilot fNIRS study

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ABSTRACT

Background: Complex walking conditions (e.g. dual tasking) have been associated with increased prefrontal (PFC) activity. However, most paradigms include a predictable environment, specifically, a predictable walking terrain. In the present study we investigate PFC activity under an unusual walking condition where each foot placement was on unexpected terrain, thus causing a mismatch between visuospatial perception and lower-extremity proprioception.
Research objective: To assess whether PFC activity increases under unstable unpredictable conditions compared to unstable but predictable conditions.
Methods: This was a prospective study involving twenty healthy adults. Participants walked in two conditions: unstable but predictable, and unstable and unpredictable. To assess walking stability, both stride-time (ST) and stride-time variability (CV) were measured. To assess PFC activity, two wireless near-infrared spectroscopy devices were used. The group hemodynamic response (GHR) was calculated for each condition. For statistical analysis, a linear-mixed-effects model was used.
Results: Walking with unpredictable perturbations did not change the ST ($t = 0.51$, $p = 0.61$) but significantly increased the parameter CV ($t = 11.74$, $p < 0.001$). The GHR of both conditions indicated brief per-initiation PFC activity that was similar across conditions. However, when GHRs were calculated relative to normal walking (i.e., the participants' own shoes), continuous activity was evident. Compared to the predictable condition, the unpredictable condition significantly increased this activity during steady-state walking ($t = 2.13$, $p = 0.033$).
Significance: Observations from the present study suggest that at least two neural components are present in the measured signal—a brief one, occurring per-initiation, and a continuous one, sensitive to the predictability of the terrain. The second component was accompanied by a decrease in walking stability. These results may contribute to our understanding of the control mechanism underlying gait and future planning of rehabilitation protocols.

1. Background and aim

Walking is a complex human behavior, controlled by spinal and supra-spinal structures [1] including cortical areas [2], one of which is the prefrontal cortex (PFC). This area is thought to be associated with cognition and executive functions, which were found to be related to gait [3] and are needed for safe and stable walking [4]. Nevertheless, the exact nature of PFC activity during walking is still unclear.

It has been proposed that two neural networks underlie gait control [5]: non-modulated and modulated. The latter is thought to be cognitively demanding, involving the PFC, and was found to be active when walking is under challenging conditions [6] or in a complex environment [7], as well as during imagined walking [8]. Moreover, in certain populations, such as the elderly [9] and infratentorial stroke patients [10], the PFC is more active, even under normal, steady-state walking conditions, suggesting that gait is under the control of the modulated network.

Recently, Bar-Haim et al. [11] introduced the *Re-Step*™ (RS), a shoe-like system that is able to alter, constantly, the shape of its sole, thereby creating a mismatch between the visually-predicted and the sensory-perceived terrain. These alterations perturb walking, forcing constant adjustments. Bar-Haim et al. have suggested that such perturbations engage the brain, prompting it to learn to make the proper adjustments. They argue that since the perturbations are unpredictable, the brain is constantly looking for solutions to the stability problem, thus indicating that higher-level cortical areas are involved. If so, it is reasonable to assume that walking with the RS system will be under the control of the modulated network and involve the PFC.

When investigating human walking, gait parameters are used as a behavioral measure. Variability, along with mean values, of these

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parameters is often used as an indicator of the neural control underlying gait. Variability measures seem to be more sensitive to both aging and pathology than mean values [12]. Stride-time variability, often reported as the coefficient-of-variation (CV), is a commonly used measure in the literature. Stride-time CV has normal values and threshold for pathology [13], and has been reported to distinguish between elderly fallers and non-fallers [14]. Recently, Koren et al. [15] have observed an increase in stride-time CV and no change in stride-time (ST) or walking velocity, when healthy adults walked with the RS system in active mode (i.e. perturbed) as opposed to passive mode (i.e. unperturbed). They interpreted these results as evidence that, beyond the mere unstable design of the shoe, these perturbations further challenge the control system, but not so much that the control policy will change.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging technology used to monitor changes in hemoglobin concentration in superficial cortical areas. These changes serve as an indirect measure of brain activity. Typically, in active brain areas, an increase in oxy-hemoglobin (HBO) and a decrease in deoxy-hemoglobin (HHB) concentrations are observed [16], due to evoked changes in cerebral oxygenation and hemodynamics. This technology seems to be promising in the investigation of cortical activity during walking [17] and has been used to study the activity of multiple cortical areas, during walking, in diverse populations and conditions [18,19].

The aim of this study was to investigate PFC activity under sensory-challenging walking conditions, in healthy young adults. We hypothesize that walking with the RS system in its active mode will increase PFC activity and will be associated with increased stride-time variability.

2. Methods

2.1. Population

Twenty healthy young adults participated in this study. This convenience sample was comprised of students recruited from the university by advertisement on social media and through word of mouth. Recruits were men and women, 18–30 years old, without neurologic or orthopedic illnesses, without cardiovascular or hemodynamic disturbances, and willing to participate. The study was approved by the local Human Subject Research Committee at Ben-Gurion University.

2.2. Experimental model and gait assessment

Developed for training and gait-rehabilitation of individuals with brain damage, RS is a shoe-like mechatronic system, combining mechanical, electronic, and computing technologies [11]. Briefly, the system has four pistons underneath each shoe. In the passive mode these are aligned to create a plane parallel to the sole of the shoe. In the active mode, the pistons, during swing phase, may change their length to create a plane oblique to the sole's plane, thus creating a mismatch between visual prediction and perceived terrain during the stance phase. The system is equipped with force sensors, able to record vertical ground reaction forces (GRFs), from which temporal gait parameters can be computed [15].

For this study, continuous (i.e., at every step) perturbation with maximal possible magnitude was used. Perturbations were controlled by a chaotic algorithm. GRFs were recorded continuously from all sensors at 100 Hz and later used to compute stride-durations. We specifically targeted this gait parameter since its CV will be the least affected by the relatively low sampling frequency of the system [15].

2.3. Prefrontal cortex activity

To assess PFC activity, change in hemoglobin concentration was monitored using a wireless, continuous-wave fNIRS device (*PortaLight*, Artinis, The Netherlands). This instrument emits near-infrared light into the brain and measure the intensity of the reflected light. Using the Modified Beer-Lambert Law, the measured intensities may be used to calculate and quantify relative change in HHB and HBO concentrations over time, reflecting the local hemodynamic response. The device has three channels (source-detector distances of 30, 35 and 40 mm) utilizing two wavelengths (760 and 850 nm), organized in a single dimension array, with one detector and three emitters. In this study, two devices were used with a total of 6 channels (1–3 for the left and 4–6 for the right hemispheres). They were positioned at 15% of the distance from nasion to inion (from nasion) and at 7% of the head circumference to the left and right from the midline. This position was previously described [20] and demonstrated by MRI to roughly represent Brodmann's area 10 [21]. The probes were attached using two-sided adhesive tape and covered with a black cloth to prevent ambient-light contamination. Sample frequency was set to 10 Hz and was continuous throughout the experiment. Raw intensities were recorded, simultaneously from both devices, using the software provided by the manufacturer (Oxysoft, version 3.0.53).

In the literature, [HBO] change is the most frequently used indicator to infer brain activity, but its reliability has been subject to debate [12,18]. Therefore, we have complied with the suggestion [22] that changes in both hemoglobin species be used and reported.

2.4. Heart rate

The cerebral hemodynamics are sensitive to physiological interference, such as heart pulsation. In order to control for its potential bias, we used *TomTom Runner Cardio* (TomTom International BV, Netherlands) to monitor heart rate during the experiment. This is a wrist-watch-like heart-rate monitor, providing continuous, second-by-second heart-rate measurement. Validity of the device has been previously reported [23].

2.5. Protocol

All experiments took place in a quiet, well-lit hallway, approximately 30 m long and closed from both sides. Initially, all subjects signed a consent form and demographic data were collected (i.e. gender, age, height, weight, and leg dominance). To familiarize participants with the RS, they walked the entire course six times with the system in passive mode.

PFC activity was assessed in two walking conditions: RS unperturbed (RSU) and RS perturbed (RSP). Participants walked along a 20-m-long course 12 times with 30-s rest periods, spent standing, between them. These 12 walks were either unperturbed or perturbed in random order (participants were blind to the condition). For reference walking activity, participants walked in their own shoes ('shoe condition') 6 times, following the same protocol.

2.6. Data processing

PortaLite- Raw data were exported to MATLAB to assess signal quality. First, motion artifacts were detected and corrected (see details below). Following artifact removal, quality of the signal recorded was assessed using several techniques: 1) a spectrum analysis of the time series was performed and was visually inspected to detect heart pulsation around 1–1.5 Hz as an indication to a physiological measurement; 2) a signal-to-noise ratio (SNR) was calculated [24] for each channel separately; and 3) correlation analysis between channels was performed, and intra-optode correlations were evaluated [24].

Since there are no cut-off values for the above mentioned methods, results were subjectively evaluated and suspected poor-quality channels were excluded from analysis. This procedure preceded any other analysis and in any case, the fNIRS measurements were continuous; therefore excluded channels contained all three experimental conditions, reducing the probability of bias.

For processing we used the *Homer2* (version 2.1), a MATLAB-based toolbox [25]. The procedure was as follows: Raw intensity was converted to optical density (OD) using the *hmrIntensity2OD* function. Then, the *hmrMotionArtifactByChannel* function was used to identify motion artifacts (SDThresh = 10, tMotion = 0.5, tMask = 1). These were corrected with the *hmrMotionCorrectSpline* function (p = 0.99) [26]. Following this procedure, each data series was visually inspected. When needed, additional corrections were made using the *hmrMotionCorrectWavelet* function (iqr = 0.1) [27]. These methods of artifact correction produced good results for large amplitudes and amplitudes similar to the physiological content of the NIRS signal [28,29]. Next, a band-pass filter was applied using the *hmrBandpassFilt* function (0.01–0.2 Hz). Finally, using the *hmrOD2Conc* function, OD was converted to relative concentrations after correcting for the differential path-length factor, according to Scholkmann & Wolf [30].

A mean value of the 5 s surrounding the median time point of each walk (−2.5 to +2.5) was selected to represent steady-state walking. The mean value of last 5 s of the rest period was designated as the baseline, which is an acceptable duration in the literature [18]. Steady-state values of oxy and deoxy hemoglobin were extracted from the time series, subtracted from the baseline value, and exported to SPSS for statistical analysis.

To calculate the Group Hemodynamic Response (GHR), the data generated from each walk and condition were normalized (to overcome differences in task duration); each time series was divided into 100 bins, with the mean value of each bin representing one percent of the task. This procedure resulted in a series of 100 values for each walk × channel. These values were then used to calculate the GHR for all the channels together.

Re-Step- Raw-force data were downloaded using custom software provided by the manufacturer (*Step Of Mind* version 1.22) and exported to MATLAB for processing to produce a series of stride-durations. (The processing procedure is elsewhere described [15]) Strides accruing in the middle 10 m of each individual walk were used to calculate mean and CV, using the equation (SD/Mean)*100. These values were then exported to SPSS for statistical analysis.

2.7. Statistical analysis

For statistical analysis we used a linear mixed-effects model (LMM) with *"subjects"* as a random effect. Post-hoc tests, when needed, used least-significant-difference correction for multiple comparisons. The effects of relevant demographics were assessed within the model.

Gait parameters (stride-time mean and CV) were analyzed in the same way. In all cases, significance level was set to $\alpha = 0.05$.

3. Results

A total of 20 subjects participated in the experiment (for descriptive statistics, see Table 1). Two were completely excluded from hemoglobin change analysis, and the left PFC channels of a third subject were excluded due to poor signal quality. Only one participant had a left dominant leg (self-reported); therefore, this variable was excluded from analysis.

Table 1
Descriptive Statistics.

	Mean ± SD/range/%
Gender	11 females and 9 males (55% and 45% respectively)
Age	Mean 25.65 ± 1.3 (range 24–29)
Height	Mean 170.8 ± 7.3 cm
Weight	Mean: 67.5 ± 8.3 kg
Shoe size	Median: 40; range: 36–46
Dominance	19 right-leg, 1 left-leg (95% and 5% respectively)

● Dominance was self-reported defined as the kicking leg.

3.1. Gait parameters

Two statistical models were used to assess gait (one for each parameter). The final models included only *"condition"* as a two-level within-subject factor. The model for stride-time revealed no difference between conditions (t = 0.51, p = 0.61). The model for CV revealed an increase of 0.36 percent from the unperturbed (1.77 ± SE 0.081%) to the perturbed (2.13 ± SE 0.081 percent) condition (Fig. 1). This difference was statistically significant (t = 11.74, $p < 0.001$).

3.2. PFC activity

3.2.1. Main results

Two statistical models were used to estimate PFC activity, one for each hemoglobin species. Within the model for HBO, values were corrected for *"heart-rate"* and *"height"*. Estimated values were then used to assess *"condition"* and *"hemisphere"* as within-subject factors. The model for HHB did not reveal a main effect for *"condition"* ($p > 0.05$), and therefore this species was not further explored.

Within the model for HBO a main effect was found for "*condition*" (F = 7.84, $P < 0.001$). Post-hoc tests demonstrated that in the perturbed condition, Δ[HBO] was significantly greater than in the shoe (t = 3.96, $p < 0.001$) and unperturbed (t = 2.13, p = 0.033) conditions. The unperturbed condition was not significantly different from the shoe condition, although a trend was noted (t = 1.87, p = 0.062). A main effect was also found for *hemisphere* (t = 4.49, $p < 0.001$), with the right hemisphere demonstrating greater Δ[HBO] than the left.

3.2.2. Temporal description

The GHRs of all conditions are depicted in Fig. 2. The response observed was similar to the reported hemodynamic response to a brief stimulation, occurring around walking-initiation.

Calculating the GHR of both RS conditions as relative to reference walking activity (i.e. shoe condition) demonstrated a continuous response throughout the walk (Fig. 3).

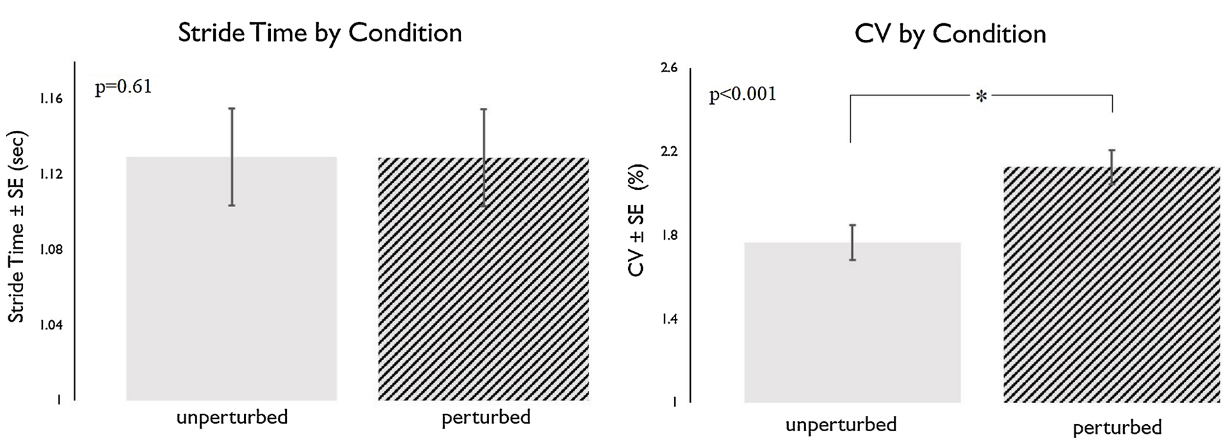

Fig. 1. Comparison of gait parameters revealed no difference in stride time (left graph) between unperturbed and perturbed walks. Stride time variability (right graph), on the other hand, was significantly increased during perturbed walks compared to unperturbed.

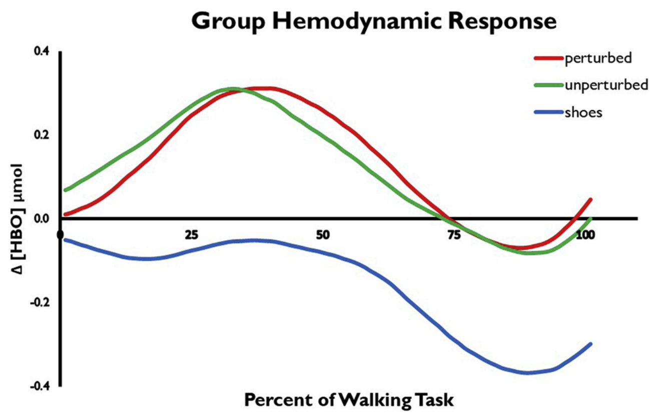

Fig. 2. In the shoe condition, [HBO] started decreasing before initiation. In the RSU, it increased before initiation, and in the RSP [HBO] fluctuated around the baseline (as was made evident by the first value). After initiation, [HBO] in all conditions increased, reaching its peak at 38, 33, and 41 percent of task duration, respectively, after which point [HBO] decreased in all conditions, reaching minimum value at, roughly, 90% of task duration. Both RS conditions returned to baseline after roughly 75% of task duration, while [HBO] in the shoe condition never exceeded baseline.
*In this graph, baseline represents the average of the last five seconds of the rest period (standing).
*The time-line here was normalized to overcome different task durations.

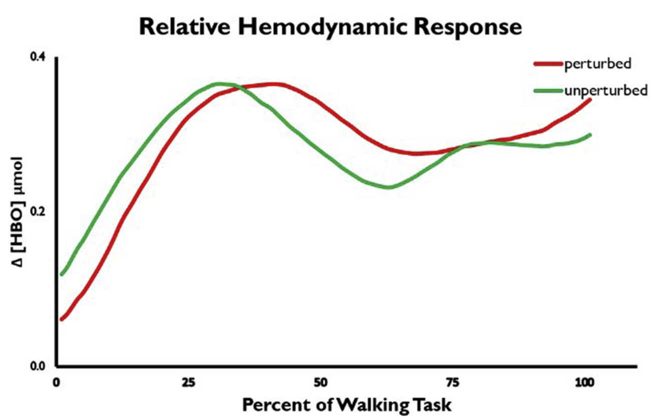

Fig. 3. Relative to reference walking activity (i.e. shoe condition), [HBO] in both RS conditions immediately increased. [HBO] in the RSU reached peak value after 31% of task duration and after 40% in the RSP condition. Values, in both conditions, then decreased slightly, but remained elevated in comparison to reference, throughout the task, suggesting that PFC activity was continuous throughout the walk.
*The time-line here was normalized to overcome different task durations.

4. Discussion

The objective of this study was to evaluate the involvement of the PFC in motor-control of walking under complex, predictable and unpredictable, walking conditions. Our results demonstrated an increase in the variability of stride-time in the perturbed condition compared with the unperturbed, representing the behavioral cost of the unpredictable perturbations. The observed increase was accompanied by an increase in the Δ[HBO] in the PFC. These results were similar between hemispheres, although Δ[HBO] in the right hemisphere was significantly increased compared to Δ[HBO] in the left.

4.1. Gait parameters

The RS is unstable by design. This instability is predictable in the passive mode but unpredictable in the active mode. To investigate the behavioral cost of this uncertainty, we used two parameters— ST and CV. The former may be indicative of a change in control policy, such as cautious gait, while the latter may reflect either stability or redundancy within the system [31]: CV may be interpreted as the ability of the control system to maintain a parameter constant, thus indicating stability; however, it may also be interpreted as the redundancy of degrees of freedom used in the control of walking, thus indicating flexibility. Our results for ST suggest no change in the control policy. But, we interpret our CV results as an indication that walking stability was challenged when prediction of the terrain was impossible.

4.2. Temporal characteristics and main effects of PFC activity

The observed hemodynamic responses, for both RS conditions, are consistent with the expected response in active brain areas [12,28]. However, they indicate a brief, per-initiation activity and not, as had been expected, continuous activity. This observation is consistent with other reports [10,32,33] in the literature. Such brief, per-initiation activity, may explain the observed difference between the RS conditions and the shoe condition; however, only continuous activity can explain the difference found between the RSU and RSP, since participants were blind to the condition. Consequently, it stands to reason that activity was in fact continuous in these conditions. For baseline activity we used quiet standing, an approach considered acceptable according to the literature [18]. This baseline does not represent PFC activity associated exclusively with standing, as additional simultaneous mind-drifting activity may be in play [18] and would need to be controlled for [34]. Assuming that mind drifting is unlikely to have occurred during the short, goal-directed walks, we cannot interpret the return of [HBO] to baseline as tantamount to the PFC activity needed to conduct, exclusively, the two tasks (standing and walking).

Therefore, to overcome the above-mentioned limitation, we used the shoe condition as a reference response in order to eliminate (at least partially) the confounding effect of mind-drifting. Calculating the RS responses relative to the shoes response (Fig. 3) demonstrated continuous activity throughout the walk, as expected. However, this was true for both RS conditions, suggesting that instability, whether predictable or not, engages the PFC.

While the initial responses in both RS conditions were very similar, statistical analysis revealed a significant difference in Δ[HBO] between them during mid-walk, indicating modulation of the initial response, possibly through a second, continuous component. Thus, our results indicate at least two components: one component is brief, is required per-initiation, and is sensitive to the footwear (as indicated by the GHRs), while the other is continuous and sensitive to the perturbations (as indicated by both the GHR and the main effect of the *condition*).

The continuous component can be explained by executive activity, such as "attention" and/or "response monitoring" [3], but may also include other components, related to motor-learning, as suggested by Bar-Haim et al. [11]. The former includes visual attention, which is assumed to be lateralized to the right hemisphere [35] including the frontal cortex [36], an assumption that, if true, might explain the difference observed between hemispheres in the current study. Further validating our observations is the fact that laterality to the right hemisphere also has been reported in young adults faced with cognitive challenges to specific executive functions [37].

The above discussion is based on our results for [HBO], however the statistical model for [HHB] did not reveal a main effect for *condition*. This observation can have several, possible, explanations: 1) [HBO] is more sensitive to cerebral hemodynamics [38] and is more appropriate to use when inferring brain activity (e.g. [39]); 2) the anatomical location used is not localized to the PFC area involved, and as a result the more generalized [HBO] response and localized [HHB] response differed [40]; This is also expected if 3) the method used to position the NIRS probes was not precise enough, creating some variability of brain area measured; and 4) the PFC area measured is not active under these condition. Although this last possibility is unlikely due to our [HBO] results, we do acknowledge that the difference observed between hemoglobin species is one of the limitations of the current study.

5. Conclusions

The results of this study indicate that walking with unstable shoes engages the PFC, increasing its activity; it is therefore likely that walking is under the control of the modulated network. Inability to predict the pattern of instability, which increases the walking challenge as indicated by the elevated CV, increases PFC activity even further, suggesting the PFC plays a role in maintaining walking stability. Although others have linked the PFC with gait, very few have investigated its role in gait stability. We hope these results may contribute to our understanding of the control mechanism underlying gait and future planning of rehabilitation protocols.

Contribution of authors

Yogev Koren: study design, data acquisition and analysis, and paper drafting.

Simona Bar-Haim: study design, data acquisition and analysis, and paper drafting.

Yisrael Parmet: study design, statistical analysis, and paper revision.

All authors approved the final version of the paper.

Declarations of interest

Dr. Simona Bar-Haim holds equity positions in Step of Mind, the company that developed the technology used in this study.

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