Study Protocol

TITLE: Innovative Biofeedback Interface for Enhancing Stroke Gait Rehabilitation

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1. Title

Innovative Biofeedback Interface for Enhancing Stroke Gait Rehabilitation

2. Precis/Abstract:

There is paucity of gait training approaches that target specific deficits, focus practice preferentially on the paretic leg, and capitalize on motor learning principles to optimize walking. Reduced paretic propulsion during terminal stance is an important post-stroke gait deficit that can negatively impact gait speed, inter-limb symmetry, and walking function. Propulsion can be measured using anterior ground reaction forces (AGRF) recorded from a force platform. We have developed an innovative real-time AGRF biofeedback gait training paradigm that targets propulsive deficits preferentially on the paretic leg. Exciting new data from our laboratory demonstrate that AGRF biofeedback training results in improved push-off, trailing limb angle, and step length from the paretic leg, without concomitant changes in the non-paretic leg. However, our current gait biofeedback interface is a simple, 2-dimensional, non-engaging display. Our **objective** is to develop a more engaging, customizable, game-based system specifically designed for post-stroke AGRF biofeedback gait training. Our project will address a major challenge for rehabilitation clinicians - to make gait training enjoyable and meaningful so that patients complete sufficient repetitions, intensity, and challenge to maximize therapeutic effectiveness. "Gamification" refers to use of video game *elements* in non-gaming systems (such as rehabilitation) to improve user engagement and shape user behavior, a goal that resonates strongly with rehabilitation clinicians and scientists. Games provide interactive, real-time, experiential learning facilitated via a computer interface. We propose to develop an AGRF biofeedback gait training game that increases patient motivation and engagement while also distracting participants from fatigue or boredom during training. Augmented reality (AR) game-interfaces add virtual characters and visual effects to real-world experiences, while reducing deleterious effects (disorientation, dizziness) often observed in fully-immersive virtual environments. The popular '*Pokemon Go'* game (2016), is an example of AR. Transformative advancements in hardware, virtual and augmented reality, and mobile computing technologies have led to revolutionary new types of computer interfaces for recreational gaming. However, intuitive and engaging games designed specifically for gait retraining are not currently available in rehabilitation clinics. The project specific aims are: (1) To design a visual effects gaming interface that streams in AGRF data as input variable; (2) Synchronize the gaming interface with AGRF data recorded during treadmill walking to develop a real-time AGRF biofeedback gait training game, including an augmented reality (AR) or virtual reality (VR) game version; (3) To obtain user data from stroke survivors and neuro-rehabilitation clinicians regarding our newly developed real-time AGRF biofeedback gait training game.

3. Introduction and Background:

Stroke is the leading cause of adult disability [1]. Even after discharge from rehabilitation, residual gait deficits are prevalent in stroke survivors, leading to decreased walking speed and endurance [2-6]. Because gait dysfunctions limit community mobility, stroke survivors and rehabilitation clinicians consider restoration of walking a major goal of rehabilitation [7-9]. Biomechanical impairments, such as reduced knee and ankle flexion during swing phase negatively affect gait function and increase the risk for falls[4, 5]. Decreased paretic propulsion during terminal stance is an important gait impairment that has received considerable attention, due to its relationships with swing phase knee flexion, hemiparetic severity, and gait speed [10-14].

Several challenges and research gaps limit the effectiveness of current clinical gait rehabilitation practices. While there is consensus that stroke survivors benefit from gait rehabilitation [15-23], agreement is lacking on which specific training interventions are most efficacious [24-29]. We believe that several challenges and research gaps contribute to this lack of consensus. First, there is a paucity of interventions customized to a stroke survivor's gait deficits, as an alternative to the "one-size-fits-all"

approach. Second, most gait training techniques provide concurrent stepping practice to both legs, likely encouraging compensations from the non-paretic leg. Very few interventions provide targeted practice of biomechanically appropriate movement patterns exclusively or preferentially to the paretic leg. Third, although thousands of steps of walking practice are needed to induce long-term improvements in post-stroke gait [30-33], the number of steps of walking practice provided during clinical and research interventions is remarkably low[34]. Fourth, to enhance neuroplasticity and motor learning, there is a need to increase patient engagement, motivation, and salience during training[32, 33]. Fifth, the progressively limited time for therapy during a clinical rehabilitation session requires the need to maximize the potential therapeutic effectiveness of each minute of out-patient rehabilitation, as well as improve strategies for home-based exercise prescription. The long-term goal of this proposal is to address these challenges by developing personalized, engaging, salient gait training treatments founded on evidence from neuroscience, biomechanics, motor learning, and gaming.

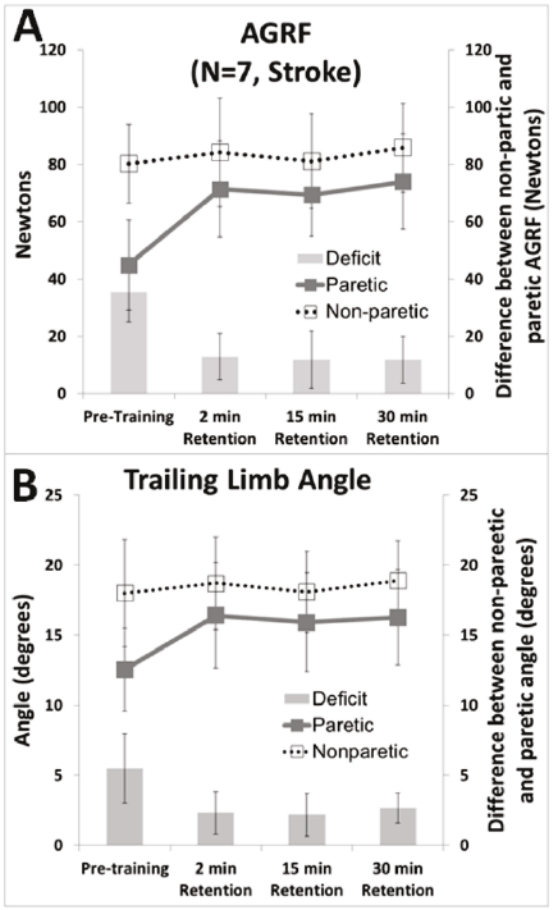

Figure 1. Real-time AGRF biofeedback improves paretic AGRF and trailing limb angle in individuals post-stroke. Peak AGRF (A) and trailing limb angle (B) for paretic and non-paretic leg (line plots) and their deficits (difference between non-paretic and paretic values, barplots). (A) The one-way ANOVA and post-hoc comparisons showed a significant increase in paretic AGRF, and significant reduction in AGRF deficit after biofeedback training (F=29.852, p<.001). (B) The one-way ANOVA for paretic peak trailing limb angle showed a main effect of time (F=4.111, p=0.022). No change in nonparetic AGRF or trailing limb angle observed with biofeedback training (p> 0.153).

Real-time biofeedback is a promising gait training intervention for targeting specific biomechanical impairments. Biofeedback can enhance an individual's awareness of the impairment targeted during gait training, enabling self-correction of aberrant gait patterns [35].Real-time biofeedback gait training has been used for modulating step length asymmetry in people post-stroke [36, 37]. Franz et. al. demonstrated that older adults increase AGRF and gait speed in a single session of biofeedback training [38]. We recently showed that in response to treadmill training combined with visual and auditory real-time biofeedback, able-bodied individuals can increase AGRF unilaterally for the targeted limb[39]. Thus, AGRF biofeedback may be a beneficial strategy to target unilateral propulsive deficits in people post-stroke. Yet, surprisingly, this approach has never been explored for stroke gait training (see our preliminary stroke data in Figure 1).

Incorporation of gaming interfaces for gait biofeedback can increase patient motivation, distract participants from fatigue or boredom, and encourage greater numbers of repetitions during gait training. "Gamification" is an informal umbrella term for the use of video game elements in non-gaming systems (such as rehabilitation) to improve user engagement and shape user behavior, a goal that resonates strongly with rehabilitation clinicians and scientists [40-42]. Researchers exploring human computer interaction aim to identify design patterns that can afford joy of use [43]. Games are designed to be more interesting and enjoyable than traditional therapy tasks, thereby encouraging higher numbers of repetitions [44-47]. Games use cues to provide accurate and immediate biofeedback about movement performance, reward desirable performance, and discourage maladaptive compensations to change behavior, while also being

engaging and motivating [45, 48-50]. Games can be personalized to each client by modifying task-difficulty according to baseline impairments, and designing task-specific programs that are meaningful to the patient, considerations that increase motor learning [46, 47, 49, 50]. Games can provide opportunity to practice activities that may not be safe within the clinical environment [44-46]. Furthermore, augmented reality (AR) is a cutting-edge gaming tool comprising an interactive visualization system (head-mounted display, computer, game console, tablet) allowing the merging of digital contents with the user's real-world environment [51]. AR allows the augmentation of our real experience using gaming-interfaces, while reducing deleterious effects (disorientation, nausea, dizziness) often observed in fully immersive virtual environments [51, 52]. From the perspective of rehabilitation clinicians, game-based therapies provide immediate, quantitative feedback about patient performance and allow for adjustment of the challenge during therapy [44-46, 49, 50]. Recreational gaming consoles are ubiquitously enjoyed by individuals of all age groups, and could have immense potential for stroke rehabilitation.

Rehabilitation studies suggest that adding video games to a conventional rehabilitation intervention can enhance therapeutic benefits, patient enjoyment and motivation. The addition of a Nintendo Wii video game to an already familiar task of treadmill walking or cycling can increase exercise intensity (heart rate, cadence, speed) during training [48, 53]. Compared to balance platform therapy, video game therapy induced superior improvements in mobility, selective attention, and balance in people with chronic traumatic brain injury [54]. In frail, community-dwelling older adults, dynamic balance exercises on fixed and compliant surfaces were feasibly coupled to interactive game-based exercise, resulting in improvements in balance control [55]. Off-the-shelf video game systems such as the Nintendo Wii [56, 57] and Kinect [58] have been used for therapy, and shown to increase enjoyment during rehabilitation in individuals with disabilities. When video games were used for upper limb rehabilitation, users stated that the game made rehabilitation more fun and helped achieve greater exercise intensity [58]. **Neurologically-impaired patients deserve, and may, in due course, demand, high-quality entertaining gaming-interfaces as part of their rehabilitation. Regrettably, specialized game-based tools that focus training on specific gait deficits are not available in rehabilitation clinics [44, 45]. However, the transformative technologies already available to game-developers and computer scientists provide an unprecedented opportunity to target this important and unmet clinical need.**

Our previous [39] and ongoing AGRF biofeedback studies, although successful, utilized a biofeedback visual interface that was simple, 2-dimensional, and not enjoyable (Figure 2)[39]. Therefore, in parallel, we initiated development of a visual interface for gait biofeedback, and developed the first visual effect game prototype/simulation that inputs/streams AGRF data (Figure 3). This project will conduct a preliminary study to test the feasibility and short-term effects of game-based biofeedback, and obtain user-data regarding the innovative gait-game design.

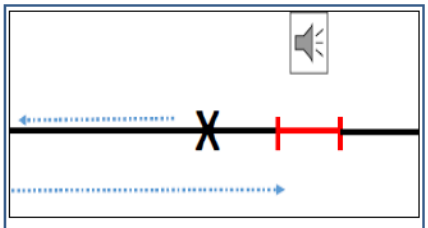

Figure 2. Schematic showing the simple, non-game-based display currently used for AGRF biofeedback. (X) indicates the current antero-posterior GRF during the stride cycle, the bar indicates the target AGRF value. Visual feedback provides user an estimate of proximity to target AGRF. Auditory feedback indicates successful AGRF targeting.

See video S1 within this manuscript:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5460355/

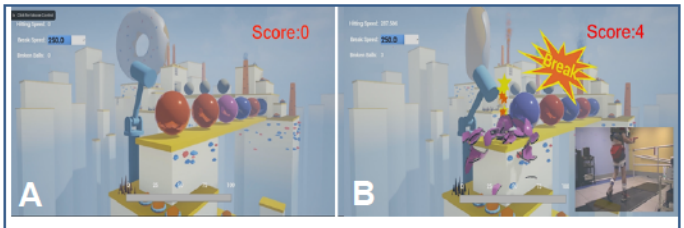

Figure 3: Screenshot from the prototype visual effects animation (Candy Cracking Game) developed by SCAD in collaboration with PI Kesar. (A) Candy balls move along a conveyor belt (. A hammer elevates and strikes the candy ball (once per gait cycle) in timing with generation of pushoff. (B) When the generated AGRF matches the targeted AGRF (successful increase of AGRF in response to biofeedback), the hammer breaks the candy ball, rewarding the user with visual effects and an increased game score. See supplementary video file or weblink below for this prototype animation.

http://ecollections.scad.edu/iii/cpro/DigitalItemViewPage.external?lang=eng&sp=1003554&sp=T&sp=Pall%2CRk1000005%40%2CQdeborah+fowler&suite=def

4. Objectives and Specific Aims

Our long-term **goal** is to develop a more engaging, motivating gait biofeedback methodologies specifically designed for post-stroke gait training. We aim to address a major challenge for rehabilitation clinicians - to make gait training appealing and meaningful so that patients engage in sufficient repetitions, intensity, and challenge to maximize therapeutic effectiveness. Our *premise* is that post-stroke individuals will demonstrate greater engagement, motivation, and therapeutic benefits during gait training sessions involving biofeedback when training incorporates intuitive, entertaining, game-based interfaces.

Our project specific aims are:

Aim 1. To design a gaming interface that streams in AGRF data as input variable. Dr. Fowler, a visual effects professor from Savannah College of Arts and Design (SCAD) will lead this aim. Tasks for aim 1 include: (i) customize game to match user interests and goals (enhance salience during practice), (ii) develop scoring system to provide knowledge of performance; (iii) provide meaningful rewards within the game; and (iv) add challenge levels to cater to variability in gait impairments across-individuals and time.

Aim 2. Synchronize the gaming interface with AGRF data recorded during treadmill walking to develop a real-time AGRF biofeedback gait training game, including an augmented reality (AR) game version. Dr. Gandy Coleman, a computer scientist at Georgia Tech, will work with the P.I. toward this development aim. Tasks for aim 2 include: (i) develop custom software to synchronize the game display with AGRF data in real-time; (ii) develop an AR version of the game; (iii) confirm that game animations are synchronized with a user's gait cycle; and, (iv) create patient reports about gait performance during training (for use by clinicians).

Aim 3. To obtain user data from stroke survivors and neuro-rehabilitation clinicians regarding our newly developed real-time AGRF biofeedback gait training game. Drs. Kesar and Wolf, stroke gait rehabilitation experts at Emory University will complete this aim. The game will be tested on 12 individuals with chronic post-stroke hemiparesis and 5 neuro-rehabilitation clinicians. Participants will complete 1-2 sessions comprising exposure to 2-3 gait biofeedback systems: (i) newly developed game-based interface (projector screen display), (ii) traditional, non-game interface, and (iii) VR version of the game (head-mounted display). Outcomes will include measures of participant engagement, user-reports and survey-responses on motivation, gait performance, fatigue, game characteristics, and adverse effects (e.g. nausea, dizziness) during game exposure.

Study Hypotheses

Aims 1 and 2 are focused on design and development of the gait biofeedback gaming interface. Aim 3 is a small-sample clinical trial evaluating the newly development biofeedback game. For Aim 3, we *hypothesize* that compared to the traditional non-game biofeedback, game-based biofeedback will induce greater improvements in paretic leg biomechanics, improve participant motivation and engagement, reduce fatigue, without significant adverse effects.

5. Study design and methods

Our 2-year project comprises aims related to the design and development phase (aims 1 and 2) and testing phase (aim 3) for an innovative, game-based, gait biofeedback system. The overview, timeline, and potential future directions for the proposal are provided in Figure 4.

The study will comprise 2 phases:

Phase 1 will include the design and development of the game. For study phase 1, the P.I. will work with collaborators at Savannah College of Art and Design (SCAD) and Georgia Institute of Technology to develop the software interface (visual display and graphics) and the hardware instrumentation for the gait biofeedback game system. During the later stage of phase 1, preliminary feedback about the game design will be obtained from 10 stroke survivors and 5 able-bodied individuals.

Phase 2 will include the preliminary testing of the game-based feedback in comparison with a non-game-based feedback during treadmill walking training. During phase 2, study participants will complete 1-2 experimental sessions comprising exposure to 2-3 types of gait biofeedback interfaces. User-feedback regarding engagement, fatigue, design will be obtained from 5 able-bodied individuals, 12 stroke survivors, as well as 8 neuro-rehabilitation clinicians. The protocol and experimental conditions for phase 2 may be influenced by the progress and feasibility testing during phase 1.

Research Procedures

Aim 1. To design a gaming interface that streams in AGRF data as input variable

Methods and sub-tasks for Aim 1: Game design is the art of applying design and aesthetics to create a game that allows interaction with the user. Our goal is to develop an interface that provides an entertaining and engaging experience for stroke survivors, motivates them with positive feedback toward correct gait patterns, while being easy to play and learn. The game must also allow the therapist /user to adjust the game difficulty. Dr. Fowler's team, as part of an ongoing collaboration with the P.I. Kesar, has developed a prototype for a visual effects game designed for gait biofeedback. The current prototype (candy-cracking game) provides the advantage of high-definition graphical display (Figure 3), in contrast to a simple, boring, and non-intuitive display currently available for biofeedback (Figure 2). The engaging visual effects animation involves candy balls that move rhythmically across a moving conveyor belt (to match the rhythmicity of gait cycles), with a hammer that elevates and strikes each

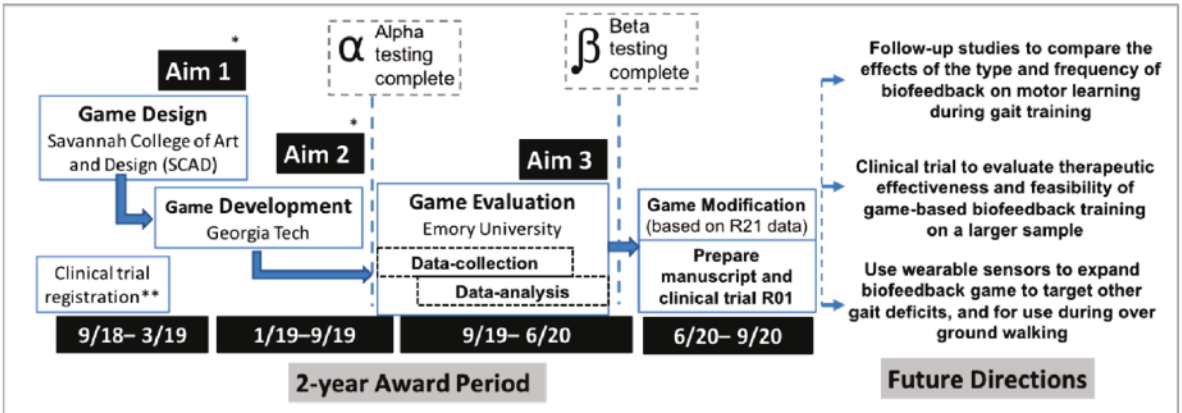

Figure 4. Timeline and future directions for the R21 proposal

**Game design and game development will occur in an overlapping timeline*

**Clinical trial registration procedures will be completed during the 1st 3 months of project onset

candy ball (to match the push-off force generation during terminal stance phase of gait) (Figure 3). The prototype animation uses AGRF data stream (recorded from the right leg during treadmill walking) as input. When the generated AGRF force exceeds the target threshold, the hammer strikes the candy and crushes it (indicator of success). Thus, the current visual effects game prototype is entertaining, game-based, and customized to match the rhythmic, repetitive movements during walking. However, several additions and enhancements are needed in the current design, as listed in table below.

Sub-tasks for Specific Aim 1	
(i) Game customization/individualization	**(ii) Game scoring system for providing knowledge of performance**
Develop game versions or themes for different interests/hobbies E.g. golf, gardening. Star Wars	Score reflects cumulative % success (steps with target AGRF achieved) Determine score metrics, and dosage/frequency of display (faded feedback)
(iii) Game Rewards	**(iv) Game challenge levels**
For successful steps, develop visual & auditory reward e.g. sparks fly out from ball, pictures of grandchildren/family	Develop provision for clinician to calibrate error-tolerance, target AGRF Develop game levels for advancing complexity/challenge as training progresses

Summary of the design process (Aim 1): The design will focus on achieving the above sub-tasks. Fundamental principles of game design will be followed, including, but not limited to: focal point, anticipation, consequence of actions, believable events and behaviors, progression, environment, spacing, appeal (graphics/sound). Dr. Fowler's design team at SCAD will comprise design students from Visual Effects, Games, User Experience, and Sound Design. The current candy cracking game prototype was implemented in Unreal Engine. For the AR version, other platforms (HoloLens or Apple ARKit) will be explored, which will also facilitate development of the AR version in aim 2.

User-evaluation of Aim 1: The pivotal point to this proposed design will be to attain a prototype that can be given to users (stroke survivors and physical therapists) so that feedback from users can contribute to game development. As part of Aim 1, we will obtain iterative user feedback (i.e., play-testing) about the game design from our investigative team, 10 stroke survivors, and 5 neuro-rehabilitation clinicians. Consistent with the gaming-literature, user-interview questionnaires and user observations will be employed iteratively to guide game development[58].

Aim 2. Synchronize the gaming interface with GRF data recorded during treadmill walking to develop a real-time AGRF biofeedback gait training game, including an augmented reality (AR) game version.

Methods and sub-tasks for Aim 2: Dr. Gandy-Coleman, a computer scientist at Georgia Institute of Technology, will work in conjunction with the P.I. to accomplish this aim. Dr. Gandy has published studies on game-design for older adults, and the psychosocial, socio-economic[59], and cognitive factors influencing game use by older adults[59, 60]. Dr. Gandy's team also developed an interactive video game for upper limb rehabilitation targeted for stroke survivors[61].

The visual effects interface designed by the SCAD team (Aim 1) will use GRF data as input for the timing of animations in the visual effects game. The current prototype visual effect (Figure 3) is a standalone video file untethered to gait hardware. As part of Aim 2, we will develop the technological solutions needed to synchronize the visual effects interface with real-time GRF data recorded during treadmill walking. To accomplish this aim, Dr. Gandy Coleman and her team at Georgia Institute of Technology will develop a custom real-time biofeedback software program to enable integration of the visual effects animation with gait laboratory hardware (i.e. analog data derived from a force platform). Dr. Coleman's team will conduct pilot tests at P.I. Kesar's motion analysis laboratory. Anterior-posterior GRF analog data recorded from the force platform under the right leg will be streamed into the custom real-time biofeedback software platform developed by Dr. Gandy Coleman's team. The biofeedback software program will input the AGRF data to the visual effects software. Our sub-goals for Aim 2 are listed in table below:

Sub-tasks for Specific Aim 2	
(i) Synchronization and Software Development - Develop custom software program to synchronize game interface with AGRF data recorded during treadmill walking - This task will culminate in a game version that will be projected on a 2D display screen during treadmill walking (non-AR)	**(ii) Develop augmented reality (AR) game version** - Use head-mounted display to superimpose simplified/minimized version of game onto user's real-world view - Two game versions (AR and non-AR) can cater to different patient preferences - Helps expand game applications to over-ground, clinical, community settings
(iii) Game pilot testing Test (N=5 able-bodied subjects) to confirm that the timing of game animations synchronize with a user's gait cycle	**(iv) Develop patient report (training session summary for clinicians)** - Develop training report to summarize pre- and post-session values of gait variables (e.g. AGRF, trailing limb angle, step length) for paretic and non-paretic leg - Will aid clinicians with documenting training effetcs, planning training progression

Summary of development process: Dr. Gandy Coleman, in conjunction with 2 computer scientists in her team, will lead the technology development. The teams will meet biweekly during the development phase (SCAD team will skype in). Aim 2 will culminate in the development of 2 versions of the game – (i) a game version that will be projected on a 2-dimensional (2D) display screen in front of the treadmill during gait training (projector-display); and (ii) a game version that will utilize AR technology to superimpose a simplified/minimized version of the game animation objects and effects onto the user's real-world view (head-mounted AR display). We believe that the AR version will expand the potential clinical applications of the game, and facilitate translation to over ground, clinical, and community-based settings. Additionally, having AR and non-AR (projector display) game versions can better cater to varied user preferences.

User-testing as part of Aim 2: Game pilot testing will be performed on 5 able-bodied individuals in the P.I.'s laboratory at Emory. The users will provide scores on a 10-point scale rating the game's accuracy, entertainment, and quality of feedback. The users will also provide comments about whether the game animation matched the motion of their targeted leg, whether the timing of the hammer striking the candy ball matched the timing of the target leg's push-off generation. Our goal is to minimize the perceptible lag between AGRF generation by the targeted leg and the timing of the pertinent visual effect animation. We will also develop the training report to summarize the values of pertinent gait biomechanics variables (AGRF, trailing limb angle, step length, circumduction) for the paretic and non-paretic leg before and after each training session. The patient report will guide therapist's decisions related to determining the dosage, challenge, and progression of subsequent training sessions, as well as aid with clinical documentation.

Specific Aim 3. To obtain user data from stroke survivors and neuro-rehabilitation clinicians regarding our newly developed real-time AGRF biofeedback gait training game.

Aim 3 will focus on evaluating the newly developed AGRF biofeedback game (both AR and non-AR versions).

Methods for evaluation on stroke survivors: The newly developed games will be tested on 12 individuals with chronic post-stroke hemiparesis and 12 able-bodied adults. Inclusion criteria for stroke participants will include ≥6-months elapsed since a cortical or subcortical stroke, ability to walk on a treadmill for ≥2-minutes, ability to communicate with study team, stroke affecting the right leg (to match control participants' biofeedback targeted leg and due to constraints with the game design prototype). Exclusion criteria include orthopedic or neurological conditions preventing walking, neurologic diagnosis other than stroke, cerebellar signs, and cognitive impairments preventing communication during the experiment[62]. Inclusion criteria for able-bodied will be ability to walk, and absence of orthopedic, neurological, or medical conditions that limit walking. Our proposed sample size is based on our studies (N=7 stroke, N=7 able-bodied) where we detected significant increase in targeted leg peak AGRF with power ≥0.80, with additional participants included to account for the self-report and survey-based game-evaluation outcomes.

Study participants will complete one session comprising exposure to gait biofeedback systems in an order determined by block randomization (3 blocks). Participants will be exposed to 2-3 types of biofeedback interfaces – (i) the AGRF biofeedback game (projector-display, non-VR), and the (ii) traditional, non-game-based, interface (currently used, shown in Figure 2). If we cannot test all 3 gait feedback conditions in 1 session, participants may be asked to complete a 2nd experimental session when 2-3 feedback conditions (and control walk) will be evaluated. In a separate session, some participants may complete preliminary or exploratory testing of the VR version of the biofeedback game (head-mounted AR or VR display), which will be used to determine feasibility and preliminary effects of VR-based feedback on gait. The participants will be exposed to each of the 2 types of biofeedback for a matched duration (2 to 6-minutes). Kinematic and GRF data will be collected as participants walk on a split-belt instrumented treadmill at a self-selected speed. Consistent with our preliminary stroke biofeedback studies, target AGRF will be calculated as 10-20% above the *paretic AGRF*. The same % target value for paretic AGRF will be used for all 3 types of biofeedback (i.e. similar challenge level). At the start of each walking task, participants will be provided scripted, verbal instructions regarding the training task (i.e. generate greater push-off force with the paretic leg) and the biofeedback interface (i.e. how the game works). Participant will be told to complete the biofeedback task for as many minutes as possible without a break. Participants can request a break during the biofeedback, as needed. During and after completion of the gait evaluation session, we may obtain outcomes as listed in the table. To assess participant engagement during each biofeedback bout, we may use 2 published scales – the Hopkins Rehabilitation Engagement Rating Scale [63] and the Pittsburgh rehabilitation participation scale [64]. We will also ask the participant to self-report on how much fatigue and engagement they felt while walking with each feedback interface, using a Likert scale, a user-experience questionnaire, and/or a NASA-task load index (NASA-TLX) scale. Qualitative comments or feedback will also be gathered. Sex and age as biological variables may influence these outcomes, and will be addressed in our study design.

Outcome variables for Aim 3	
Participant engagement during biofeedback	Hopkins rehabilitation engagement rating scale Pittsburgh rehabilitation participation scale
Motivation, boredom, and fatigue	10-point visual analog scale Open-ended, non-leading survey questions
Successful completion of targeted training task	Evaluate success rate (%steps for which target paretic AGRF was achieved)
Feedback about user experience and game (game ease-of-use, game aesthetics, challenge, ability to understand the game instructions)	10-point scale self-reports Open-ended, non-leading survey questions
Adverse effects or events	Nausea, dizziness, other negative responses

Methods for additional evaluation on neuro-rehabilitation clinicians: We may obtain feedback from 5 clinicians specializing in neuro-rehabilitation, and with ≥2 years clinical experience. The clinicians will participate in 1-2 sessions comprising exposure to the 2-3 biofeedback systems (similar to above). At the end of the session, we will demonstrate to the clinicians how the game can be calibrated for each patient by modifying the target, challenge, and sensitivity. We will obtain self-report scores and questionnaire responses regarding game ease-of-use, technological complexity, customization, game aesthetics, and potential challenges limiting clinical use. Additionally, we may obtain clinicians' feedback about the format and comprehensibility of a gait metric report.

Detailed study procedures related to specific measurements are listed below.

1) Procedures for Clinical Assessment of Walking Function:

All subjects will review and sign consent forms before clinical testing. Clinical testing will be used to obtain the demographic and clinical characteristics of the study participants. Clinical testing may comprise all or a subset of the following: (1) measurement of subjects'

over ground self-selected walking speed (10-meter walk test) at self-selected (SS) and fast speeds; (2) over ground walking endurance measured by the distance ambulated during the 2-minute (for post-stroke individuals who are unable to walk for 6-minutes) or 6-minute walk test; (3) assessment of static and dynamic balance (measured using the dynamic gait index and the Berg balance score); (4) lower extremity portion of the Fugl-Meyer score[65]; (5) step activity monitoring; (6) lower extremity proprioception (in which each limb segment will be flexed or extended approximately 10 degrees and the subject will be asked to identify whether the limb is moving and in what direction); (7) Lower extremity sensation utilizing monofilaments. For monofilament testing, each limb segment will be tested and the smallest diameter filament that can be felt reliably (4 out 5 trials) will be recorded. Additional clinical measures may include measures of cognitive impairments and self-reports (e.g. Stroke Impact Scale, Walk-12 questionnaire, Activity-specific Balance Confidence Scale, reports of physical activity levels). All these measurements will provide a characterization of the severity of subject's gait function and gait impairments. For able-bodied subjects, the clinical testing may not be performed or may only comprise a subset of the outcomes listed above.

In addition, during this session, after completion of clinical testing, ***assessment of muscle strength*** and range of motion testing may be performed using standard clinical procedures for bilateral ankle and hip extensor and flexor muscles.

2) Procedures for Gait Analysis during game-evaluation:

Each participant will participate in 1 to 3 gait analysis sessions. All gait analysis and training procedures will be performed in the Motion Analysis Laboratory at Emory's Rehabilitation Hospital. The lab is equipped with a 7-camera motion analysis system and a split-belt treadmill. The participants will walk on a split-belt treadmill instrumented with force platforms within each belt. For stroke survivors, to ensure safety, subjects will be able to hold on to a handrail as well as wear a harness supported from an overhead beam during treadmill walking. For additional safety, a physical therapist will be present during the session(s) and (if needed) will guard the subject during walking. For able-bodied individuals, either the left or right leg will be the targeted leg during testing and biofeedback training. For stroke participants, the leg affected by the stroke (paretic leg) will be the targeted leg during biofeedback training. The procedures during the gait session(s) are listed below in chronological order.

(i) **Subject setup:** To setup for motion analysis, we will attach biomechanical retroreflective markers to participant's bilateral hip, knee, ankle, and foot segments as well as the pelvis and trunk segments. The materials and procedures used for marker setup will be similar to ongoing study protocols in our lab and our previous publications. Motion analysis procedures are described in detail in the next section.

(ii) **Subject familiarization**: Next, the subject will be familiarized to the laboratory setup and treadmill walking at a slow speed

(iii) **Determination of treadmill speeds:** We will determine the participant's comfortable self-selected (SS) and fastest comfortable (Fast) treadmill walking speeds during short 30-second walking trials, with standing rest breaks interspersed.

(iv) **Collection of baseline gait data:** Baseline motion analysis data (marker positions using the 7-camera system and ground reaction forces using the treadmill-embedded force platforms) will be collected as the participant completes short (10 to 30-second) treadmill walking trials at 2-7 different walking speeds (ranging from SS speed to the Fast speed). These trials will provide information about the subject's capacity for safe speed-modulation as well as the peak AGRFs and other biomechanical parameters at each speed for the paretic and non-paretic legs.

(v) **Calculation of AGRF and speed modulation ranges:** Next, while the participant is provided a rest break, the experimenters will calculate the participant's minimum and maximum peak AGRF to be used as a target AGRF during biofeedback for the study. The minimum AGRF (AGRFmin) will be set as the AGRF generated at the SS speed. The maximum AGRF (AGRFmax) will be set as approximately 25% greater than the AGRF generated at the Fast speed. The SS and Fast speeds determined and evaluated in step (iv) above will be used as the minimum and maximum speeds for the study. By setting these lower and upper limits for speed and AGRF parameters using each participant's baseline walking trials, we will ensure that the biofeedback procedures use safe parameters customized to each participant's walking capacity.

(vi) **Collection of short (30-60 seconds) gait trials to obtain data for game calibration:** After providing the participant a seated or standing break (as requested), we will conduct 5-10 short gait trials (30-120 seconds). These data will be used to calibrate the internal settings for the gait-game and obtain estimates of the appropriate AGRF target.

(vii) **Collection of two to three 2-6 minute biofeedback training bouts comprising exposure to the gait-game interfaces:** During this part of the session, 2 types of AGRF biofeedback training bouts (2-6 minutes long) will be implemented (bout order randomized across participants). The bouts will involve exposure to each of the 2 types of gait biofeedback interfaces – conventional feedback and game-based feedback.

(viii) **Collection of post-training and retention gait data:** Before (pre), during, and immediately after (post) each of the biofeedback bouts (as well as control bout without feedback), gait biomechanics may be recorded during short 30-second trials at SS and/or Fast speeds. To measure short-term retention or recall of motor learning, additional post-tests may be recorded after a 2-minute standing break. Self-reported measures of exertion, engagement, fatigue may also be obtained for each bout.

(ix) **Collection of self-report data regarding engagement, adverse effects, challenge, muscle soreness/fatigue during biofeedback:** In order to evaluate the feasibility and subject perceptions in response to biofeedback training, we may ask the participant to rate their engagement or motivation, level of challenge encountered during biofeedback, and amount of fatigue on a 0 to 10 visual analog scale. Any other feedback, comments, and adverse effects reported by the subject will also be recorded.

3) ***Procedures for gait biofeedback:*** During biofeedback, auditory and visual biofeedback will be provided using a visual display screen and a speaker pointed

toward the participant. The visual feedback display will vary according to the type of biofeedback interface being evaluated. For the traditional non-game biofeedback, the visual display comprises a horizontal line graph with a moveable cursor that represents the current measured value of antero-posterior ground reaction force for the targeted leg (The MotionMonitor, Innovative Sports Training Inc., Illinois, USA). The targeted peak AGRF range appears as a target line with vertical bars on either end, representing a 6-Newton error-tolerance range centered around the target AGRF[39]. The auditory feedback comprises an audible "beep" produced every time the cursor entered the target range, i.e. the participant achieves the targeted peak GRF value during their gait cycle[39, 66]. This same AGRF biofeedback audio-visual system has been successfully used in previous studies in both able-bodied and stroke survivors, showing the feasibility of the biofeedback setup[39, 66]. For game-based biofeedback, the newly-developed game-based interfaces will be used. The game-based biofeedback may be displayed on a projected screen or with VR goggles.

4) ***Subject safety and monitoring during gait testing:*** During the treadmill walking, stroke subjects will wear a harness suspended from the ceiling (no body-weight support) for safety. In addition, if needed, the stroke subjects will be allowed to hold on to the hand rails during walking. Heart rate, Borg rate of perceived exertion, and blood pressure will be recorded at baseline. Additionally, heart rate will be monitored throughout the session with a heart rate sensor that is placed on the chest under clothing (Polar USA, Lake Success, NY). If heart rate exceeds 80% of the age predicted heart rate maximum, walking will be stopped until it returns to baseline. In addition, blood pressure will be monitored at each rest break. If a subject's blood pressure exceeds 190/100 mmHg, the session will be stopped and their blood pressure will be continually monitored until it returns to baseline. We may also measure skin resistance using a small sensor wrapped around the finger. Subject's rating of perceived exertion on the Borg Scale of Perceived Exertion will also be monitored intermittently throughout the session. If a subject reaches level 16 on the Borg scale or appear too tired, they will be given a rest break[67].

5) Procedures for Motion Analysis:

As stated above, retro-reflective markers will be attached to the subjects' lower extremities[68, 69]. Elastic bands (Fabrifoam, USA) will be wrapped around the thighs, calves and pelvis to which small, thermoplastic shells containing reflective markers will be attached. Additional markers will be taped to the subjects' shoes and on the upper back, shoulder, hip, knee, and ankle joints with adhesive skin tape. Marker data will be collected using a 7-camera motion analyses system (Vicon, Oxford, UK). We may also attach non-reflective adhesive markers to a few anatomical locations. During treadmill walking, ground reaction forces during treadmill walking will be collected using a treadmill instrumented with two 6-component force platforms under each belt (Bertec, USA). During over ground walking, ground reaction forces will be collected using a force plate embedded within the lab floor (AMTI, USA). In addition, in order to record muscle activity, small electromyography (EMG) sensors may be attached to various muscles. The EMG sensors will be attached using hypo-allergenic adhesive. EMG signals may be recorded from the following muscles: tibialis anterior, soleus, gastrocnemius,

quadriceps femoris, hamstrings, gluteus medius, and erector spinae. All analog data (force platform, EMG, footswitch, and stimulation channels) will be collected at 2400-Hz.

In addition to the walking trials described above, motion analysis data may be collected during 1- to 10-second long static postures (standing and sitting). During treadmill walking, subjects will wear a ceiling-mounted safety harness during all trials. An emergency shut-off switch will be positioned within arm's reach of the experimenter and can be used at any time by the experimenter to stop the treadmill. Subjects will be allowed rest breaks as often as requested. Similar to the described above, subjects' heart rate, perceived exertion, and blood pressure will be monitored during the session.

Risks

Risks associated with clinical testing, gait training, and motion analyses include falling, fatigue, poor heart rate and blood pressure response to walking and minor skin irritation from the adhesive tape. To minimize risk, subjects will wear a safety harness during the treadmill testing and will be given a rest break whenever requested. Heart rate will be monitored continuously and blood pressure will be monitored at rest breaks. Throughout the experiment, the experimenter has access to an emergency safety switch that can be used to stop the treadmill immediately.

Risks associated with gait biofeedback: The safety, feasibility, and effects of AGRF biofeedback have been evaluated in able-bodied and post-stroke individuals[39, 66]. Here, we evaluate the short-term effects of a short, 2 to 6-minute AGRF biofeedback bouts with different biofeedback interfaces. The speed ranges (SS and Fast) and AGRF ranges (AGRFmin and AGRFmax) will be planned using each individual's own baseline walking data, making them customized to their own walking capacity. Potential risks during biofeedback bout training may be similar to those encountered during strenuous exercise – tiredness, muscle fatigue, muscle soreness, and potential for joint discomfort. Potential risks from the VR versions of the game include dizziness, nausea, and sense of disorientation.

Potential Benefits

These procedures are experimental, and the responses of individual subjects to the gait training sessions may vary widely. We do not anticipate that the participants will gain any benefits from study participation. The long-term findings of this study can help us better understand the effects of and guide the design of clinical gait rehabilitation which can benefit other stroke survivors in the future.

Type of Information Collected

During clinical testing, to help characterize the clinical characteristics of the subject group, information such as age, time since the stroke, height, weight, side of hemiparesis, etc. will be collected. To help characterize the level of impairment of the subject group, information such as walking speed, endurance, walking function score, lower extremity sensation, etc. will be collected. During motion analysis and gait training, the 3-dimensional camera system will be used to track the 3-D positions of the subject's segments; these data will be used to compute joint angles, ground reaction forces, joint moments, joint powers, etc. All subject data will be de-identified and then compiled on an excel spreadsheet and imported into SPSS 21 (SPSS,

Chicago, IL) for statistical analysis. De-identified data will be disseminated through group discussions, presentations and publications.

Management of Subject Data
Subjects will not be anonymous to the researchers. As a first step during data management, subject identities will be de-identified by assigning each subject a number. Any computer files containing information that link the identifiable subject data with the de-identified subject number will be password protected and stored on a secure Emory University computer. Only de-identified data will be used to compile spreadsheets of the various outcome measures collected as part of this study (joint angles, clinical impairment scores, EMG, etc.). De-identified data may be stored for future use until 5-years after completion of the study. All signed consent forms will be stored in the subject's folder (organized by de-identified subject numbers) in a locked file cabinet at the University. Participants will not be audiotaped, photographed or videotaped without their permission during this study.

6. Participant selection

For Aim 1 and 2, for preliminary testing of the game design and to get user-feedback on game usability, we plan to collect user-survey and feedback data on 10 stroke survivors and 10 able-bodied individuals. For Aim 3, which is the clinical trial portion of the project, we plan to collect data on a sample of 12 individuals post-stroke and 8 able-bodied neurorehabilitation clinicians.

Inclusion Criteria for Post-Stroke Subjects are: 1) age 30-90 years, 2) chronic stroke (>6 months post stroke) affecting the left leg, 3) ambulatory with or without the use of a cane or walker, 4) able to walk for 2 minutes at the self-selected speed without an orthoses, 5) resting heart rate 40-100 beats per minute.

Exclusion Criteria for Post-Stroke Subjects are: 1) cerebellar signs (ataxic ("drunken") gait or decreased coordination during rapid alternating hand or foot movements, 2) history of lower extremity joint replacement, 3) inability to communicate with investigators, 4) neglect/hemianopia, or unexplained dizziness in last 6 months, 5) neurologic conditions other than stroke, 6) orthopedic problems in the lower limbs or spine (or other medical conditions) that limit walking or cause pain during walking.

Inclusion Criteria for Able-Bodied Individuals are: 1) age 18 to 90 years, 2) no history of neurologic disease, 3) no history of orthopedic disease or injury affecting the lower extremity.

Exclusion Criteria for Able-Bodied Individuals are: 1) history of neurologic disease, 2) history of orthopedic disease or injury to the lower extremity in the past 6 months, 3) pain or discomfort during walking, 4) cardiovascular or medical condition affecting ability to exercise or walk.

Subject Recruitment. Study participants will be recruited from the general community within and outside Emory University.

Withdrawal from study. Participation in the present study will be voluntary and subjects will be able to opt out of the study at any time.

Inclusion of children: Our subject population will be representative of adults with stroke and healthy adults. The incidence of stroke is considered rare in children, estimated to be less than 13 cases per 100,000 children[70] and their inclusion would not provide additional information compared with the data gathered in adults.

7. Statistical analysis

Hypotheses testing will be done with a p-value set at 0.05. The primary biomechanical outcome variables will be peak AGRF and trailing limb angle. Secondary variables will be user self-reports regarding game engagement, motivation, and fatigue.

Power Analysis: The current protocol is designed as a preliminary study, and will be used to conduct systematic power analysis, effect-size and sample-size calculation, which will be utilized to design a larger-scale future study.

8. Adverse event reporting

We will record and notify the IRB of any adverse events that occur during the protocol.

10. Device information

Equipment for Motion Analysis and Gait Retraining: A 7-camera system will be used to collect motion analysis data (Vicon, Oxford, UK). Ground reaction forces during treadmill walking will be collected using a treadmill instrumented with two 6-component force platforms under each belt (Bertec, USA). During over ground walking, ground reaction forces will be collected using a force plate embedded within the lab floor (AMTI, USA). In addition, small electromyography (EMG) sensors will be attached to various muscles to collect EMG data (Noraxon Inc., Arizona, USA). The EMG sensors will be attached using hypo-allergenic adhesive. Pressure-sensitive foot switches (25-mm diameter MA-153, Motion Lab Systems, LA) will be attached to the underside of the subjects' shoes; the foot switch data will be used to record gait events (Noraxon Inc, Arizona, USA). All these devices widely used for measurement of human movements.

Equipment for gait biofeedback: The auditory and visual biofeedback will be provided using a visual display projector screen and a speaker pointed toward the participant. The visual feedback display comprises a horizontal line graph with a moveable cursor that represents the current measured value of antero-posterior ground reaction force for the right leg. The biofeedback software is a plugin provided by The MotionMonitor, Innovative Sports Training Inc., Illinois, USA. The game-based biofeedback interfaced will be designed and developed as part of this current project, with help from our collaborators at Savannah College of Arts and Design (SCAD) and Georgia Institute of Technology. We may use a commercial off-the-shelf VR headset such as the Oculus for the VR display.

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