Příloha I: Dotazník hodnotící zamrznutí (freezing) při chůzi FoG-Q

1) V <u>nejhorším</u> stavu chodíte:

0 Normálně.

1 Téměř normálně – trochu pomaleji.

2 Pomalu, ale zcela samostatně.

3 Potřebuji asistenci nebo pomůcku.

4 Nedokážu chodit.

2) Ovlivňují obtíže při chůzi vaše denní aktivity a nezávislost?

0 Vůbec.

1 Mírně.

2 Středně.

3 Těžce.

4 Nedokážu chodit.

3) Máte při chůzi, v otočkách nebo při rozejití pocit, jako kdyby vaše chodidla byla přilepená k podlaze (tzv. zamrznutí neboli freezing)?

0 Nikdy.

1 Velmi zřídka – zhruba jednou za měsíc.

2 Zřídka – zhruba jednou za týden.

3 Často – zhruba jednou za den.

4 Stále – pokaždé, když jdu.

4) Jak dlouho trvala vaše nejdelší freezingová epizoda?

0 Nikdy jsem ji neměl/a.

1 1-2 s.

2 3-10 s.

3 11-30 s.

4 Nemohl/a jsem chodit více než 30 s.

5) Jak dlouho trvá vaše typické váhání (tzv. hesitace) při zahájení chůze (zamrznutí při tom, když začínáte první krok)?

0 Vůbec

1 Trvá to déle než 1 s, než se rozejdu.

2 Trvá to déle než 3 s, než se rozejdu.

3 Trvá to déle než 10 s, než se rozejdu.

4 Trvá to déle než 30 s, než se rozejdu.

6) Jak dlouho trvá vaše typické váhání (tzv. hesitace) při otáčení (zamrznutí v otočce)?

0 Vůbec

1 Pokračuji v otočce za 1-2 s.

2 Pokračuji v otočce za 3-10 s.

3 Pokračuji v otočce za 11-30 s.

4 Nedokážu pokračovat v otočce déle než 30 s.

Příloha II – seznam publikací autorky

1.1. Originální články související s prací

1) **Poláková K**, Růžička E, Jech R, Kemlink D, Rusz J, Miletínová E, Brožová H. 3D visual cueing shortens the double support phase of the gait cycle in patients with advanced Parkinson's disease treated with DBS of the STN. Plos one, 2020, 15.12: e0244676. (IF 2,870)

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1.2. Ostatní originální články

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(kumulativní impact factor 32,325)

Příloha III – Publikace in extenso

PLOS ONE

RESEARCH ARTICLE

3D visual cueing shortens the double support phase of the gait cycle in patients with advanced Parkinson's disease treated with DBS of the STN

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Abstract

Background

Gait disturbances have emerged as some of the main therapeutic concerns in late-stage Parkinson's disease (PD) treated with dopaminergic therapy and deep brain stimulation (DBS). External cues may help to overcome freezing of gait (FOG) and improve some of the gait parameters.

Aim

To evaluate the effect of 3D visual cues and STN-DBS on gait in PD group.

Methods

We enrolled 35 PD patients treated with DBS of nucleus subthalamicus (STN-DBS). Twenty-five patients (5 females; mean age 58.9 ±6.3) and 25 sex- and age-matched controls completed the gait examination. The gait in 10 patients deteriorated in OFF state. The severity of PD was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (HY). The PD group filled the Falls Efficacy Scale-International (FES) and Freezing of Gait Questionnaire (FOGQ). Gait was examined using the GaitRite Analysis System, placed in the middle of the 10m marked path. The PD group was tested without dopaminergic medication with and without visual cueing together with the DBS switched ON and OFF. The setting of DBS was double-blind and performed in random order.

Results

The UPDRS was 21.9 ±9.5 in DBS ON state and 41.3 ±13.7 in DBS OFF state. HY was 2.5 ±0.6, FES 12.4 ±4.1 and FOGQ 9.4 ±5.7. In the DBS OFF state, PD group walked more slowly with shorter steps, had greater step length variability and longer duration of the double support phase compared to healthy controls. The walking speed and step length

Competing interests: The authors have declared that no competing interests exist.

increased in the DBS ON state. The double support phase was reduced with 3D visual cueing and DBS; the combination of both cueing and DBS was even more effective.

Conclusion

Cueing with 3D visual stimuli shortens the double support phase in PD patients treated with DBS-STN. The DBS is more effective in prolonging step length and increasing gait speed. We conclude that 3D visual cueing can improve walking in patients with DBS.

1. Introduction

People with Parkinson's disease (PD) in advanced stages suffer frequently from gait disturbances, which could be partly influenced by dopaminergic medication. Gait impairment in PD is characterized by hypokinesia with lower speed, shortened step length, narrow step width, reduced counter-rotation of the trunk and decreased arm swing [1]. Some people with PD may also develop freezing of gait (FOG), that is short, unpredictable periods where they are unable to voluntarily initiate or maintain gait [2]. FOG mainly occurs when the patient is not on dopaminergic medication, and can be provoked by specific triggers including a specific motor action (e.g., turning), other factors that could be cognitive (e.g., dual-tasking), affective (e.g., threatening situations) and environmental (e.g., narrow doorways) [2, 3].

Pathophysiology of gait impairment in PD is complex and involves several cerebral structures across the locomotor network. A deficiency of the internal cueing mechanism due to basal ganglia disorder is suggested to lead to inappropriate scale and timing of the automatic movement sequences [1]. With the loss of dopaminergic neurons, some gait parameters (speed, stride length) [4] respond to dopaminergic medication, whereas temporal parameters (cadence, step and swing duration, double support time) improve to a lesser extent [5] or not at all [6].

Treatment with invasive methods, such as deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) in PD, is effective in alleviating disabling motor complications [7, 8]. The treatment may improve posture, quiet standing postural control and the parameters of gait that were responsive to levodopa prior to surgery [9, 10]. STN-DBS can also reduce FOG in the OFF-medication state [7, 11–13]. The effects of DBS on postural stability and gait, however, tend to decrease with time [14–16] and the long-term effect of STN-DBS on FOG in the ON medication state is disputable [17]. A postoperative deterioration of gait was documented in a considerable number of PD patients after implantation of STN-DBS [8, 11, 14, 18, 19] with higher risk of falls, worsening of dynamic postural control [8, 11, 14, 18–20] and even new development of FOG [7, 11, 21].

To overcome FOG, some PD patients use various strategies, involving particular internal or external cues, which help to initiate or maintain gait. These include, for example, stepping over obstacles, modification of gait pattern or use of alternative methods of locomotion, i.e. cycling or skating [22–24]. The external cues are usually less attentionally demanding. The precise mechanisms underlying the effectiveness of cueing is unclear, however there are some reasonable explanations, e.g. involvement of goal-directed behavior with circumnavigation of parts of the basal ganglia, mechanisms assisting in filtering information [25] or optic flow compensating sensory deficit [26, 27].

The immediate effect of external cues on walking speed, step length, and step frequency of the gait of PD patients has been documented [28–30]. A variety of wearable devices were lately presented, with smaller [31] or greater effect on FOG [32, 33]. Case reports suggested that 3D

visual cues might be more effective in reducing FOG than 2D cues [22, 23]; however detailed studies are not available.

We aimed to evaluate the effect of 3D visual cues and STN-DBS on gait in patients with advanced PD. We hypothesized that the 3D visual cueing would mainly reduce the frequency and severity of FOG, while STN-DBS would more likely influence the dopa-sensitive gait parameters (i.e. speed, step length). The mechanisms of both methods are different, and the benefit could be thus complementary. Both methods are well-established, nevertheless a more detailed analysis of the exact effect of visual cueing on gait parameters in the native state (DBS OFF) compared to the changes caused by DBS has not yet been documented.

2. Materials and methods

2.1. Participants

We investigated 35 non-demented PD patients (6 females; mean age 60.6 ±6.3, disease duration 17.8 ±4.5 years), treated with dopaminergic medication together with STN-DBS. The exclusion criteria were dementia and any other neurological or non-neurological condition that may affect gait. The severity of PD was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr (HY) stage. Subjects filled in a shortened version of the Falls Efficacy Scale-International (FES-I, score range 7–28) and the Freezing of Gait Questionnaire (FOGQ). The final PD group included 25 subjects (5 females; mean age 58.9 ±6.3) who completed the whole study protocol. Ten recruited PD patients did not complete the gait examination, as they were unable to walk independently when the DBS was switched OFF. The details of the PD group can be found in Table 1 and S1 Table.

Twenty-five age- and sex-matched healthy controls (5 females; mean aged 59.1±6.2 years) were involved for evaluation of the gait.

The study was approved by the Ethics Committee of the General University Hospital in Prague (86/16 VES 2017 AZV-VFN) and was in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Table 1. Characteristics of the PD group.

	Complete evaluation (n = 25)		Unable to complete (n = 10)	
	Mean ±SD	(min-max)	Mean ±SD	(min-max)
Age (years)	58.9 ±6.3	(50–73)	65.0 ±4.1	(58–72)
Disease duration (years)	18.0 ±4.9	(10–31)	17.5 ±3.8	(12–24)
DBS duration (years)	4.8 ±3.7	(0.7–15)	14 ±3,9	(10–23)
L-Dopa Eq (mg)	995.2 ±402.2	(399–1896)	1500 ±829,8	(399–3171)
TEED (mA2.Ω.Hz.ms)	100.3 ±63.7	(13.3–222.1)	112 ±48,8	(40.0–196.0)
UPDRS I (range 0–16)	1.3 ±1.5	(0–5)	1.3 ±1.0	(0–3)
UPDRS II (range 0–52)	10.0 ±5.6	(1–21)	17.8 ±4.9	(12–31)
UPDRS III ON (range 0–56)	21.9 ±9.5	(7–43)	32.2 ±12.3	(18–56)
UPDRS III OFF (range 0–56)	41.3 ±13.7	(12–66)	62.7 ±7.8	(54–79)
Hoehn and Yahr (range 1–5)	2.5 ±0.6	(1.5–4)	3.2 ±0.6	(2.5–4)
FOGQ (range 0–24)	9.4 ±5.7	(1–24)	15.0 ±2.3	(12–20)
FES (range7-28)	12.4 ±4.1	(7–22)	17.1 ±6.5	(8–28)

DBS, deep brain stimulation; L-Dopa Eq, levodopa equivalent; TEED, total electrical energy delivered; UPDRS, The Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; FOGQ, Freezing of Gait Questionnaire; FES, Falls-Efficacy Scale. Complete evaluation, 25 PD patients who finished the investigation. Unable to complete, 10 PD patients who were not able to complete the investigation due to deterioration of gait in DBS OFF state.

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2.2. Assessment and experimental protocol

Gait was tested using the GaitRite Analysis System, a 4.9 m long pressure-sensitive walking mat was placed in the middle of the 10 m marked path. PD group and healthy controls were instructed to wear comfortable shoes and walk over the mat at self-preferred comfortable speed.

For visual cueing of gait, 16 squared wooden rods sized 2x2x100 cm were placed at distances of 60 cm [34] across the walking pathway, perpendicular to the walking direction. The scheme of the investigated path is presented on the S1 Fig.

The examination of gait in the PD group was performed in the medication-OFF state following a withdrawal of dopamine agonist for 72 hours, and the last dose of levodopa was taken 12 hours before the testing. The examination in the PD group was held in four conditions: (i) with STN-DBS switched off (DBS OFF) without cueing, (ii) DBS OFF with visual cueing of gait, (iii) STN-DBS switched on (DBS ON) without cueing, (iv) DBS ON with cueing. The cued gait trial in each condition always followed after gait without cueing. The setting of DBS was double-blind and performed in random order. Gait examinations were carried out at least 90 minutes after each change of DBS setting, when the patients were asked to relax. Gait tests in each condition were repeated twice. DBS ON was set individually to optimal parameters at standard pulse frequency (130Hz), with the voltage in the range of 1.0 to 4.1V or current 1.2 to 3.0mA, pulse width 60, 90 or 120μs.

In healthy controls, gait was tested in two conditions only, without and with visual cues.

2.3. Data analyses

Computerized analysis of gait recordings was performed using the GaitRite software. We gathered spatial (step length and variability; base width) and temporal characteristics (step time and variability, double support time, gait speed and cadence) of gait.

2.4. Statistical analysis

Descriptive statistics for the collected data was performed to determine the distribution of demographic, clinical and gait variables. Since ten of the recruited patients were unable to complete the gait examination in the DBS OFF state, we did not include their data in the final analysis. Gait parameters were calculated as an arithmetic mean value of results in two trials in each condition. Given the number of individuals tested and the normal distribution of residuals in the models used, the application of the parametric tests is justified. To exclude the effect of the different height we used repeated measures analysis of covariance (ANCOVA) tests factored for disease status corrected for leg length to compare difference in the gait parameters in the PD and control group, for evaluation of individual differences, p-value of Tukey HSD test was reported. Paired T-tests were performed for some parameters in the PD group. Bonferroni correction for multiple comparisons was performed for 8 independent tests. STATISTICA data analysis software system, version 12.0. (statsoft.com) was used for statistical analysis of data.

3. Results

At baseline, the majority of the PD group (23 of 25) mentioned the fear of falling, according to the FES. Twenty PD patients admitted FOG occurrence at least once per month according to FOGQ. Even so, only 3 of them developed FOG on the investigated path during a comfortable walk in the DBS OFF state; the effect of 3D visual cueing and DBS was thus insignificant.

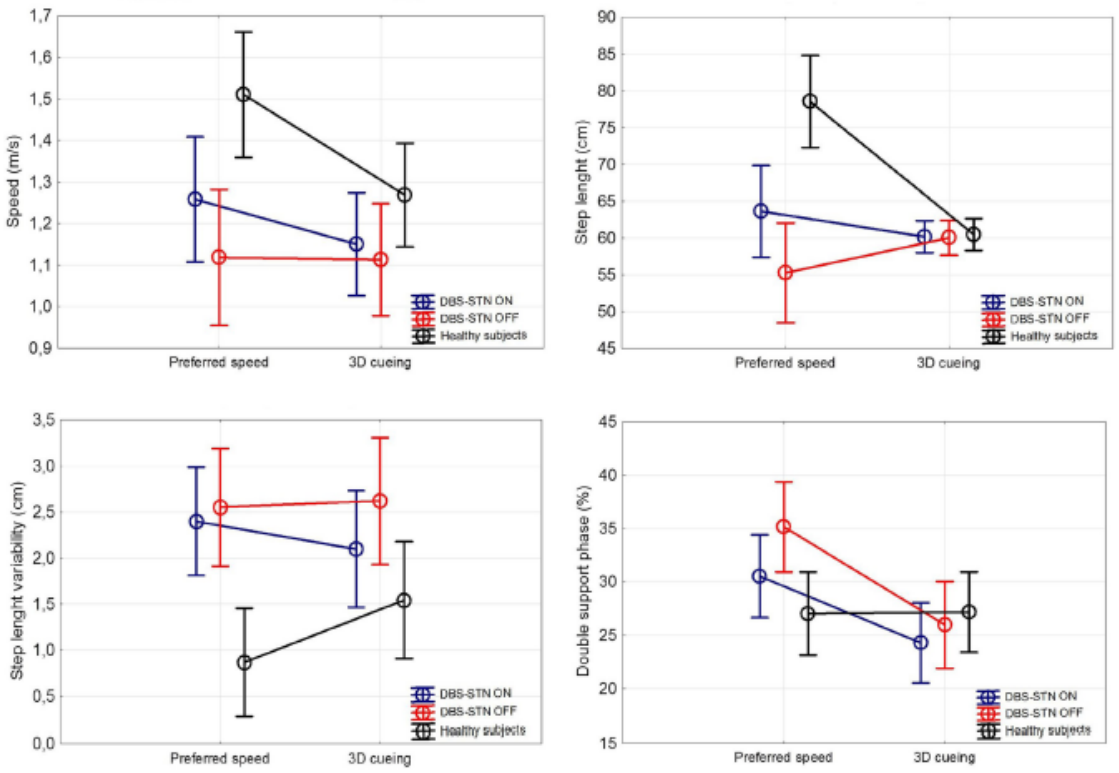

Fig 1. The comparison of effects of 3D visual cueing and DBS on gait. ANCOVA factored for disease status corrected for leg length. DBS OFF, PD group with deep brain stimulation turned off; DBS ON, PD group with deep brain stimulation turned on; Preferred speed, gait without cueing; 3D cueing, gait with presence of 3D visual cues.

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In the PD group, the gait in the DBS OFF condition was significantly slower ($p = 0.00044$, $F(1,47) = 14.276$, $\eta^2 = 0.23$) with shorter steps ($p = 0.000002$, $F(1,47) = 28.86$, $\eta^2 = 0.380$), greater step length variability ($p = 0.002$, $F(1,47) = 10.61$, $\eta^2 = 0.184$), and longer duration of the double support phase ($p = 0.025$, $F(1,47) = 5.36$, $\eta^2 = 0.102$) compared to healthy controls. No difference was found in cadence, step time or base of support.

The speed of gait ($p = 0.000168$, $F(1,23) = 3.49$, $\eta^2 = 0.132$) and step length ($p = 0.000164$, $F(1,23) = 3.90$, $\eta^2 = 0.145$) significantly increased in the DBS ON versus DBS OFF condition, however both parameters remained mostly unchanged with 3D visual cueing.

The double support phase ($F(1,23) = 1.02$, $\eta^2 = 0.042$) was significantly reduced during gait with 3D visual cueing ($p = 0.000164$, Tukey HSD test) as well as in DBS ON state ($p = 0.000165$, Tukey HSD test) compared to DBS OFF in the PD group; however the difference in double support phase reduction was greater with visual cueing than in DBS ON ($p = 0.0095$, $t(24) = 2.8$). Step length variability was not significantly affected in the PD group by either 3D cueing or DBS. For gait parameters see Fig 1 and S1 Table.

Ten patients, out of those recruited, were unable to complete the gait examination in the OFF state due to inability to walk independently. Those patients were significantly older, with longer duration of PD and higher severity of the disease. They also had a higher score in FES as well as FOGQ; for detailed characteristics see Table 1.

4. Discussion

Gait disturbances have emerged as some of the main therapeutic concerns in late-stage PD even when treated with DBS, because they impair mobility, lead to falls and have a strong impact on quality of life [10]. Subjective gait or balance difficulties including a fear of falling were also reported by the majority of the PD group in the present study. The gait analysis revealed slower gait with shortened step length, longer duration of double support phase and higher step length variability in the PD group compared to healthy controls in accordance with earlier studies [35–37]. Contrary to our hypothesis, we did not prove a significant influence of either DBS or visual cueing on the FOG, as the number of captured episodes was too low. The majority of the PD group admitted FOG in the daily life at baseline, but only a very few developed FOG on the investigated path. We did not involve specific triggers, i.e. turns or narrow passage. Moreover, a higher attention during the investigation in laboratory condition may also played a role. Even the inability of the 10 most affected PD patients to complete the examination provides further explanation.

The main effect of the 3D cueing in the PD group was the significant reduction of prolonged double support. Double support phase represents the period of gait cycle when both feet are in contact with the ground and provide more control over the center of the mass movement. During this phase, the patients may correct present disturbances [38]. Its longer duration is thus attributed to impairment of dynamic balance [39] and postural control [40]. With decreased walking speed, the double support phase may also increase, both in time and as a percentage of the gait cycle [38]. However, the speed of the PD group remained unchanged during the 3D visual cueing in the present study in contrast to DBS. Therefore, we assume that the 3D visual cueing mainly improved the stability of gait associated with the shortening of the double support phase. The effect of DBS on the double support phase was also present; however, the visual cueing proved to have greater effect on this parameter.

The external cues also showed improvement in speed, step length, and cadence in other studies [28–30]. The step length was, however, not affected by the external 3D visual cues in this study. We used fixed distance of the cues, which was only slightly longer than the average step length of the PD group in DBS OFF state. The DBS stimulation prolonged the step length significantly and increased walking speed, as expected as both parameters (step length and speed) are highly dopa-responsive [4–6]. The effect on different gait parameters is consistent with different mechanisms of both methods. STN-DBS activates neurons in the basal ganglia-thalamic-cortical system [41] and thus modulates cortical areas that participate in the preparation and execution of movements. Besides, STN-DBS modifies pallido-nigrofugal projections to brainstem areas, which participate in locomotor pattern generation [42]. Visual cues on the other hand work as external drivers that facilitate a compensatory shift to goal-directed control of movement during gait. Focused attention to the stepping process enables the shift from the typical automatic control of gait into a more conscious movement [1]. The striatal dopamine depletion occurring in PD is supposed to impair internal drivers that regulate the automaticity of gait. More conscious motor control strategy during cued gait may help to bypass the impaired basal ganglia. This theory is supported by increased cortical activity observed during targeted movement [43, 44]. Other theory suggests that augmented visual feedback of selfmotion compensates for weakened proprioceptive signal from the lower limbs in PD due to the

sensory deficit [26]. Optic flow information received by the participant was revealed to be an important aspect contributing to the improvement of gait with visual cues as they use the visual information from visual cues in both on-line and feedforward fashions [27].

Last documented altered parameter in our PD group was greater step length variability, which was not affected either by 3D cueing or DBS. Increased gait variability is described throughout the disease course and its magnitude tends to increase with disease severity [45]. It is suggested to be an important predictor of the risk of falling [45, 46] and is considered as an expression of reduced automatic control of walking. Unlike other spatiotemporal features, variability is relatively independent of stride length. Lately, there is a growing evidence, that the traditional linear measurement can mask the true structure of motor variability since the biomechanical data from a few numbers of strides are averaged during the analysis. Recent research of gait dynamics based on nonlinear methods revealed that fluctuations in certain gait parameters are not random but display a deterministic behavior, which may degrade in some condition resulting in local instability [45, 47]. Those methods are, however, based on a larger number of gait cycles.

One of the main limitations of the study was, that we were unable to investigate the 10 most affected patients due to the deteriorated motor status when their therapy (medication, DBS) was discontinued. The worsened motor symptoms in the OFF state in the rest of the PD group allowed us to perform only 2 trials in each condition with limited number of gait cycle.

Although we have not been able to directly verify the effects on freezing, we conclude that 3D visual cueing can aid walking in PD patients treated with DBS. Combination of the two methods is beneficial as DBS improves mainly the dopa-sensitive parameters (gait speed, step length) and visual cueing additionally improves the stability associated with normalization of the double support phase. Nevertheless, further research in a larger group is recommend. Essential is also to focus on optimal distance of visual cueing, including dynamic adjustment and performance of the nonlinear measurements of gait for deeper understanding of variability. A long-term effect of visual cues on the gait if used during rehabilitation is expected, however deeper evaluation is needed.

5. Conclusion

Cueing with 3D visual stimuli shortened the double support phase of the gait cycle in PD patients treated with STN-DBS. The DBS was more effective in prolonging step length and increasing gait speed. Combination of the two methods is beneficial, however further research of optimal distance of visual spatial cueing, including dynamic adjustment, and use during rehabilitation is recommended.

Supporting information

S1 Fig. A scheme of the investigated path without (upper) and with 3 D visual cues (lower). The marked investigated path was 10 m long with GaitRite Analysis System, a 4.9 m long pressure-sensitive walking mat, placed in the middle of the path. Sixteen squared wooden rods sized 2x2x100 cm were placed at distances of 60 cm across the walking pathway, perpendicular to the walking direction of the participants. PC; a computer connected to the GaitRite system, recording data from each gait trial.
(TIF)

S2 Fig.
(TIF)

S1 Table. Characteristics of all recruited patients (n = 35). DBS, deep brain stimulation; L-Dopa Eq, levodopa equivalent; TEED, total electrical energy delivered; UPDRS, The Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; FOGQ, Freezing of Gait Questionnaire; FES, Falls-Efficacy Scale. All recruited patients (n = 35).
(TIF)

S2 Table. Temporal and special gait parameters of the PD patients and healthy controls. Values are mean ± SD (n = 25). Repeated measure ANCOVA factored for disease status corrected for leg length. Presented p values are post-hoc Tukey HSD test versus DBS OFF condition. #Controls versus patients were tested separately by one-factor ANCOVA with correction for leg length. * significance remained after Bonferroni correction for multiple testing DBS OFF, patients with deep brain stimulation turned off.
(TIF)

Author Contributions

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Supervision: Evžen Růžička, Robert Jech, Hana Brožová.

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RESEARCH ARTICLE

Pavement Patterns Can Be Designed to Improve Gait in Parkinson's Disease Patients

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ABSTRACT: **Background:** Public spaces are usually designed with respect to various patient populations, but not Parkinson's disease. The objective of this study was to explore what type of easily applicable visual cueing might be used in public spaces and some interiors to improve gait in people with Parkinson's disease.

Methods: Thirty-two patients with freezing of gait walked an 8-meter track on 6 different floor patterns in single- and dual-task conditions in random sequence. The reference pattern was a virtual large transverse chessboard, and the other patterns differed either in size (small floor stones), orientation (diagonal), nature (real paving), regularity (irregular), or no pattern. Time, number of steps, velocity, step length, cadence, and dual-task effect were calculated. The number and total duration of freezing episodes were analyzed.

Results: Virtual, large, transverse floor stones improve time ($P = 0.0101$), velocity ($P = 0.0029$), number of steps ($P = 0.0291$), and step length ($P = 0.0254$) in Parkinson's disease patients compared with walking on no pattern. Virtual floor stones were superior in time and velocity to the real ones. Transverse floor stones were better than diagonal, whereas regular pattern stones were superior to irregular in some gait parameters. Subjectively, the reference pattern was preferred to the irregular one and to no pattern. No direct effect on freezing of gait was observed.

Conclusions: Parkinson's disease patients may benefit from floor patterns incorporating transverse oriented large rectangular visual cues. Because public space can be regulated with respect to people with medical conditions, the relevant legislative documents should be extended to allow for parkinsonian gait disorder. © 2019 International Parkinson and Movement Disorder Society

Key Words: cueing; freezing; gait; Parkinson's disease; public space

Freezing of gait (FoG) is defined as a sudden inability to create effective stepping movements[1] despite the intention to walk,[2] and patients describe this experience as if their feet were glued to the ground.[3] FoG in Parkinson's disease (PD) is prevalent,[4] interferes with gait, leads to falls, and reduces quality of life.[5]

Rational FoG therapy is based on proper evaluation of the type of FoG present, that is, on deciding whether it is levodopa responsive, -resistant, or -induced.[6] In each case, either adjustments of pharmacological treatment or deep brain stimulation is recommended.[7-11] However, all types of FoG respond to various rehabilitation modalities. These can be used either as a rescue strategy when FoG occurs or to reduce the number of FoG episodes by optimizing spatiotemporal control of gait.[6,12] One of the most widely used techniques with good evidence is cueing,[12] defined as the use of a temporal or spatial stimulus to regulate movement.[13] The

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efficacy of cueing for FoG is based on shifting from habitual to goal-directed gait control.[12]

In previous studies, various parameters of cueing have been explored. Transverse lines seem to be more effective than parallel.[14] Similarly, regular (ie, predictable) are better than irregular and unpredictable,[15-17] and 3-dimensional visual cues are in some cases superior to 2-dimensional.[18,19] When one compares the effect of real and virtual cues, the former seem to produce greater effect in terms of stride length, cadence, and FoG frequency, but both are generally comparable.[20] However, most studies show that proper cueing parameters are highly individual.[21]

One of the easiest ways to apply cueing at home is to tape strips on the floor or to pave floor stones. When combined with general simplification of the interior (eg, getting rid of superfluous furniture and loose rugs), making narrow spaces wider if possible, and installing proper lightning, these strategies might greatly improve walking safety.[22] However, continual use of cueing has the disadvantage of inducing fatigue and may lead to cueing-dependence.[12] In the exterior, patients have to use portable audio players or devices able to generate augmented reality for visual ones, for example, Google Glass[23] or Cinoptics.[19] A more simple use of visual cues might be laser projectors installed on canes, walkers,[24] or shoes.[25] However, because of daylighting, not all laser projectors are able to function properly outdoors.

In most European countries, public spaces are designed and built with respect to wheelchair users and people with vision impairment.[26] Because PD patients both with and without FoG might also benefit from some environmental adjustments (eg, regular floor patterns that may easily be used in public spaces), more attention should be paid to this population. Therefore, we wanted to explore what type of visual cueing might be used in public spaces, especially in pavements and some interiors, for example, health-care facilities or PD specialized nursing homes. To our knowledge, this is the first study to explore various modalities of cueing with respect to usually employed floor patterns.

Methods

Patients

Thirty-two PD patients with FoG (median age, 67.5 years; median disease duration, 13 years; median MDS-UPDRS III, 24; median levodopa-equivalent daily dose,[27] 1155 mg) were recruited from the Movement Disorders Centre, Charles University, Prague. We recruited patients in the last quarter of 2017 and included all who were willing to participate on the grounds of the following criteria: a clinical diagnosis of PD according to UK Brain Bank diagnostic criteria,[28] age > 18 years, Hoehn and Yahr stage <5,[29] absence of severe cognitive impairment, and presence of FoG. For patients to be considered freezers, they either had to score ≥ 1 in question 3 of the Freezing of Gait Questionnaire (FoG-Q),[30] or FoG had to be present in the Rapid Turns test.[31] Patients were excluded if they suffered from other serious neurologic or orthopedic condition that could affect their gait, severe sensory deficits such as blindness, or peripheral neuropathy.

The study was approved by the Ethics Committee of General University Hospital in Prague (1247/17 S-IV). Written informed consent was obtained from all patients.

Experimental Protocol

All patients were assessed in the ON state by a movement disorders specialist (K.P.) who collected demographic and clinical information. After history taking and performing MDS-UPDRS,[32] the patients filled out a questionnaire consisting of the Parkinson's Disease Activities of Daily Living Scale (PADLS),[33] Gait and Falls Questionnaire, which comprises FoG-Q,[30] and questions related to the number of falls in past 12 months and to the patients' experiences of the effect of various architectonical elements on their gait (types of floor patterns, hallways, doors, narrow spaces, staircases, escalators, and elevators). Afterward, the Montreal Cognitive Assessment[34] was performed. In the subsequent subtraction task (backwards counting by 3s),[35] number of correct and incorrect answers in 10 seconds was recorded.

The patients were then asked to walk an 8-meter-long track, turn in the nonpreferred direction as established in the Rapid Turns test, and get back. They walked on 6 different floor patterns in single- and dual-task conditions (backwards counting by 3s) and could use walk aids if necessary. Both the floor patterns and single- and dual-task conditions were ordered randomly for each patient. We used the following 6 floor patterns. Four of these patterns were virtual, which enabled them to be easily switched (Fig. 1):

1. No pattern (gray carpet).
2. Real 50 × 50 cm transverse regular black-and-white (chessboard) floor stones.
3. Virtual 50 × 50 cm transverse regular black-and-white (chessboard) floor stones (reference pattern).
4. Virtual 5 × 5 cm transverse regular black-and-white (chessboard) floor stones.
5. Virtual 50 × 50 cm diagonal regular black-and-white floor stones.
6. Irregular virtual pattern, consisting of geometrical figures and signs.

We recorded the time, total number of steps, and number of steps in turning. We calculated gait speed, step length (without turning), and dual-task effect (DTE).[36] All gait trials were recorded using 3 cameras (fixed bird's eye, moving leg zoom, and moving frontolateral whole-body

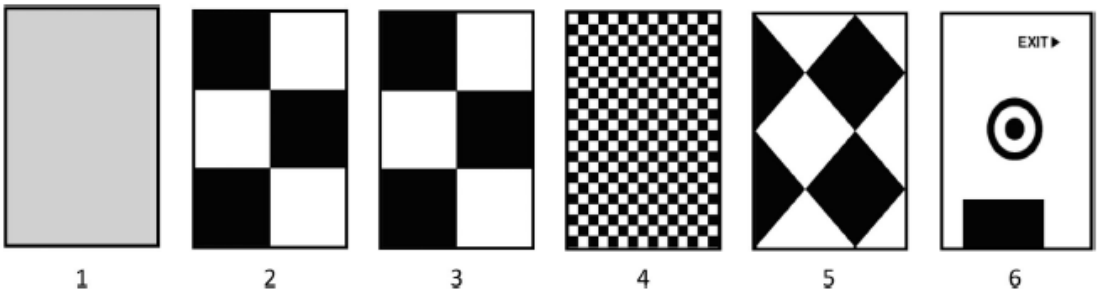

FIG. 1. Utilized patterns: 1: No pattern. 2: Real 50 × 50 cm chessboard. 3: Virtual 50 × 50 cm chessboard. 4: Virtual 5 × 5 cm chessboard. 5: Virtual 50 × 50 cm diagonal chessboard. 6: Irregular virtual pattern.

view; Suppl. 1), and answers in dual-task conditions were recorded using a portable microphone device. A blinded movement disorders specialist (H.B.) then reviewed all gaits and confirmed the presence of FoG during gait, counted the number of FoG episodes, and timed the total duration of all FoG episodes. We counted the number of correct and incorrect answers in dual task from the audio recordings. After walking the tracks, patients were asked to evaluate on a visual analog scale, how the patterns influenced their walking (Suppl. 2).

Finally, patients were assessed using the Short Falls Efficacy Scale-International,[37] Beck Depression Inventory,[38] STAI X-1, and STAI X-2,[39] by a movement disorders specialist (K.P.).

Gait speed and step length were selected as primary outcome measures and FoG, DTE, number of correct answers per second in dual-task conditions, number of steps when turning, and subjective evaluation as secondary. Our hypotheses were that visual cueing would improve primary and secondary outcomes compared with no cueing (pattern 1 vs 3). Second, we expected only regular pattern to be effective (pattern 3 vs 6). Third, we anticipated large floor stones to be efficient as opposed to small ones (pattern 3 vs 4). Fourth, we hypothesized that transverse floor stones would be superior to diagonal (pattern 3 vs 5). Finally, we assumed that the effect of virtual floor stones would be similar to the real ones (pattern 2 vs 3).

TABLE 1. Clinical and demographic characteristics of PD patients

	Patients with PD ($n = 32$, 10 ♀, 22 ♂)	
	Mean (SD)	Range
Age (years)	65.4 (7.2)	46–75
Disease duration (years)	13.5 (5.6)	2–25
Hoehn and Yahr stage	2.5 (0.6)	2–4
MDS-UPDRS Total	64.3 (32.3)	29–158
MDS-UPDRS III	27.9 (18.7)	4–91
GFQ	17 (10)	3–42
FoG-Q	11.6 (6)	1–23
Short FES-I	12.8 (4.4)	7–28
MoCa	25.6 (3.8)	14–31
BDI	9.4 (6.2)	2–30
STAI X-1	42.5 (5.6)	26–51
STAI X-2	41.1 (5.3)	30–56

PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; GFQ, Gait and Falls Questionnaire; FoG-Q, Freezing of Gait Questionnaire; Short FES-I, shortened version of the Falls Efficacy Scale-International; MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory.

Virtual Reality Equipment

A system projecting virtual patterns on the floor was fixed on a 5-m-high ceiling. As the projected pattern was too long to be created by only 1 projector, the projected image was assembled using 3 Digital Light Processing (DLP) projectors. The projection was controlled by an application we developed in the software environment called VVVV (vvvv.org). This application allowed for the control of light conditions at 150 lx (recommended light level for halls and corridors), as well as of all projected content, and for the blending of the projected images. The projection system configuration is shown in Suppl. 3.

Statistical Analysis

Because of the nature of observed variables (counts, scales, and velocities), the nonparametric Mann-Whitney-Wilcoxon test was adopted to study the effects of floor patterns. P values were adjusted for multiple comparisons by a Holm method per each gait parameter. Effect size was evaluated using Cohen's d. Analysis was performed using R statistical package version 3.4.4.[40] $P < 0.05$ was considered statistically significant.

Results

Demographic subject data are shown in Table 1. The distribution of answers in PADLS was near normal, that is, 83% of the patients chose answer "b" (mild

difficulties, 43.8%), "c" (moderate difficulties, 28.1%), or "d" (high level of difficulties, 12.5%).

In the single task, we found significant differences in time (P = 0.0101; d = 0.052), gait speed (P = 0.0029; d = 0.116), number of steps (P = 0.0291; d = 0.052), and step length (P = 0.0254; d = 0.143) between reference and no pattern. Patients had a significantly increased step length (P = 0.0395; d = 0.165) when walking on the reference pattern, compared with the irregular virtual pattern. We found no differences between walking on small and large floor patterns. However, differences in time (P = 0.0092; d = 0.173), gait speed (P = 0.0070; d = 0.082), number of steps (P = 0.0008; d = 0.118), and step length (P = 0.0033; d = 0.158) were significant for the reference pattern using transverse floor stones compared with diagonal ones. Finally, there were significant differences in time (P = 0.0160; d = 0.043) and gait speed (P = 0.0024; d = 0.122) in favor of the reference pattern with virtual floor stones, compared with real ones. Subjectively, significant differences of the patients' evaluation of floor patterns were found only in favor of the reference pattern compared with the irregular (P = 0.0066; d = 0.756) or no pattern (P = 0.0136; d = 0.939). These results are summarized in Table 2, and key results are shown in Figure 2. With respect to the number of FoG episodes and total FoG episodes duration, we found no differences between the 6 floor patterns. Indeed, 68%–91% of the patients did not experience FoG when walking on the 8-m-long track depending on the pattern and single- or dual-task conditions. This was the case even though they reported FoG in FoG-Q (see Table 1), and in 64% of the patients, FoG was also present in the Rapid Turns test.

Both the mean and median gait speed and step length decreased in the dual task regardless of the pattern. In the case involving the number of steps when turning, the median DTE was 0.0 for all patterns, but the mean varied from -31.3% to -0.2%. Similarly, the median number of correct answers per second decreased significantly in the dual task (pattern 1, P = 0.0126; pattern 2, P = 0.0126; pattern 3, P = 0.0126; pattern 4, P = 0.0044; pattern 5, P = 0.0126; pattern 6, P = 0.0126). Details are provided in Suppl. 4.

Discussion

The results of this study show that large, virtual, transverse floor stones improve some gait parameters such as time, gait speed, number of steps, and step length in PD patients compared with walking on no pattern. Moreover, the improvement in step length compared with no pattern, irregular pattern, or diagonal floor stones greatly exceeded the minimal clinically important difference (MCID) established for older adults.[40] In the case of gait speed, MCID is also available for PD patients.[41] Our results did not reach the threshold for small MCID established by distribution-based analyses, effect size metrics, and sample variability within gait speed. However, applying established cut points in the UPDRS motor scale, the improvement in gait speed when walking on large, virtual, transverse floor stones was slightly above the associated small MCIDs compared with no pattern and diagonal and real floor stones. Moreover, the MCID values established by Hass et al are derived from a slightly less affected PD population compared with ours, and they only walked straight ahead, whereas our patients also had to turn. Therefore, MCID for gait speed comprising a turn has not been to our knowledge established yet.

TABLE 2. Significance of gait parameter differences depending on task (single × dual) and on floor pattern in a single task

	ST vs DT	Rea. vs *reference*	Sma. vs *reference*	Diagona. vs *reference*	Irregular vs *reference*	No pattern vs *reference*
Time	P < 0.0000	P = 0.0160; R shorter; d = 0.043	NS; d = 0.039	P = 0.0092; R shorter; d = 0.173	NS; d = 0.008	P = 0.0101; R shorter; d = 0.052
Gait speed	P < 0.0000	P = 0.0024; R faster; d = 0.122	NS; d = 0.053	P = 0.0070; R faster; d = 0.082	NS; d = -0.105	P = 0.0029; R faster; d = 0.116
Total number of steps	P < 0.0000	NS; d = 0.051	NS; d = 0.055	P = 0.0008; R lower; d = 0.118	NS; d = 0.038	P = 0.0291; R lower; d = -0.052
Number of steps without turn	P < 0.0000	NS; d = 0.048	NS; d = 0.052	P = 0.0444; R lower; d = 0.152	NS; d = 0.020	P = 0.0239; R lower; d = -0.023
Step length	P < 0.0000	NS; d = -0.059	NS; d = -0.090	P = 0.0033; R larger; d = 0.158	P = 0.0395; R larger; d = -0.165	P = 0.0254; R larger; d = 0.143
Step length without turn	P < 0.0000	NS; d = -0.079	NS; d = -0.125	NS; d = 0.092	NS; d = -0.149	P = 0.0220; R larger; d = 0.145
Subjective evaluation	—	NS; d = 0.210	NS; d = -0.495	NS; d = 0.087	P = 0.0066; R preferred; d = -0.756	P = 0.0136; R preferred; d = 0.939

ST: single-task; DT: dual-task; Rea. = real 50 × 50 cm transversal regular black and white floor stones; Sma.: virtual 5 × 5 cm transversal regular black and white floor stones; Diagona.: virtual 50 × 50 cm diagonal regular black and white floor stones; Irregular: irregular virtual pattern consisting of geometrical figures and signs; No pattern: no pattern (grey carpet); Reference: virtual 50 × 50 cm transversal regular black and white floor stones; R: reference pattern; NS: not significant, d: Cohen's d.

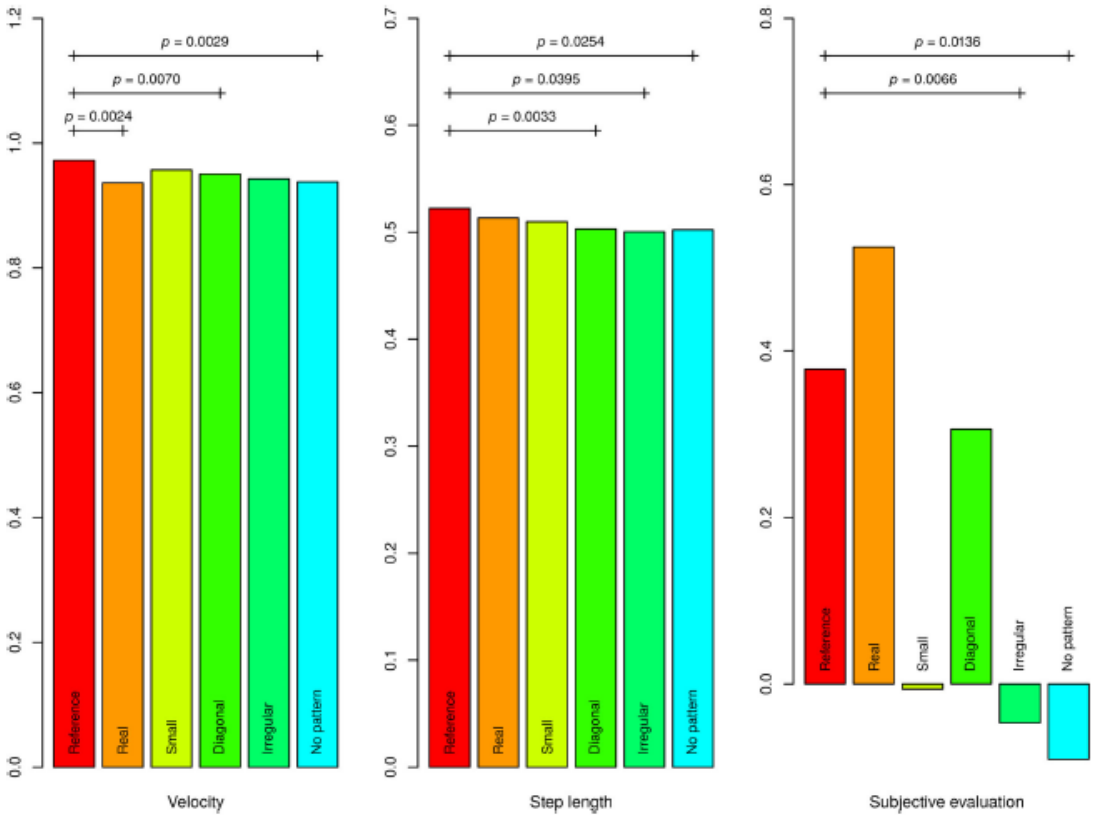

FIG. 2. Differences in velocity, step length and subjective evaluation between the six utilized floor patterns in single task. [Color figure can be viewed at wileyonlinelibrary.com]

We did not observe any direct effect on FoG when walking on any of the 6 patterns. This was probably because most patients did not experience FoG in the laboratory settings, even though they reported FoG in FoG-Q, and in approximately two-thirds, FoG was present in the Rapid Turns test. Such discrepancy has already been noted.[6,31,42] Nevertheless, the positive effect of large, virtual, transverse floor stones on step length was significant and is probably related to FoG. Several studies have shown that factors such as diminished step length and step-to-step reduction in amplitude may lead to FOG,[43] and stabilizing these gait parameters by visual cues might prevent its occurrence.[12,13] Therefore, it seems reasonable to suppose that visual cues help to increase and maintain step length and thus alleviate FoG.

Surprisingly, there were no significant differences in any spatiotemporal parameters between large and small floor stones. This might suggest that regularity and transverse orientation common to both patterns are more important than size. However, this should be further investigated because it contradicts to some extent the findings of Chee et al.[27] In their study, however, decreased step length was imposed on the patients, which was not the case in our experiment. The only effect of small floor stones that could be observed was the increase of mean DTE with respect to the number of steps when turning discussed below.

A further interesting result is that virtual floor stones were superior in time and gait speed to the real ones of the same size and orientation. This is probably because walking in a virtual reality environment was so unusual for the patients that it drew more attention to the cues given than the real ones. The importance of paying attention to the cues has already been described.[13,44] In time, however, patients will probably adapt to virtual cues so that their effect will diminish and will probably become equally as effective as real cues. Nevertheless, our results are in contrast with the findings of previous research in which real cues resulted in similar or even greater improvement of various gait parameters.[20,45] However, it is not specified in these studies, whether

environmental light conditions were adapted when using virtual cues. If not, real cues could have been seen more sharply. Moreover, patients in these studies used either laser lines[45] or virtual reality glasses.[20] In the former case, laser lines might not have been extraordinary enough to attract more attention than real cues. In the latter case, the use of virtual reality glasses might have been even more unusual than the virtual environment in our study. However, virtual reality glasses have been reported to distract patients and narrow their field of view, thus blocking sensory visual feedback needed for gait.[19] Such a negative impact might have been the cause of the superiority of real cues in this study.

Large, real, transverse floor stones might be easily used on pavements and floors, be it in private houses of PD patients or in public spaces such as hospitals, nursing houses, public offices, and so forth. In most European cities, however, pavements are made of concrete without any pattern. In historical city parts, cobblestones are used and ordered into various shapes, often diagonal. In public interiors, various patterns are being used, usually based on aesthetic reasons. The findings of this study suggest that the current architectonical practice might be optimized to meet the needs of PD patients similarly to how it takes into consideration other disabilities (eg, wheelchair users or people with vision impairment).

Two objections may be raised against this suggestion. First, because the height of each individual varies, so does the step length, and consequently also the requirements with respect to the floor stone size, that is,. cueing frequency. However, assuming people's height is normally distributed, that is, 68% is to be found within 1 standard deviation of the mean and 99.7% within 3, choosing cueing frequency on the grounds of mean height might be more efficient.[46] Furthermore, because cobblestones are often used and their size is completely inappropriate and concrete pavements lack any pattern, any change might be considered an improvement.

Second, one might object that the effect of cueing fades in time[12] so that the effectiveness of floor stones might be questioned. However, this is true for all cueing, which is nevertheless still used. Theoretically, the habituation of cues might be diminished by changing various pattern characteristics, for example, its color. Therefore, if pavements were not built uniformly, the effect of floor stone cueing might be prolonged. However, the effect of nonuniform pavements would have to be studied because irregularity might cause FoG.

Large, virtual, transverse floor stones are rather suitable for the interior because of the negative impact of daylight on projected images. In the interior, however, the advantage of virtual floor stones lies in the modifiability of their characteristics: their frequency might be tailored to the user and their color and other characteristics changed to prevent habituation. Therefore, a device capable of projecting such modifiable patterns should be developed for commercial use.

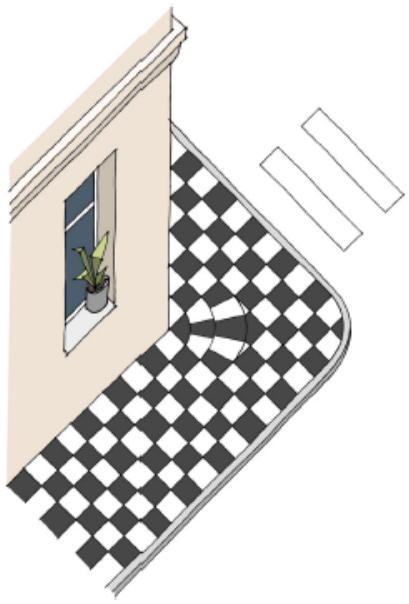

FIG. 3. Possible way how to utilize floor stones in corners to help with turning. [Color figure can be viewed at wileyonlinelibrary.com]

The beneficial effect of visual cues used in this study was only observed under single-task conditions and was lost while dual-tasking. This might be explained by impaired ability to prioritize, which is common in PD and especially in freezers.[47,48] To evaluate the effect of cueing as it could be expected in real-life situations, patients were not instructed what to focus on either in single-task or in dual-task situations. Although single-task patients spontaneously used cues, dual-task patients probably lost their focus on the provided cues and paid attention to counting. This suggests that in clinical practice, dual-task gait training should be introduced in patients with FoG with the goal of improving dual-task gait performance and possibly increasing the patients' attentional capacity to be able to use cueing.[49] Moreover, it is reasonable to instruct the patients to try to avoid unnecessary dual-tasking during walking (eg, using a mobile phone or carrying objects instead of putting them into a backpack).

Furthermore, our results differ from those of other studies[36,50-53] and even from the conclusion of a systematic review,[54] which claims that visual cueing does improve gait performance in dual-tasking. However, Galletly et al[50] investigated the effect of cueing in a population with mild deficits (mean UPDRS III score, 14.4 ± 6.1; mean MMSE score, 28 ± 3), which could

also suggest better ability to dual-task. In the 3 other studies,[36,51,53] patients were asked to synchronize their steps to a flash of light generated by a light-emitting diode attached to glasses. Such a use of visual cues differs from the one employed in this study, so that the results cannot be easily compared. Moreover, they used a motor dual task, which is less demanding in terms of attention than a cognitive one.[50] Finally, in Rochester (2010),[52] the effect of a 3-week cued gait training and not the immediate effect of cues was investigated.

Therefore in dual-task conditions, auditory cueing[36,51,53,55] or self-instruction strategies[56] might be more effective than visual cueing. However, Lohnes et al[56] did not confirm the effect of auditory cues in dual-tasking probably because they used a more challenging cognitive secondary task. Therefore, the issue remains controversial.

Even though the median DTE with respect to number of steps when turning was 0.0 for all floor patterns, its mean might indicate some effect of virtual diagonal floor stones and virtual small ones. In the former case, the mean DTE was the lowest, whereas in the latter case the highest (Suppl. 4). DTE with respect to number of steps when turning was positive in 45% of the patients and in 29% equaled 0.0. This might suggest that some patients used the diagonal floor stones as cues when turning. Consequently, such floor stones might be incorporated into corners, as suggested in Figure 3. In contrast, mean DTE with respect to number of steps when turning increased by more than 50% in nearly 47% of the patients (or even by more than 100% in 5 patients and by 200% in 1 patient). This might indicate that small floor stones are the least appropriate probably because they put too much load on attention.

The limitations of this study include a relatively small number of patients and testing in laboratory settings. Therefore, future studies should verify the present findings in real-world situations and in a larger sample size. Moreover, because most of the patterns used in this study were virtual, their positive effect should be tested in real ones.

Conclusions

The present findings suggest that PD patients benefit from using large transversal visual cues, which might be incorporated in floor patterns in both the exterior and the interior. Because public indoor and outdoor space can be and is regulated with respect to people with some medical conditions, the relevant legislative documents should be extended to allow for parkinsonian gait disorder.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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ORIGINAL ARTICLE

Validation of the Freezing of Gait Questionnaire in patients with Parkinson's disease treated with deep brain stimulation

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Abstract
Background The Freezing of Gait Questionnaire (FoG-Q) is a fast and sensitive assessment tool for freezing (FoG).
Objective The objective of the study is for validation of a Czech version of FoG-Q. A further, explorative aim was to examine what FoG-Q indicates about the presence and severity of gait impairment in patients treated with DBS in their full OFF state.
Design The study was a cross-sectional validation study.
Methods We translated FoG-Q following standardized validation protocol. We assessed 35 patients with PD and STN DBS using history taking, UPDRS, Hoehn and Yahr staging, Mini Mental State Examination, Frontal Assessment Battery, FoG-Q, Short Falls Efficacy Scale International, and Beck Depression Inventory, Second Edition. UPDRS III, clinical and instrumental gait assessment, was repeated OFF MED/DBS OFF and OFF MED/DBS ON.
Results Internal consistency of FoG-Q was excellent ($\alpha = 0.91$) as well as convergent (significant correlations with UPDRS II item 14, UPDRS III item 29, several TUG parameters, and FoG Score) and divergent validity (no association with UPDRS I). OFF MED/DBS OFF, the total FoG-Q score correlated with UPDRS III items 29, 30, and PIGD subscore, step time variability, and negatively with step length and velocity.
Limitations Limitation of the study is a relatively small sample size.
Conclusions In conclusion, the Czech translation of FoG-Q is valid. With respect to gait and balance, FoG-Q does, to a certain extent, reflect the native state of the disease in patients treated with high frequency STN DBS.

Keywords Freezing · Gait · Parkinson's disease · Validation · Questionnaire

Introduction

Freezing of gait (FoG) is a paroxysmal gait disorder characterized by the inability to create effective stepping movements despite the intention to walk [1]. When FoG occurs, patients have physical impression that their feet are glued to the ground [2]. FoG accompanies a variety of diseases, including synucleinopathies like Parkinson's disease (PD) or multiple system atrophy, but also other conditions like progressive supranuclear palsy, normal pressure hydrocephalus, or vascular parkinsonism [3]. In PD, as the most common of these, FoG has been reported in up to 26% of the patients, even before the start of levodopa treatment [4], with its prevalence increasing up to 80% in advanced stages [3]. FoG is perceived by patients as a particularly disabling symptom that significantly affects their fall rates, levels of activity, and quality of life [5].

FoG is a precarious symptom for objective assessment, since even patients who subjectively report FoG often do not freeze when seen by their neurologist [6]. Therefore, subjective assessment methods such as the Freezing of Gait Questionnaire (FoG-Q) [7], the New Freezing of Gait Questionnaire (NFoG-Q) [8], or the self-administered version of the FoG-Q (FoG-Qsa) [9] still play a crucial role in establishing the occurrence of FoG. However, the current gold standard to definitely classify a patient as a "freezer" is the

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direct observation of FoG by an experienced examiner [10]. A more detailed objective analysis of FoG should be performed by 3 independent expert observers using a structured video assessment of complex gait tasks, including turns and walking in narrow space [11].

Since FoG-Q is well-validated [12], used worldwide [13–17], and recommended by the MDS Rating Scales Committee [18], it is a fast and sensitive tool for assessing FoG in clinical practice especially in combination with repeated full narrow turns. FoG-Q, originally developed by Giladi et al. [7], consists of six questions related to FoG and walking. The two questions that address gait difficulties in general (without specific regard to FoG) are in fact the most commonly reported weakness of this questionnaire, because they account for the possibility of false positivity in non-freezers [18].

FoG-Q has been shown to report about FoG as experienced by patients [12]. The most common is the OFF-related FOG [7, 11, 12]. However, not all patients with PD experience their full OFF state, i.e. those treated with deep brain stimulation (DBS) because their DBS is always ON. Therefore, one may wonder whether a low FoG-Q score necessarily indicates the absence of freezing in full OFF or not, and thus whether it distinguishes between freezers and non-freezers. Even though FoG-Q is commonly used in this population of patients, it has not, to our knowledge, been studied whether or what it indicates about the native state of the disease in advanced patients treated with DBS.

Therefore, the aim of the present study was to validate a Czech version of FoG-Q. A further, explorative aim was to examine what FoG-Q indicates about the presence and severity of gait impairment in case of patients treated with DBS in their full OFF state, i.e. medication (MED) OFF and DBS OFF.

Methods

Cross-cultural adaptation of the FoG-Q

We received authorization from N. Giladi to validate the scale and followed the standardized protocol by Beaton et al. [19]. The questionnaire was independently translated by two health professionals (OG and MH) native in Czech with good English language skills. Both versions were compared, and a consensus was reached with the help of other health professionals (HB and ER). The pre-final version was tested in 15 patients with PD for correct understanding by asking the patients how they understood each question. The pre-final version was translated back into English by a native English speaker with good Czech language skills who was not familiar with the original scale. The back-translation was then consulted with and authorized by N. Giladi. The final version (Appendix 1) was tested.

Patients

Thirty-five Czech-speaking patients with PD and implanted STN DBS were recruited from the Movement Disorders Centre of the university Department of Neurology. Inclusion criteria were a clinical diagnosis of PD according to UK Brain Bank diagnostic criteria [20], a Hoehn and Yahr stage of < 5 in the OFF state [21], variable severity of motor complications and/or gait disturbances as assessed by a movement disorders expert, and absence of severe cognitive impairment, i.e. a score above 24/30 on the Mini Mental State Examination (MMSE) [22]. Patients were excluded if they suffered from other serious neurologic or orthopaedic condition that could affect their gait, or severe sensory deficits such as blindness or peripheral neuropathy.

The study was approved by the Ethics Committee of General University Hospital in Prague (125/09). Written informed consent was obtained from all patients.

Clinical and instrumental assessment

The patients were first interviewed by a movement disorders specialist, and their demographic and clinical information was recorded using UPDRS I, II, and IV [23]; Hoehn and Yahr staging [21]; MMSE [22]; Frontal Assessment Battery (FAB) [24]; FoG-Q [7]; Short FES-I [25]; and Beck Depression Inventory, Second Edition (BDI-II) [26]. Afterwards, patients were examined OFF MED (withdrawal of dopamine agonist for 72 h, last dose of levodopa taken 12 h before the testing) with DBS ON and DBS OFF (90 min after turning STN-DBS OFF) by the same physician using UPDRS III [23] and clinical and instrumental gait assessment. These included Timed Up and Go test (TUG) [27], FoG Score [28], and walking 6 m on GAITRite carpet at normal speed. This examination was then repeated OFF MED with DBS ON. In the OFF MED and DBS OFF state, 11 patients were unable to complete the TUG test. The occurrence of FOG was directly observed by an experienced examiner.

Statistical analysis

Descriptive statistic methods were used to analyse the clinical and demographic characteristics of the participants.

Next, we verified whether the mean scores of individual items and their standard deviations were similar, and whether the item–total correlations were above 0.4. Floor and ceiling effects were set at 15% [29]. Internal consistency was analysed using Cronbach's alpha (α), and item analyses were conducted by examining α after excluding each the six FoG-Q items [30]. Values above 0.90 were considered to have a high internal consistency [31].

After visual inspection of the Q-Q plot, both convergent and divergent construct validity was tested using Pearson's

correlation coefficient (PCC). We calculated correlations between FoG-Q and UPDRS scores to assess the extent to which this replicated the pattern reported in the original FoG-Q study [7]. The strongest correlations were expected with UPDRS II (especially item 14 which specifically addresses FoG) and UPDRS III item 29 (gait), with several parameters of the TUG test (time, number of steps, and the occurrence of FoG), and with the FoG Score. Except for UPDRS II, values in two states were used: OFF MED + DBS ON and OFF MED + DBS OFF. The weakest correlation was expected for UPDRS I (mentation, behaviour, and mood).

Further correlations were expected with UPDRS II items 13 and 15 and in both states (OFF MED + DBS ON/OFF) with the total score of UPDRS III, UPDRS PIGD subscore [32], HY staging, Short FES-I, and with several spatiotemporal parameters of gait, i.e. with step length, double support time, velocity, and stride-to-stride variability [4, 33–36].

All analyses were performed using Statistical Package for the Social Sciences (SPSS, version 22.0, IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$. Because of the exploratory nature of the study, we did not correct for multiple testing.

Results

The 35 evaluated patients with PD had a median age of 61 years, disease duration median of 21 years, and a median HY stage of 2.7. Total FoG-Q scores ranged between 1 and 24 points with a mean of 11 (SD ± 5.547). Further clinical characteristics of the patients are presented in Table 1.

Item-total correlations of FoG-Q ranged between 0.75 and 0.90 (Appendix 2). Internal consistency as measured by Cronbach's α was 0.91 (excellent internal reliability). Based on our item analysis, all items contributed significantly to the total FoG-Q score. Reliabilities of FoG-Q after the exclusion of individual items are to be found in Appendix 3.

In the OFF MED state, statistical analysis further revealed significant correlations between FoG-Q and UPDRS II item 14 and with UPDRS III item 29, several TUG parameters (time, number of steps, and presence of FoG), and FoG Score. Details are provided in Table 2. These results show good convergent validity. By contrast, we found no association between FoG-Q and UPDRS I (mentation, behaviour, and mood), which can be interpreted as an indicator of good divergent validity.

Total FoG-Q score also correlated with age, HY staging, Short FES-I, UPDRS II item 13, UPDRS II item 15, UPDRS II, and UPDRS IV Dyskinesias (items 32–35), but not with UPDRS IV Motor fluctuations (items 36–39). OFF MED with DBS ON, the total FoG-Q score correlated positively with UPDRS III item 29, UPDRS III item 30, UPDRS PIGD subscore, the total UPDRS score, duration of the double support phase, and step length variability, and negatively with step length and speed. OFF MED with DBS OFF, the total FoG-Q score correlated with UPDRS III item 29, UPDRS III item 30, UPDRS PIGD subscore, and step time variability, but not with the total UPDRS score.

Furthermore, we observed negative correlations with step length, and velocity. Details are provided in Tables 3 and 4.

Table 1 Clinical and demographic characteristics of patients with PD. *PD*, Parkinson's disease; *TEED*, total electrical energy delivered; *J*, joule; *UPDRS*, Unified Parkinson's Disease Rating Scale; *DBS*, deep brain stimulation; *Short FES-I*, shortened version of the Falls Efficacy Scale-International; *MED*, medication; *MMSE*, Mini-Mental State Examination; *FAB*, Frontal Assessment Battery; *BDI-II*, Beck Depression Inventory, Second Edition

	Patients with PD ($n = 35$, 6 women, 29 men)	
	Mean (SD)	Median
Age (years)	61 (6)	63
Disease duration (years)	21 (5)	20
Time since DBS implantation (years)	5 (3)	5
TEED 1.sin. (J)	103 (71)	89
TEED 1.dx. (J)	103 (74)	76
Levodopa Equivalent (mg)	1110 (591)	900
Hoehn and Yahr stage	2.7 (0.7)	2.5
UPDRS III (OFF MED, DBS OFF)	47 (15)	48
UPDRS Total (OFF MED, DBS OFF)	68 (20)	65
UPDRS Total (OFF MED, DBS ON)	44 (18)	43
Short FES-I	14 (5)	13
MMSE	28 (2)	29
FAB	15 (2)	15
BDI-II	7 (5)	6

Discussion

This study validated the Czech translation of FoG-Q. We demonstrated excellent internal consistency ($\alpha = 0.91$), which is

Table 2 Convergent validity of the Freezing of Gait Questionnaire. *PCC*, Pearson correlation coefficient; *MED*, medication; *UPDRS*, Unified Parkinson's Disease Rating Scale; *TUG*, Timed Up and Go Test; *FoG*, freezing of gait

	PCC	*p* value
UPDRS II item 14	0.524	0.001
UPDRS III item 29 (OFF MED)	0.662	< 0.001
TUG time (OFF MED)	0.551	0.001
TUG steps (OFF MED)	0.586	< 0.001
TUG freezing (OFF MED)	0.548	0.001
FoG Score (OFF MED)	0.605	< 0.001

Table 3 Correlations of the Freezing of Gait Questionnaire. PCC, Pearson correlation coefficient; *UPDRS*, Unified Parkinson's Disease Rating Scale; *HY*, Hoehn and Yahr; *Short FES-I*, shortened version of the Falls Efficacy Scale-International

	PCC	*p* value
Age	0.516	0.002
Disease duration	0.030	0.864
UPDRS I Total	0.131	0.454
UPDRS II item 13 (falls)	0.626	< 0.001
UPDRS II item 15 (walking)	0.700	< 0.001
UPDRS II Total	0.583	< 0.001
UPDRS IV Dyskinesias (items 32–35)	0.486	0.003
UPDRS IV Motor fluctuations (items 36–39)	0.078	0.657
HY staging	0.724	< 0.001
Short FES-I	0.558	< 0.001

comparable with the results of previous studies [12–16]. The Czech version of FoG-Q shows good convergent construct validity as indicated by correlations with UPDRS II item 14, III item 29, TUG time, TUG steps, TUG FoG, and FoG Score. Divergent validity was also good, i.e. there was no correlation with UPDRS I subscore (mentation, behaviour, and mood). Both these results repeat the findings of previous validation studies [12–16]. Our item analysis and internal consistency results are congruent with the conclusions of Giladi et al. [7], who stated that none of the FoG-Q items can be excluded for the reason of high to excellent total-item correlation (the scale cannot be shortened without a sacrifice to the internal consistency of the items and homogeneity of the scale).

FoG-Q score correlated with age in our group, which is consistent with previous findings that FoG increases with age [4, 37]. Although both mean and median age of our patients were comparable to other validation studies [7, 12–16], they had much higher median disease duration (20 years), or at least a larger minimal range thereof (13–34 years). Their HY stage in the ON state was nevertheless similar to other studied populations [12–15], most likely due to DBS treatment. The aforementioned longer disease duration might explain the lack of correlation between the FoG-Q Total score and disease duration and caused stronger correlation with UPDRS II item 13 (falls) and 15 (gait) compared to other studies [7, 12–16]. Similarly to Nilsson et al. [15], who also had a larger median of disease duration (20.3 years), we found a stronger correlation of FoG-Q Total score with UPDRS II than other studies [7, 12, 16].

In the patients' full OFF (OFF MED, DBS OFF), FoG-Q Total score did not correlate with UPDRS III Total score (PCC = 0.302, $p = 0.08$) in comparison to the state OFF MED with DBS ON (PCC = 0.383, $p = 0.02$). This is probably given by the fact that since FoG-Q is a questionnaire, it only reflects the state known to the patients. However, patients treated with DBS do not experience their full OFF. In this sense, FoG-Q does not reflect the native state of the disease in this population. We found strong correlations with UPDRS III items that are related to gait (UPDRS III item 29), balance (UPDRS III item 30) or both (PIGD subscore) even in the patients' full OFF state (Table 4). This could be explained by the fact that our patients were treated with high-frequency STN DBS, which has smaller effect on gait, balance [38], and FoG severity [39]. Therefore, with respect to gait and balance, FoG-Q does, to a certain extent, reflect the native state of the disease in patients treated with high-frequency STN DBS.

Similarly, we observed several correlations with spatio-temporal gait parameters (velocity, step length, and its variability) both OFF MED with DBS ON and in full OFF. These findings are consistent with other studies which report decreased stride length, increased cadence preceding FoG, presence of a highly abnormal frequency of leg movements during FoG, marked stride-to-stride variability, and asymmetry and variability of swing time in patients with PD and FoG [4,

Table 4 Correlations of the Freezing of Gait Questionnaire with clinical gait parameters and gait-related UPDRS III items in OFF MED state with DBS ON and OFF. *PCC*, Pearson correlation coefficient. *MED*, medication; *DBS*, deep brain stimulation; *UPDRS*, Unified Parkinson's Disease Rating Scale

	OFF MED, DBS ON		OFF MED, DBS OFF	
	PCC	*p* value	PCC	*p* value
UPDRS III item 29 (gait)	0.662	< 0.001	0.686	< 0.001
UPDRS III item 30 (balance)	0.611	< 0.001	0.556	0.001
UPDRS III PIGD subscore	0.757	< 0.001	0.821	< 0.001
UPDRS III Total	0.383	0.02	0.302	0.08
Step length	−0.616	< 0.001	−0.505	0.01
Double support phase	0.524	0.002	0.311	0.12
Velocity	−0.397	0.02	−0.442	0.02
Cadence	0.070	0.70	−0.016	0.94
Step length variability	0.652	< 0.001	0.472	0.02
Step time variability	0.346	0.08	0.449	0.02

33–36]. The correlations in full OFF state can be explained again by the relatively smaller efficacy of high-frequency STN DBS on gait, balance, and FoG severity (see above). We noted a lack of correlation with cadence in our study. This is most likely because, in comparison to TUG, walking on GaitRite does not involve initiation of gait and turning, which are two triggers of FoG. In addition, cadence increases shortly before the FoG episode [4]. To support this conclusion, our patients did not generally experience FoG when walking on GaitRite, and consequently did not increase cadence. Interestingly, FoG-Q lost its correlation with the duration of the double support phase in full OFF, but instead gained correlation with step time variability in this state. The former finding can most likely be explained by the fact that patients markedly slowed down in full OFF state, which may have caused an increase of the duration of the double support phase regardless of FoG severity [40]. Correlation with step time variability has already been noted by Hausdorff et al. [41] who proposed several explanations for this fact. Among other explanations, they discuss a "threshold" relationship in which increased stride-to-stride variability is a risk factor for FoG, which is consistent with the "threshold model" of FoG [3, 36]. A marked increase in step time variability in full OFF does likely reflect FoG severity.

In contrast to two previously published studies [15, 16], we found correlation only with UPDRS dyskinesia subscore (IV items 32–35), but not with motor fluctuations subscore (IV items 36–39). This may again be explained by the specifics of our study population, the fact that they were treated with DBS, which reduces motor fluctuations [38]. In fact, the range of the summary score of UPDRS IV items 36–39 was 0–4 with both a mean and median of 2.

One limitation of the current study is a relatively small sample size. This limitation, however, is comparable to other studies that validated FoG-Q including the original one [7, 13, 15]. A re-evaluation with a larger sample would nevertheless be advantageous. Also, 11 patients were unable to complete gait examination in the OFF MED state with DBS OFF.

Conclusions

In conclusion, we have shown that the Czech version of the FoG-Q is a valid tool for the assessment of FoG in patients with PD and DBS without severe cognitive impairment. With respect to our explorative aim, FoG-Q might be considered to reflect gait and balance impairment in native state of the disease (full OFF) in patients treated with high frequency STN DBS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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Gait and Balance Impairment after Acute Methanol Poisoning

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Abstract: Neurological sequelae including gait impairment were reported in survivors after methanol intoxication; however, no systematic study has been published so far. We aimed to analyse gait and balance impairment in a group of Czech methanol poisoning survivors. We examined 43 patients (age 46 ± 13 years) 2–8 months after methanol poisoning and 43 healthy controls. Investigations contained a shortened version of Falls Efficacy Scale (FES), clinical tests of gait and balance including Timed Up and Go test (TUG) and gait analysis using GaitRite® system, neurological and neuropsychological examination, brain imaging, EMG and tests of alcohol consumption. Nineteen patients admitted balance and gait impairment according to FES. Mild to moderate parkinsonian signs showed seven patients. Patients were slower (*8.8 versus 5.7 s*, $p < 0.001$) and performed more steps (*11.1 versus 7.9*, $p < 0.001$) in TUG compared with the controls. Gait analysis revealed shorter step length (*76.5 versus 88.7 cm*, $p < 0.001$), increased double support phase (*18.8 versus 15.5%*, $p < 0.001$) and wider base of support (*11.3 versus 9.6 cm*, $p = 0.006$) in patients. Eleven patients had deficit of executive function and performed higher cadence compared to the patients with normal execution (*122.7 versus 115.0 step/min.*, $p = 0.025$). Lower limb polyneuropathy was verified in nine patients, without relation with gait or balance parameters. Neuroimaging revealed lesions mainly in the basal ganglia. Methanol poisoning survivors presented slower wide-based gait with shortened steps corresponding with frontal gait disorder. Higher stepping cadence associated with executive deficit supported the evidence of frontal lobe dysfunction related to impairment of basal ganglia and connections in frontal cortico-basal ganglia loops.

Methanol is a colourless liquid, resembling ethanol in smell and taste. Intoxications occur as isolated accidental episodes or as a mass or cluster poisonings due to consumption of illicit adulterated spirits [1–3]. In the Czech Republic, it was a rare condition until a mass poisoning outbreak in 2012–2014 with 137 intoxicated patients due to ingestion of adulterated alcoholic beverages [4,5]. The mortality and the prevalence of health sequelae in survivors were high despite efficient treatment [6–9].

Absorption of methanol after oral administration is rapid with the attainment of peak methanol concentrations within 30–60 min. after ingestion. The minimal lethal dose of ingested methanol in adults is about 1 mg/kg of body-weight; however, the toxicity of methanol itself is relatively low. The products of biotransformation in the liver (formaldehyde and formic acid) in combination with metabolic acidosis are responsible for the major toxic effects in human beings [10–12]. The severity of clinical symptoms also depends on the concomitant amount of ingested ethanol due to competitive inhibition along the metabolic pathway [13,14].

Acute symptoms of methanol intoxication usually develop after initial inebriety. The main complaints are headache, nausea, epigastric pain or vomiting. After a latent period of 12–24 hr may appear visual disturbances, epileptic seizures or even rapid deterioration to stupor, coma and sudden death in some cases [2,10]. Biochemical analysis proves severe metabolic acidosis with high osmotic gap, increased pCO_2 and high *S*-formate and *S*-lactate levels [12].

Late-term neurological and visual symptoms occur in survivors with delay of days up to weeks after intoxication [15,16]. Parkinsonism [17], pyramidal signs [18], gait disorders [19–23] and seldom dystonia [19,24,25] were described in previous studies. Neuroimaging findings can reveal structural damage of the basal ganglia with predominant affection of putamen [26]. Symmetrical bilateral putaminal lesions range from partial changes to all-embracing haemorrhagic necrosis [20,26–28] and are supposed to be caused by the predilect accumulation of formic acid in high concentrations within the putamen; however, the reasons for this phenomenon are unclear [26]. A direct toxic effect of formic acid due to the inhibition of cytochrome *c* oxidase is also considered [29]. A reduction in the blood flow through the basal veins of Rosenthal upon secondary hypotension during intoxication [27] may also have a key role in affection of basal ganglia and the optic nerve, which are susceptible to anoxia and metabolic acidosis [30]. Others propose that formic acid is able to increase enzymatic activity of dopa-B-hydroxylase and impair dopaminergic pathway [31]. Secondary myeloclastic effect of accumulated

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formic acid within the optic nerve leads to visual disturbances [32]. Among other findings are [20,26,27] occasionally lesions in caudate nucleus, brainstem or cerebellar area [33,34] or subcortical white matter lesions.

No systematic study of gait disorders after methanol intoxication has been published so far, although several papers mentioned gait impairment with a parkinsonian pattern, characterized as slow shuffling [19], with stooped flexed posture [20], reduced arm swing [21], small steps and impaired balance [22]. Others reported broad-based propulsive gait [35] with difficulty in initiating movement. Hesitation [20] and festination [23] were seen in a few cases. Ataxic (unstable) gait with worsening after exclusion of visual control and sensory loss on the distal part of the legs was described in patients in Estonia [32].

The primary aim of our study was to analyse the gait and balance disturbances in a group of survivors after acute methanol poisoning. Considering the previous reports, we suggested that prevailing gait pattern will be characterized by parkinsonian features. We further aimed to evaluate the severity of gait impairment and to correlate gait parameters to other clinical findings in our group of patients.

Patients and methods

The study was approved by the General University Hospital Ethics Committee and was in compliance with the Declaration of Helsinki.

Participation in the study was offered to all 83 survivors from a total of 137 patients, who were poisoned by methanol during the mass outbreak between September 2012 and January 2014 in the Czech Republic [36]. Fifty patients agreed to take a part in the study; however, we had to exclude seven of them due to inability to walk independently, blindness, hemiparesis after previous stroke or refusal to complete the examination. We included 43 patients (nine females, 34 males; mean age 46 ± 13 years, ranged 24–73 years) about 2–8 months after the proven acute methanol intoxication. A detailed record of history of the poisoning and acute care facility data were collected and analysed centrally in the Czech Toxicological Information Center [4]; for more detail, see table 1.

A healthy control group consisted of 43 age- and sex-matched volunteers (nine females, 34 males; mean age 46 ± 13 years, ranged 24–73; $p = 0.484$), who were free of any neurological, psychiatric or other disabling illness. All controls denied intake of any medication acting on the central nervous system, and only occasional alcohol consumption was referred, not fulfilling the criteria of harmful use.

Table 1.
Admission laboratory and clinical parameters of acute methanol poisoning in 43 patients.

	Median (IQR)	Min–max
S-MetOH (mg/l)	935.0 (406.0–2030.0)	85.0–7307.0
S-EtOH (mg/l)	5.0 (0.0–350.0)	0.0–4460.0
S-Formic acid (mg/l)	610.0 (256.0–748.0)	0.0–1400.0
S-Lactate (mmol/l)	1.9 (1.4–3.7)	0.7–11.4
Arterial pH	7.3 (7.1–7.4)	6.7–7.5
GCS	15 (15–15)	3–15
Latent period (hr)	17.5 (12.0–36.0)	2.0–96.0
Time to presentation(hr)	30.0 (14.0–40.0)	1.0–96.0

Values are presented as median (interquartile range); (minimal and maximal values).
S-MetOH, serum methanol concentration; *S*-EtOH, serum ethanol concentration; *S*-lactate, serum lactate concentration; GCS, Glasgow Coma Scale; S, serum.

Neither patients nor controls were under alcohol influence during the examination. No participant had a severe rheumatic or orthopaedic disease, trauma, congenital malformation of lower extremities or other illness interfering with gait.

All patients filled in a shortened version of the Falls Efficacy Scale-International (FES-I, score range 7-28, cut-off 8), which contains seven simple questions concerning instability and fear of falling in usual daily activities [37]. Neurological symptoms in patients were rated by the Natural History and Neuroprotection in Parkinson Plus Syndromes – Parkinson Plus Scale (NNIPPS-PPS, ranging from 0 to 335 points), which evaluates signs of parkinsonism as well as dystonic, cerebellar, pyramidal features, myoclonus, bulbar/pseudobulbar, orthostatic and urinary symptoms [38]. The Mini-Mental State Exam (MMSE, score range 0–30, cut-off 24) was used to assess cognitive state [39], the Frontal Assessment Battery to evaluate frontal lobe function (FAB, score range 0–18, cut-off <16 was used to define executive impairment) [40] and the Digit Span Backwards for measuring verbal working memory ability. Tests of executive function targeted on initiation (Controlled Oral Word Association Test, COWAT) [41], set shifting (Trail Making Test – part B, TMT-B) [42] and inhibition (Stroop Interference) [43].

All participants underwent a set of clinical tests focusing on gait and balance. The Timed Up and Go test (TUG) was used to assess functional mobility. The examination includes rising from a chair, walking 3 m forward, 180° turning and walking back to the chair to sit down [44]. The number of steps and time needed to complete the examination were recorded.

Postural stability was evaluated by the pull test [45] that measures the ability to recover from a backward pull to the shoulders. The test is rated as normal if the subject recovers independently and may take 1 or 2 steps or an ankle reaction. Abnormal results of the test included three or more steps backward to recover or the need to be assisted to prevent falling.

The Romberg test [46] was performed to examine static standing balance. The subject stands with feet together with eyes open and then closed for 20 sec. Inability to maintain the position after removing visual input indicates sensory impairment [47].

The Functional Reach Test (FRT) [48] assesses stability by measuring the maximum distance an individual can reach forward while standing in a fixed position. The distance was calculated as a difference between the primary and the final position of the fist at the 3rd metacarpal head.

The 360 Degree Turn Test (360° Turn) [49] evaluates dynamic balance. The subject performed a complete circle (360 degrees) in comfortable and fast speed clockwise and counterclockwise, while the time and the number of steps to complete the turn were recorded.

To provide a more detailed temporo-spatial analysis of gait pattern, we used the GaitRite Analysis System. It consists of a 4.6-m-long computerized pressure-sensitive walking mat, covered by sensors, which are arranged in a grid-like pattern to identify footfall contacts. All participants were instructed to walk over the mat at comfortable preferred speed, fast walking speed and with eyes closed at preferred speed. All gait examinations were repeated twice. We gathered spatial (step length, base width) and temporal characteristics (step time, double support time, gait velocity and cadence) of the gait of both investigated groups. (For details of the gait parameters see Appendix S1).

A magnetic resonance investigation of the brain (MRI, Gyroscan Philips 1.5 T with the following protocol: axial T2-weighted image, fluid-attenuated inversion recovery, pre- and post-contrast T1-weighted image and spectral pre-saturation with inversion recovery coronal images centred to the orbital region), was performed in all patients

except three, who had a computed tomography (CT, native scans) due to contraindications for MRI.

The Alcohol Use Disorders Identification Test (AUDIT; range 0–36, cut-off 7) was used as a screening questionnaire of alcohol consumption [50] in patients, because risk drinking of alcohol was reported in discharge reports at the time of methanol intoxication in 26 (60%) patients. Each patient underwent an alcohol breath test and a set of laboratory examinations including ethyl glucuronide in urine (EthGlu, positive/negative detection in urine), carbohydrate-deficient transferrin (CDT, normal range 0%–2%) and gamma-glutamyltransferase (GGT, normal range 0.1–0.7 μkat/l) for objective evaluation. Electromyography (EMG) of lower limbs was performed in patients to measure nerve conduction velocity in search of possible neuropathy.

Descriptive statistics for the collected data was performed to determine the distribution of demographic, clinical and gait variables. Gait parameters were calculated as an arithmetic mean value of results in two trials in each condition. Intergroup differences in methanol and control group were assessed using a two-sample *t*-test (for parameters with a normal distribution according to Shapiro–Wilk test) or the Mann–Whitney and Wilcoxon rank-sum test (for non-normally distributed parameters). To evaluate the influence of leg length on gait parameters, an analysis of covariance (ANCOVA) was performed (with leg length as covariates); similarly, ANCOVA was used in comparison of results of AUDIT to exclude the influence of age. Pearson's chi-squared test and Spearman tests were performed to assess correlations between variables (i.e. biochemical parameters, GCS, neuropsychological tests, FES, NNIPPS and gait parameters) and intergroup differences in methanol patients with abnormal findings on MRI and EMG; executive tests were assessed by the Mann–Whitney test.

Results

In the neurological examination as reflected by NNIPPS-PPS, we did not find clinically relevant group abnormalities in any subdomain. Seven patients (16%) fulfilled the criteria of parkinsonism (presence of bradykinesia with either rigidity or tremor resulting in combined NNIPPS subscore >4) corresponding to mild (subscore 5–10) to moderate (subscore 11–20) parkinsonism severity. Cerebellar features found in 16 (37%) subjects were only of minimal severity according to NNIPPS (cerebellar subscore ranged 1–6). Nineteen patients (44%) admitted subjective balance and gait impairment with FES total score ranging from 9 to 24. MMSE was within normal range except in three patients (7%). FAB demonstrated impaired frontal functions in 16 patients (37%). Executive deficit (based on performance score below 1.5 S.D. from normal mean in at least two executive tests including TMT-B, COWAT, Digit Span Backwards and Stroop Interference) was documented in 11 patients (26%). Results are presented in table 2.

Gait and balance parameters of methanol survivors and control group are summarized in table 3. In the TUG test, the patients were clearly slower and walked with greater cadence compared with the control group (both $p < 0.001$). From the measures obtained using the GaitRite system, gait velocities at a comfortable pace were similar in both groups; however, the patients showed greater cadence than controls ($p = 0.002$), but their increased cadence at a fast gait speed was significantly lower than in controls. In the fast speed condition, the patients produced a significantly shorter step length and a higher step time and had lower velocity and a clearly longer duration of the double support phase of gait cycle in comparison with the controls (all $p < 0.001$). The base of support was wider in the patients, especially in comfortable pace of walking ($p=0.006$), and further widened while walking with closed eyes ($p = 0.022$). The methanol group was also slower in fast turning ($p < 0.001$) and achieved shorter distance in FRT ($p < 0.001$). Only two patients (5%) had difficulties in the Romberg test and six patients [14] scored abnormal at the pull test.

The patients with executive impairment (N = 11) had a significantly higher cadence in comfortable gait compared to patients (N = 32) with normal executive function (122.7 *versus* 115.0 step/min., $Z = -2{,}236$, $p = 0.025$). No significant correlations were found between gait parameters and NNIPPS-PPS, FES, MMSE, FAB score. We also did not prove significant correlations between measured gait parameters and admission laboratory parameters obtained at the acute care facility during hospitalization.

Positive screening of the harmful use of alcohol according to AUDIT was present in 22 of the methanol patients (51%). The alcohol breath test was negative in all participants during the examination, EthGlu in urines was positive in 26 (61%), elevated serum CDT was observed in 14 (33%), and increased levels of GGT were found in 16 (37%) patients. Patients with positive screening according to AUDIT were significantly younger (41.2 ± 11.9 *versus* 53.4 ± 13.3 years, $p = 0.004$) and showed no significant differences in gait or balance measures compared to patients with negative screening if effect of age was eliminated. Interestingly, we found a higher gait velocity at a comfortable pace in patients with positive screening of CDT (1.59 ± 0.23 *versus* 1.38 ± 0.21 m/sec., $p \leq 0.01$) and EthGlu (1.52 ± 0.25 *versus* 1.32 ± 0.16 m/sec., $p \leq 0.01$). Even so, we failed to prove any significant correlation between serum and urines biochemical parameters and the results of gait or balance tests.

EMG verified distal lower limb polyneuropathy was only mild. Patients with positive finding on EMG were of higher age compared to those with negative findings (58.4 ± 11.3 *versus* 42.0 ± 12.1 years, $p < 0.001$); however, no significant differences in gait parameters were observed in comparison with the other patients.

Neuroimaging of brain revealed lesions mainly in the basal, including bilateral putaminal necrosis and/or lesions in the pallidum, rarely in the brainstem, cerebellum and subcortical white matter (more details in table 2).

Discussion

In the current study, we attempted to confirm the hypothesis that patients after methanol intoxication suffer from parkinsonian gait impairment as suggested in previous studies [19–23]. Indeed, the group analysis of gait measures revealed shorter steps and lower velocity in fast speed with inability to adapt length and duration of the steps to gain appropriate speed in methanol patients compared with the healthy individuals. Those characteristics are, however, not specific only for parkinsonian gait. In the clinical assessment, we did not

Table 2.
The results of questionnaires, clinical scales and complementary methods of the Methanol Group.

	Abnormal N (%)	Median (IQR)	(Min–max)
NNIPPS-PPS – total score (335)	35 (81%)	7.0 (2.5–13.0)	(0–46)
Mental function (40)	23 (53%)	1.0 (0.0–3.5)	(0–10)
Bulbar–pseudobulbar signs (24)	12 (28%)	0.0 (0.0–1.0)	(0–4)
ADL/mobility (32)	7 (16%)	0.0 (0.0–0.0)	(0–5)
Tremor (32)	14 (33%)	0.0 (0.0–1.5)	(0–5)
Rigidity (20)	4 (9%)	0.0 (0.0–0.0)	(0–6)
Myoclonus (12)	0 (0%)	0.0 (0.0–0.0)	(0–0)
Limb bradykinesia (32)	16 (37%)	0.0 (0.0–3.0)	(0–12)
Axial bradykinesia (24)	10 (23%)	0.0 (0.0–0.0)	(0–4)
Ocular motor function (21)	4 (9%)	0.0 (0.0–0.0)	(0–3)
Axial dystonia (12)	0 (0%)	0.0 (0.0–0.0)	(0–0)
Limb dystonia (16)	0 (0%)	0.0 (0.0–0.0)	(0–0)
Pyramidal signs (4)	7 (16%)	0.0 (0.0–0.0)	(0–3)
Cerebellar function (44)	16 (37%)	0.0 (0.0–1.0)	(0–6)
Orthostatic symptoms (12)	14 (33%)	0.0 (0.0–3.0)	(0–12)
Urinary symptoms (10)	0 (0%)	0.0 (0.0–0.0)	(0–0)
MMSE (30; cut-off score 24)	3 (7%)	29.0 (27.0–29.0)	(15–30)
FAB (18; cut-off score 16)	16 (37%)	16.0 (15.0–17.0)	(8–18)
TMT-B (sec.)		117.8 (76.0 ± 139.0)	(37.0–314.0)
COWAT (number of words)		40.6 (35.0 ± 51.0)	(2.0–59.0)
Digit span backwards (correct points total)		5.3 (22.0 ± 45.0)	(16.0–89.0)
Stroop interference (sec.)		34.1 (11.0 ± 15.0)	(6.0–25.0)
FES-I (28; cut-off score 9)	19 (44%)	8.0 (7.0–11.0)	(7–24)
AUDIT (36; cut-off shore 7)	22 (51%)	8.0 (5.0–15.5)	(1–34)
EMG verified peripheral polyneuropathy	9 (21%)		
MRI abnormalities			
a) supposedly associated with methanol	16 (37%)		
Basal ganglia (pallidum, putamen)	13 (30.2%)		
Cerebellum (incl. dentatus)	1 (2.3%)		
Brainstem (pons, mesencephalon)	4 (9.3%)		
Subcortical haemorrhage	2 (4.7%)		
Optic nerve atrophy	2 (4.7%)		
b) other MR abnormalities			
Cerebral cortical atrophy	10 (14%)		
Cerebellar atrophy	1 (2.3%)		
Leukoaraiosis	2 (4.7%)		
White matter lesions	2 (4.7%)		

Values represent abnormal N (%), number of patients with abnormal findings (percentage of total, n = 43); Median (IQR), median (interquartile range); (min–max), (minimal and maximal values).

observe other typical parkinsonian features, such as stooped flexed posture, reduced arm swing, freezing, hesitation [20] or propulsive gait [35]. In fact, except of seven subjects, the majority of the patients lacked any considerable signs of parkinsonism in the neurological examination scored by NNIPPS-PPS.

The results of gait analysis support alternative interpretation of the further differences between the methanol group and the healthy controls [51]. Namely, a wider base of support at a comfortable gait speed can be present in cerebellar ataxia [52,53], vestibular disorder [54] or impairment of proprioception [55]. However, we did not observe clinically relevant features of cerebellar involvement or vestibular disorder either in neurological examination or according to NNIPPS-PPS subscores. The neuroimaging findings were also unsupportive as only one patient had a cerebellar lesion and one a marked cerebellar atrophy. Sensory ataxia could be considered, based on the detection of wide-based gait that further deteriorated when patients walked with eyes closed; nevertheless, distal sensory polyneuropathy was verified by EMG only in one-fifth of the patients, and its presence did not show any relation to gait or balance parameters.

All the evidence leads us to suppose that the gait pattern revealed by gait analysis in methanol patients corresponds with frontal gait disorder [56], a higher-level gait disorder [57,58], known also under terms including gait apraxia [59,60], lower body parkinsonism [61], marche a petits pas or vascular parkinsonism [62]. Frontal gait disorder has typically been described as slower wide-based gait with shortened steps accompanied by postural instability and fear of falling, with normal voluntary movements of the upper limbs, and the absence of a rest tremor [63]. In the patients, most of these features were documented in comparison with the healthy control group. Slower gait compared with controls was shown in

Table 3.
The gait and balance parameters of survivors of methanol poisoning and the control group.

		Methanol patients	Healthy controls
TUG 3 m	Time (sec.)	8.8 ± 2.0***	5.7 ± 0.9
	Steps	11.1 ± 2.2***	7.9 ± 1.2
Turning fast	Time (sec.)	2.1 ± 0.6***	1.6 ± 0.3
	Steps	5.7 ± 5.0***	3.9 ± 0.8
Functional reach test	Forward (cm)	32.5 ± 8.2***	43.7 ± 9.4
	Backward (cm)	23.1 ± 7.8***	32.2 ± 8.6
Romberg test	Positive	2/43 (5%)	0/43
Pull test	Abnormal	6/43 (14%)	0/43
Parameters in GaitRite system			
Velocity norm. (m/sec.)	Comfortable	1.30 ± 0.23	1.26 ± 0.23
	Fast	1.72 ± 0.27***	2.19 ± 0.37
	Eyes closed	1.19 ± 0.35	1.37 ± 0.23
Cadence (step/min.)	Comfortable	117.4 ± 12.7**	109.0 ± 8.9
	Fast	134.7 ± 12.6***	148.5 ± 14.3
	Eyes closed	117.3 ± 16.6	117.7 ± 10.4
Step time (sec.)	Comfortable	0.52 ± 0.06**	0.56 ± 0.05
	Fast	0.45 ± 0.04***	0.41 ± 0.04
	Eyes closed	0.53 ± 0.11	0.52 ± 0.45
Step length (cm)	Comfortable	66.5 ± 8.3	70.3 ± 6.9
	Fast	76.5 ± 10.2***	88.7 ± 8.8
	Eyes closed	60.0 ± 12.7**	69.3 ± 8.9
HH base support (cm)	Comfortable	11.3 ± 2.9**	9.6 ± 2.2
	Fast	11.2 ± 2.9	10.5 ± 2.9
	Eyes closed	13.2 ± 3.4*	11.0 ± 3.4
Double supp % of cycle	Comfortable	23.2 ± 3.1	23.2 ± 2.9
	Fast	18.8 ± 2.7***	15.5 ± 3.8
	Eyes closed	25.3 ± 5.7	22.9 ± 3.4

Values are mean ± S.D. (n = 43).
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ANCOVA compared with healthy controls.

both TUG and a computerized gait analysis at fast speed of walking. The analysis revealed wider base of support, shorter steps and higher cadence of stepping in methanol patients. The ability to increase walking speed by increasing the cadence of stepping is typically impaired in frontal gait disorder [58], while it remains preserved in Parkinson's disease [64]. Moreover, documented fear of falling with increased FES scores together with slower turning and worse performance in FRT reflects a compromised static and dynamic balance in methanol patients compared with the control group.

The estimated presence of frontal gait disorder in the patients is further supported by the documented impairment of other frontal functions. Cognitive deficit of the frontal type in patients after acute methanol poisoning was documented in previous works [15]. In accordance with those results, we proved a cognitive decline according to FAB and particularly executive impairment, correlating with a higher cadence in comfortable gait. Executive dysfunction has previously been reported in connection with difficulty in maintaining walking stability and an elevated fall risk [65–67], typically accompanying the frontal gait disorder [63].

Frontal gait disorder reflects disrupted connections in the cortico-basal ganglia loops [57]. Neuroimaging studies in general fail to define a specific related pathology and describe rather non-specific findings such as diffuse subcortical white matter changes that may be associated with the so-called vascular parkinsonism as well as with gait and balance abnormalities in non-disabled elderly [62,68]. Conversely, typical MRI findings after methanol intoxication show structural damage of the basal ganglia [20,26,27] that was also demonstrated in one-third of the patients, including mainly bilateral putaminal necrosis and lesions in the pallidum [61,62]. However, we failed to find a statistically significant association between imaging findings and gait parameters in our group of patients. The explanation could be in a mostly subclinical impairment in the patients, which was detectable only on a detailed gait analysis, with no evident clinical manifestation of a movement disorder during the standard neurological examination.

The major limitation of our study is the fact that we could not investigate the most affected subjects due to high mortality of the methanol poisoning or inability to walk independently in the severely affected subjects. Secondly, without controls with an appropriate history of alcohol consumption, we cannot clearly exclude the effects of chronic ethanol consumption in the patients, despite the absent relevant correlations between the gait parameters and the biochemistry or EMG findings. In the further research, it will be appropriate to evaluate the development of the proven deficit over time in a prospective study.

Conclusion

Survivors of methanol poisoning did not present a typical parkinsonian gait pattern. Compared with the healthy controls, the patients presented slower wide-based gait with shortened steps that correspond to the pattern of frontal gait disorder. Higher stepping cadence associated with executive dysfunction supports the evidence of frontal lobe dysfunction related to the basal ganglia dysfunction and disrupted connections in the frontal cortico-basal ganglia loops as the sequelae of methanol poisoning.

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Disclosure

All the authors declare no competing interests.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Gait parameters.