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VReeze: an open-source virtual reality for the examination of freezing of gait in Parkinson's disease – a study design of a crossover repeated measures study for validation

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ABSTRACT

Introduction Parkinson's disease is the second most prevalent neurodegenerative disease worldwide, with up to 70% of patients exhibiting freezing of gait (FOG). FOG is defined as transient episodes when one is unable to effectively engage in the stepping process (despite the intention to walk), which decreases or completely ceases forward movement. Although several FOG triggers have been identified, eliciting FOG remains challenging in research, hindering progress in research and therapy. Virtual reality (VR) offers a promising approach to evoke FOG during overground walking by combining environmental and neuropsychological triggers. This project aims to validate an existing open-source VR-FOG toolbox that integrates multiple triggers.

Methods A within-subject repeated measures crossover study design with a 1-hour washout period will be used for this project to validate the VR-FOG toolbox. This will consist of three blocks (baseline non-VR, VR non-FOG and VR-FOG). All participants will first complete a baseline walking trial without VR, then be randomised to either the VR non-FOG environment—a virtual replica of the laboratory—or the VR-FOG environment containing multiple virtual FOG triggers. After a 1-hour washout period, they will complete the remaining VR condition. A crossover design will minimise ordering effects of VR conditions on FOG frequency and duration. Twenty participants with Parkinson's disease with FOG will be tested at St. Pölten University of Applied Sciences (Austria) and 20 at the University of Exeter (UK) and will be recruited from local communities. Multisite testing will verify that the VR-FOG environment triggers FOG regardless of testing location.

Ethics and dissemination Ethical approval was obtained from the Lower Austrian Ethics Commission and the University of Exeter review boards. All data will be anonymised, used solely for this project and securely stored in General Data Protection Regulation-compliant repositories. Study results will be presented at scientific conferences and published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The multisite data collection will ensure that the virtual reality-freezing of gait (VR-FOG) environment is valid and can elicit FOG independent of testing location.
⇒ The crossover repeated measures design, with a 1-hour washout period, will ensure that carryover effects will not occur for eliciting FOG between the VR conditions.
⇒ The study is not suitable for people with motion sickness/cybersickness.
⇒ As the study focuses specifically on individuals with FOG, the findings cannot be generalised to the broader effects of VR on gait and balance.

INTRODUCTION

Parkinson's disease (PD) is the second most common and fastest growing neurodegenerative disease worldwide mainly affecting individuals over the age of 60.[1–5] Within this demographic, nearly 27% of individuals in the early stages of the disease and 70% of those in the moderate to advanced stages exhibit the paroxysmal phenomenon of freezing of gait (FOG), which previous literature has defined as 'a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk'.[6–9]

FOG poses a severe risk to safety due to the sudden cessation of effective stepping despite the continued momentum of the centre of mass.[8 10] As the overall fall prevalence in people with PD (pwPD) is between 60% and 70% per year, approximately two times that of healthy older adults, the evidence clearly demonstrates the substantial threat FOG has to their safety, independence, mobility and well-being.[11 12] Typically, pwPD experience

FOG when walking through narrow spaces, turning, dual-tasking (ie, walking while performing a secondary task), during gait initiation, approaching a destination, during periods of heightened emotional states (eg, anxiety and stress) and under time constraint.[6 7 13] However, despite these triggers being well documented, FOG is challenging to observe in controlled environments as (1) triggers are diverse and (2) due to the paroxysmal nature of FOG.[6 7 14–17] Moreover, one of the main challenges when examining FOG is the heterogeneous nature of both PD and FOG.[15 16 18–23]

In PD, atrophy in multiple cortical and subcortical regions results in a heterogeneity of symptoms, causing different phenotypes of PD to exist.[18–23] For motor symptoms, pwPD are typically classified into two main phenotypes of tremor dominance or postural instability and gait disorders (PIGD).[20–23] Of these main phenotypes, FOG mostly occurs in the PIGD phenotype and is characterised by an independent and divergent neuropathology from the disease's cardinal symptoms (ie, bradykinesia, akinesia, tremor, rigidity and postural instability).[6 7 24–26] While an operational definition of FOG exists, considerable heterogeneity exists regarding its aetiology.[6 7 15 16] For instance, preliminary evidence indicates that FOG has three phenotypical expressions: (1) anxiety, (2) sensory-attention and (3) asymmetric motor phenotypes.[15 16] Anxiety FOG occurs when pwPD with FOG are in stressful and anxious situations.[14–16] Sensory attention FOG often occurs when walking through disorganised settings, encountering incongruent floor patterns and walking through narrow spaces.[14–16] Finally, the asymmetric motor phenotype FOG can occur during asymmetric movements such as gait initiation and turning.[14–16] However, as FOG is difficult to observe in controlled environments, clear evidence underlying the aetiology and phenotypes is sparse and somewhat equivocal.

Currently, FOG triggering methods such as the 'Turning-in-Place', 'Stepping-in-Place' and the 'Turning and Barrier Course' were developed to elicit freezing in controlled settings.[6 7 27 28] While these methods demonstrated high sensitivity and validity, they either do not induce forward walking (Turning-in-Place and Stepping-in-Place) or are a setup that does not include the multitude of FOG triggers (Turning and Barrier Course).[6 7 27 28] Based on the evidence, the likelihood of FOG occurring may increase when a freezing subtype is presented with triggers specific to that phenotype (eg, anxiety subtype presented with an anxiety trigger) and less likely when presented with triggers from other subtypes (eg, anxiety subtype presented with a motor trigger). Therefore, to effectively trigger FOG across the different phenotypes, protocols must encompass the variety of known triggers.

To address this limitation, advances in virtual reality (VR) allow virtually creating multiple FOG triggers that may otherwise be too difficult or dangerous to study.[13 29 30] In a literature review, Canning *et al*[13] synthesised the evidence, which concluded that although current VR protocols for treating FOG hold no advantages over standard therapies, FOG triggering environments can successfully elicit freezing in participants for further scientific investigation.[13] The main limitation of VR research thus far is that most paradigms use a seated surrogate gait task or only examine a specific FOG trigger.[13 29–31] For instance, Ehgoetz Martens *et al*[30] created a fear-of-height paradigm projected through a head-mounted display to examine FOG while walking. The authors found that this VR environment successfully triggered over 300 FOG episodes across 86% of their participants during steady-state walking while 'ON' medication.[30] Although the protocol developed by Ehgoetz Martens *et al*[30] offered valuable early insights into the use of VR for studying FOG, its primary objective was to examine the role of anxiety as a potential trigger. This limits its widespread use for investigating FOG across the different freezing phenotypes.

Additionally, current VR-FOG protocols are not open-source, which restricts their impact and adoption by scientific and clinical communities. Specifically, an open-source software can be downloaded and used worldwide by both researchers and clinicians. For instance, the validated VR-FOG toolbox from this project can be implemented by neurosurgeons to objectively examine the effectiveness of interventions (such as deep brain stimulation) in treating FOG for their patients. Similarly, a validated VR-FOG toolbox will substantially support clinical trials aiming to test the efficacy of new pharmacological therapies. Furthermore, an open-source VR software would allow independent physical therapists and clinicians (who may lack the financial resources or the technical expertise) to have full access to a validated, readily implementable and individualised digital solution to objectively assess the effectiveness of their therapies.

Therefore, the primary aim of this project is to validate the developed VR-FOG triggering environment with two independent samples of freezers.

METHODS

FOG VR design and environment

To overcome the aforementioned limitations in VR environments for triggering FOG, we developed an open-source VR-FOG environment that encompasses multiple FOG triggers. The premise for the VR-FOG environment is set within a virtual hallway (figure 1) setting.[32] Participants will begin at one end of the walkway and traverse along the length of the path to the opposite end. On reaching the opposite end, participants will be required to turn around and walk back in the direction in which they came from. Participants will repeat this continuously for the entire duration of the 6 min of the VR environment.

While traversing the virtual walkway, participants will randomly encounter multiple FOG triggers such as a narrow tunnel (figure 1a), 360° turns (figure 1b), anxiety-inducing (ie, fear of heights) triggers (figure 1b), furniture along the sides of the walkway (figure 1c), traffic stop lights (figure 1c) and doorways (figure 1d).[6 7 13 29 30] The doors and narrow tunnel are designed to simulate

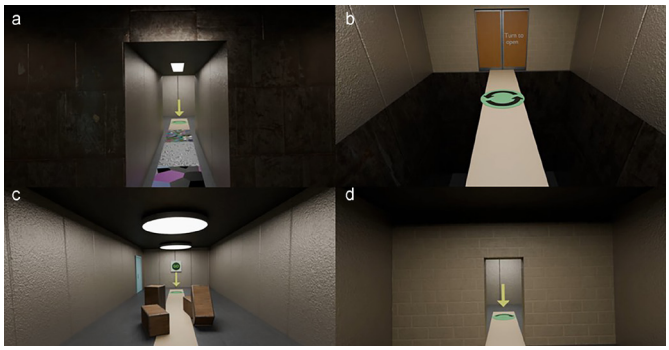

Figure 1 A depiction of the various triggers within the VR-FOG condition. The VR-FOG is designed to present random combinations of the various FOG triggers throughout the 6 min duration. Depicted in the panels are narrow tunnels with alternating floor panels (top left, (a)), an anxiety condition superimposed with 360 degree turns to open a doorway (top right, (b)), walkway with clutter combined with stop-go sign to induce gait initiation (bottom left, (c)) and passing through doorways (bottom right, (d)). VR-FOG, virtual reality-freezing of gait.

walking through narrow spaces in the real world, which are common FOG triggers.[6 7 14 29] Similarly, the furniture strewn along the sides of the walkway simulates a cluttered environment, which often causes freezing as it becomes challenging for people to manoeuvre in.[6 7 14] The 360° turn is induced as specific dots on the walkway superimposed with a circular arrow, indicating the direction the participants should turn in.[6 7 14] The direction of the turn is always randomised in the VR environment, so that an even amount of left and right turns is collected. To investigate gait initiation, we incorporated in the VR environment a traffic stop light, with the words 'stop' (in red) and 'go' (in green). When the stop light flashes stop, participants are required to stop walking until the light turns green and displays 'go', on which they will begin to walk again. For the anxiety triggers, we utilised the 'high' anxiety VR environment described in Ehgoetz Martens *et al*,[30] which asks participants to walk across a virtual pathway that, within the virtual environment, is suspended over a 6 m deep pit.[30] Furthermore, we will use a virtual 'mountain top' scene which, within the VR, will suspend the virtual walkway over a mountain top range to elicit FOG through an additional fear of heights condition.

At the end of the walkway, after the participants have turned around to walk back, the aforementioned FOG triggers are presented again. However, the order, frequency, placement and timing of the FOG triggers are randomised within the VR environment. Additionally, it is possible that on some occasions, after turning around, the participants do not encounter a trigger, which was previously there in the walkway. This randomisation feature is implemented to reduce the likelihood of trigger adaptation, which may otherwise reduce the probability of eliciting FOG. This VR environment is further outfitted with a customisable toggle feature, which allows users to preselect the FOG triggers presented in the VR environment.

Validation study

Study design

A within-subject repeated measures crossover study design with a 1-hour washout period will be used for this project consisting of three blocks (baseline non-VR, VR non-FOG and VR-FOG).[33] Previous research demonstrates that a 1-hour washout period is a sufficient time period between conditions when assessing gait and postural control impairments for protocols examining FOG.[33 34] Furthermore, Thevathasan *et al* suggest that this time period reflects what would be conducted during standard clinical practice.[33] A crossover design was selected to attenuate ordering effects of the VR conditions on the frequency and duration of FOG episodes. Overall, this will serve as a robust measure for validating the developed VR-FOG environment.

Participant recruitment

Twenty participants will be tested at the St. Pölten University of Applied Sciences (Austria) and 20 participants will be tested at the University of Exeter (United Kingdom) and recruited from the local communities. The following inclusion and exclusion criteria will be used at both data collection sites:

Inclusion criteria

a. pwPD aged 60–85 years old as diagnosed by the UK Brain Bank Criteria.[35 36] The lower age limit will be selected in order to reduce age-related variability.
b. Able to walk unassisted.
c. Stable medication for the past 1 month and/or stable Deep Brain Stimulation for at least 1 month.
d. Freezers will be identified by: (1) confirmation from a neurologist of a history of FOG or during assessment prior to participation and (2) individuals self-reporting FOG with the FOG questionnaire (FOG-Q).

Exclusion criteria

a. People that exhibit atypical Parkinsonism such as those with progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies and corticobasal syndrome.
b. Physical discomfort using VR.
c. Medically diagnosed neurological or cardiovascular diseases other than PD, which affect the ability to walk.
d. Uncorrected visual or hearing impairments that limit or could limit the ability to see feedback or comply with instructions given during testing.
e. Musculoskeletal and/or orthopaedic conditions before data collection that impact the ability to walk.

Patient and public involvement

None.

Sample size calculation

The effect size for our study is estimated based on Ehgoetz Martens *et al*,[30] where a VR environment was used to trigger FOG and tested while participants were 'ON' medication. The effect sizes used for our sample size estimation were derived from the average number of freezing episodes per trial, which resulted in a partial η^2_p value of 0.103. Average number of freezing episodes was selected as the goal of the VR-FOG environment is to trigger multiple FOG episodes from all the built-in virtual triggers. Subsequently, this resulted in an a priori power analysis of 16 participants to achieve β=0.8 for a within-subjects repeated measures Analysis of Variance (ANOVA) with three levels. However, as the primary goal of the project is to develop an open-source VR that is capable of triggering FOG using various triggers, independent of any testing location, two data collection sites were deemed necessary to achieve this goal while accounting for drop-out effects on the sample size. Thus, to account for a drop-out of 20%, we aim to recruit 20 participants per testing location for a total of 40 participants.

Participant clinical and health assessments

Participants will complete the FOG-Q, Characterising Freezing of Gait Questionnaire, movement disorders society—unified Parkinson's disease rating scale (MDS-UPDRS Motor Subscale (Part III)) and dopaminergic medication dosage will be recorded.[15 37 38] Individuals will be scored by the following FOG-Q criteria: 0—never, 1—about once a month, 2—about once a week, 3—about once a day, 4—whenever walking. Onset of the disease, since medical diagnosis, and length of the disease duration will be recorded.

To assess the general health and neurocognitive ability of each participant, the following health assessments will be administered by the research team: the Parkinson's Disease Questionnaire (PDQ-39), the Hamilton Anxiety Scale (HAS), the Montreal Cognitive Assessment (MOCA) and the trail making tests (TMT) part A–B will be administered.[39–42] Collectively, these tests examine daily quality of life, anxiety, global cognition and attentional set-shifting ability, respectively.

Data collection

At the beginning of data collection, all participants will complete a 1 min baseline walk without a VR head mounted display (VR-HMD) along the walking path at the St. Pölten University of Applied Sciences or University of Exeter gait laboratories. Afterwards, all participants will be presented with a 1 min VR familiarisation phase. On completion, and to mitigate ordering effects on FOG occurrence, participants will be allocated to either the VR non-FOG environment or the VR-FOG environment in a counterbalanced design. After a 1-hour washout period, participants will be presented with the remaining VR condition. Both the VR-FOG and VR non-FOG environments will each last 6 min. The 6 min duration will be selected as this is the standard amount of time used during clinical gait tests.[43–45] For all VR trials, both data collection sites will use the same VR-HMD model, which is a Meta Quest V.3 (Meta, Menlo Park, California) headset. Data collection will occur during the participants 'ON' medicated state as it will more accurately depict their daily lives. The 'ON' medication state will be defined as 30 to 60 min after the last administered dose of the participants' levodopa prescription. This will be confirmed with participants on arrival to the laboratory. Furthermore, to avoid wearing off effects, participants will be instructed to take their medication as prescribed even if the next administration occurs during data collection.

VR familiarisation phase

Since people might have a different experience with VR or no experience at all, all participants will receive an introduction to VR through a tutorial (after the baseline trials), so that they become comfortable using the application. It will consist of a ~1 min navigation in the VR environment that includes a minimal number of triggers (ie, one of each trigger type). During this period, participants will walk in the VR environment to familiarise themselves with the setup. After the VR familiarisation period, participants will proceed to the VR environments specific to their group allocation.

VR non-FOG block

This VR non-FOG environment will last for 6 min. The virtual non-FOG environment will be created based on measurements of the physical dimensions of the real laboratory. It will be calibrated with the HMD coordinate system, so that both worlds match. Specifically, participants will walk within a VR digital copy of the gait laboratory (figure 2) that is scaled to each testing location's laboratory. The walkways will be 12 m long at the St. Pölten University of Applied Sciences laboratory and 10 m long at the University of Exeter. Both walkways will be located at the centre of the real and virtual environments. In line with the open-source nature of the VR tool, the walkway length was not standardised as the goal of the VR-FOG environment is to elicit FOG independently of testing location. Thus, since walkway lengths vary between laboratories and clinics, the VR-FOG environment can be easily scaled to each testing location within this project.

Participants will be instructed when they reach the end of the walkway to turn around and walk back in the opposite direction. In a previous publication, our group developed a to-scale virtual rendition of our laboratory to determine the effects of VR on gait in healthy adults.[46] We expanded and adapted this framework to match the physical dimensions of the laboratory within the St. Pölten University of Applied Sciences and University of Exeter. The VR is designed to be a to-scale virtual representation of the real-world laboratory whereby the VR walking path is aligned with the actual walkway. This VR environment will be used in the non-FOG VR environment. Participants can walk naturally within the VR environment with

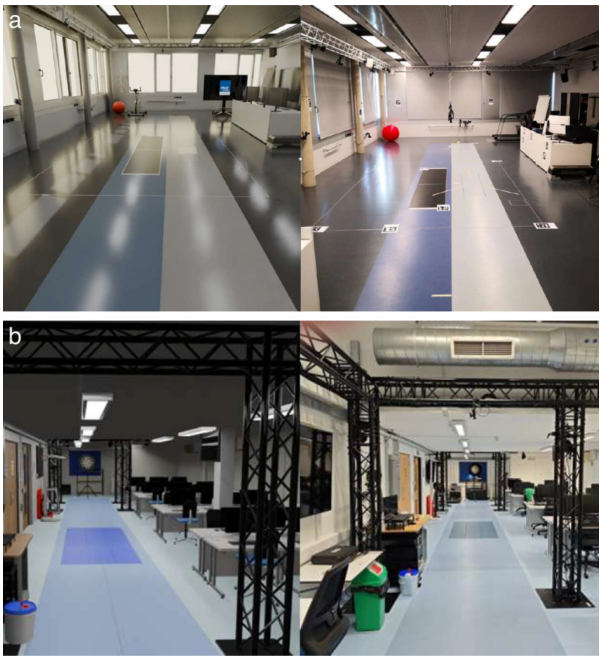

Figure 2 (a) A depiction of the VR lab (left panel), a scaled rendition of the real-world laboratory in Austria (right panel). (b) A depiction of the VR lab (left panel), a scaled rendition of the real-world laboratory in the United Kingdom (right panel). VR, virtual reality.

a first-person view synchronised to their progression in the real-world environment.

Virtual reality-freezing of gait block

This VR-FOG environment (figure 1) will last for 6 min. While wearing a VR-HMD, participants will walk in the real laboratory, which is synchronised to the VR, so that their progression in the VR environment matches their gait in real time. In this block, participants will be presented with the VR-FOG environment as described previously. The start of the virtual hallway is synchronised with the starting point within the real laboratory. Participants will be asked to walk from their starting point to the opposite room at the end of the VR hallway. On reaching the opposite end of the virtual walkway, participants will receive instructions in the VR to turn around and walk back in the opposite direction. Participants will be presented with the aforementioned FOG triggers (previously described in section 2.1) in a random order within the VR-FOG environment. The end of the VR pathway is synchronised with the end of the real laboratory data capturing area.

Primary outcome measures

FOG will be defined as any point when the feet of the participants come to an involuntary stop or when participants ineffectively engage in normal stepping during data collection.[6 7] Throughout data collection, participants will be recorded with a synchronised video camera system of both the participants' frontal and sagittal plane as they walk. Two independent reviewers will visually screen these data to determine the onset and duration of FOG episodes within the trials.[47] In the event of potential differences between the reviewers for FOG occurrence, a third reviewer will be consulted, and the results will be discussed. To avoid bias when rating the FOG episodes, all reviewers will be blinded to the VR conditions. However, as the baseline condition will be conducted without a VR-HMD, reviewers will not be able to be blinded to this condition. Previous research demonstrates this is a valid and reliable method for determining FOG episodes.[47] All reviewers have received previous training in scoring FOG episodes and have extensive experience assessing FOG. The total number of FOG episodes and percentage of time spent frozen will be the primary outcome measures of this project.[27 28 30] The percentage of time spent frozen will be calculated by summing all FOG episodes per condition (baseline, VR non-FOG and VR-FOG) and dividing that by the total time to complete each condition.[27 28 30] These outcome measures will be used to validate VR-FOG. All ambiguous episodes that do not fall under the operational definition of FOG defined earlier will be separately recorded and disseminated during publication as these data are still relevant to researchers and clinicians studying pwPD. Ambiguous episodes will include:

- Festination: the involuntary shortening and hastening of gait.[48 49]
- Start hesitation: when individuals have difficulty initiating gait.[50]
- Shuffling of gait: episodes where the individual slides the feet along the ground instead of lifting the feet for effective stepping.[51]

Secondary outcome measures

Three-dimensional gait analysis

To assess three-dimensional full body motion and capture the biomechanical features of FOG, a Vicon system (Nexus, V.2.14, Vicon, Oxford UK) combined with force plates (AMTI, Watertown, Massachusetts) at 120 Hz and 1200 Hz, respectively, will be used at the St. Pölten University of Applied Sciences while 120 Hz and 1200 Hz will be used at the University of Exeter using an identical motion capture system. Furthermore, both data collection sites will maintain comparable lighting, flooring and environmental conditions to minimise intersite variability (see figure 2). Participants will be outfitted with a full-body marker set using the pyCGM2 (an adaptation of the Conventional Gait Model).[52] Based on our earlier work, raw trajectory and ground reaction force data will be filtered with a fourth order low-pass Butterworth filter with a 10 Hz and 15 Hz cut frequency, respectively.[46 53] Data will be exported to visual 3D (C-Motion, Germantown MD) for reconstruction as a 15-segment full-body model for 3D kinematic and kinetic calculations.[53] The same data processing and analysis procedure will be implemented for all the data collected from both sites.

Clinical examinations

The MDS-UPDRS Motor Subscale (part III) is a standardised tool that will be used to evaluate and track the severity of motor symptoms in our participants.[38] The

MDS-UPDRS Motor Subscale assesses motor symptoms of PD, including tremor, rigidity, bradykinesia, gait and posture, through a standardised physical exam. Each item is rated on a scale from 0 (normal) to 4 (severe), with higher total scores indicating greater motor impairment.[38] Furthermore, the FOG-Q and Characterizing Freezing of Gait Questionnaire (CFOG-Q) will be administered, both of which are self-administered questionnaires, to characterise the frequency, severity and phenotypical expression of FOG in each participant.[15 37] Finally, the Levodopa Equivalent Daily Dosage will be calculated as a standardised metric to quantify the total daily dose of dopaminergic medications in pwPD and is expressed in terms of an equivalent dose of levodopa.[54]

Neurocognitive assessments

Cognitive and neuropsychological function will be assessed with the MOCA, TMT A and B as well as the HAS.[39 42 55 56] The MOCA is a screening tool for evaluating global cognitive function by assessing attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientations.[56] Additionally, we will implement the TMT A and B to evaluate visual attention and task switching in participants. In this test, participants will be instructed to connect 25 dots as fast and as accurately as possible.[39 42] Overall, the TMT assesses visual search speed, scanning, processing speed, mental flexibility and executive function. Finally, the HAS is a 14-item scale that examines psychic and somatic anxiety.[55] All tests are proven to be valid and reliable to evaluate the cognitive and neuropsychological ability in pwPD.

Health-related quality of life

To assess general quality of life, the PDQ-39 will be used. The PDQ-39 is a patient-reported outcome measure designed to assess the impact of PD on quality of life.[57 58] It consists of 39 questions across eight domains: mobility, emotional well-being, social support and communication.[57 58]

Safety measures and adverse events

The measurements conducted in this research are non-invasive and pose no additional risk to the participants compared with what would occur during normal walking in their daily lives. To ensure safety during data collection, all participants will be accompanied by a kinesiologist or physical therapist at all times. Further, due to ethical requirements, participants in Austria will wear a load-tested ceiling harness that will catch participants in an unlikely loss of balance. For the participants tested in the United Kingdom, all participants will be outfitted with a safety belt to ensure safety, allowing the research team to catch participants in the unlikely loss of balance. All adverse events, such as falls and cybersickness, will be recorded and reported in the dissemination. For participants new to VR, a minor possibility exists that cybersickness may arise. However, no issue of cybersickness is anticipated as this typically occurs only in VR environments where the physical acceleration experienced does not match the visual input.[59 60] This is called the sensory conflict model and is not the case for this study.[59 60] Furthermore, participants can self-request rest periods at any time, and the 1-hour wash-out period between VR blocks will provide ample amounts of time for rest.

Statistical analysis

Statistical analyses will be performed in IBM SPSS Statistics V.24 or greater (SPSS, Chicago, Illinois, V.24.0). Data will be checked for statistical assumptions of normality with a Shapiro-Wilks test as well as for kurtosis and skewness. A within-subjects repeated measures ANOVA with three levels (baseline, VR non-FOG, VR-FOG) will be used to assess the data. Pairwise comparisons for post-hocs with a Bonferroni correction will be applied if statistical significance is found.

ETHICS AND DISSEMINATION PLAN

Participants will be recruited between May 2025 and November 2026. All eligible participants who voluntarily agree to participate will be asked to sign a written informed consent form, in line with the declaration of Helsinki. Ethical approval was obtained from the local ethics committee of each testing site (Lower Austria Ethics Committee—GS3-EK-F/933–2024—and the University of Exeter, Department of Public Health and Sport Sciences—8930511). To disseminate this project, the results will be submitted to several open-access and peer-reviewed journals as well as conferences. Specifically, we aim to publish four main themes from the results of this project including: (1) validation of the VR-FOG environment, (2) examination of postural stability when walking with and without VR, (3) examination of gait coordination when walking with and without VR and (4) publication of the participant dataset. Additionally, to reach as broad an audience as possible, the project will be presented on a regular basis through professional workshops and scientific conferences.

All data acquired will only be used in an anonymised form and exclusively for the proposed project purpose. Furthermore, all data will be stored and backed up in secure on-site data repositories that are GDPR compliant.

DISCUSSION

The purpose of this study is to validate the VR-FOG environment with two independent samples of freezers. The novelty of this project, compared with previous FOG triggering methods, is that by using a VR-HMD, it allows for free range overground walking, includes multiple FOG triggers, which covers the breadth of all suggested FOG phenotypes, and the VR progression is adaptive to reduce the likelihood of habituation to the VR triggers. By validating the VR-FOG environment with two independent samples, this project will provide an open-source digital

solution for examining FOG that is independent of testing location.

The crossover design will serve as a robust measure for validating the developed VR-FOG environment by attenuating potential ordering effects of the VR conditions on the frequency and duration of FOG episodes. The particular strength of the crossover design for this research allows for the validation of the VR-FOG with a reduced sample size, thereby increasing the statistical power by controlling for interindividual variability in a heterogeneous demographic. Moreover, by having two data collection sites (St. Pölten University of Applied Sciences and the University of Exeter), this study design will ensure accuracy and validity of the results for the VR-FOG environment, which will be independent of testing location.

However, while the study design provides the aforementioned advantages, it is simultaneously limited by the need for a longer washout period, which increases data collection time and may cause fatigue in the participants by the end of testing. To attenuate effects of fatigue, participants will be allowed to rest whenever they desire, and the 1-hour washout period will serve as a rest period in between the VR conditions. Another limitation of this crossover design is that the baseline condition cannot be counterbalanced. In our study, participants will first complete the baseline condition before exposure to either of the experimental VR conditions (VR non-FOG and VR-FOG). This ordering reduces the risk of learning effects contaminating the baseline data but at the same time introduces an asymmetry in the sequence: only the first exposure is preceded by the baseline condition, whereas subsequent conditions may benefit from participants already being accustomed to the task and environment. As a result, although VR non-FOG and VR-FOG will be counterbalanced (baseline—VR-FOG—VR non-FOG vs baseline—VR non-FOG—VR-FOG), any residual practice effects, habituation or fatigue that extend beyond the initial period may still differentially influence performance in the VR conditions.

We expect that the VR-FOG environment will elicit more FOG episodes and increase the time spent frozen, compared with the other two conditions (baseline and VR non-FOG), as it is the VR-FOG environment that includes multiple FOG triggers. This multitude of virtual FOG triggers will cover the known freezing phenotypes, which are individualistic, thereby encompassing the current spectrum observed across individuals with FOG. As FOG is a complex and heterogeneous motor symptom that is difficult to observe in controlled settings, advancements in the quantification and aetiology of FOG are limited.[6 7 14–16 61] Currently, several theories have been proposed to explain and identify its origin, briefly summarised:

- *Crosstalk theory*: FOG occurs due to conflicting signals between overlapping frontostriatal circuits involved in motor, cognitive and emotional functions.[16 62] This interference overloads the dopamine-depleted striatum, causing synchronised activity of the basal ganglia's output nuclei, which increases inhibition of brainstem locomotor areas.[16 62]
- *Abnormal gait pattern generation:* FOG is triggered when stepping deteriorates from multiple gait malfunctions co-occurring and crossing a critical threshold of dysfunction.[6 7]
- *Problem with central drive and automaticity:* FOG arises from an impairment of the basal ganglia to regulate motor automaticity with insufficient compensation by frontal networks.[6 7]
- *Abnormal coupling of posture with gait:* a decoupling occurs between the upper and lower body causing an ineffective shift of the centre of mass between the legs to engage in effective stepping.[6 7]
- *Perceptual malfunction:* FOG occurs from a malfunction in perceptual processing and integration of environmental sensory information to guide appropriate stepping.[6 7]
- *Frontal executive dysfunction:* FOG stems from a deterioration in executive function, which limits the attentional resources available to compensate for the impaired basal ganglia.[6 7]

For a more detailed description of the prevalent FOG theories, we refer the readers to several prominent literature reviews on the topic.[6 7 14] While the pathophysiology and origin of FOG remain inconclusive, the establishment of its heterogeneity is clear.[6 7 14–16 30 61] Therefore, the VR-FOG environment includes multiple triggers across various FOG phenotypes in an open-source VR platform, to create a valid and reliable method for investigating FOG during freely navigating overground walking in controlled settings. In doing so, this project will provide a major advancement in elucidating this motor phenomenon by creating simulations of real-world FOG triggers.

The design of the VR-FOG environment was based on the known triggers of FOG reported in the current literature.[6 7 13 14 30] The initial designs were subsequently refined with focus groups and an expert panel including neuromechanists, movement disorders specialists, physical therapists and computer scientists. The designs were then tested with a series of user tests and a pilot study to assess feasibility and adverse effects of the VR environments. Additionally, outcome measures were selected as valid metrics to quantify FOG frequency and severity during testing.[30]

This project will further provide a free technical framework for future investigations of specific neurophysiological components underlying FOG. Specifically, by developing phenotype-specific FOG virtual realities, research avenues can be explored for a personalised approach to FOG examination and treatment through non-invasive means. Furthermore, by developing the VR-FOG environment as an open-source software, researchers and clinicians (who may lack the financial resources) would have full access to a validated and readily implementable digital solution to assess the effectiveness of their therapies.

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