**1. Significance and Goal**

The doubling of human life expectancy over the last century, from a global average of 35 years in 1900 to more than 70 years today[1], is a remarkable success story. This progress is evident in the increasing prevalence of centenarians, from 0.002% in 1950, 0.015% in 2010, and 0.027% in 2020[1], demonstrating humans can lead fulfilling extended lives. Despite numerous health challenges throughout their long lives, these exceptional individuals exhibit striking resilience. Resilience is defined as the ability to recover from significant stress events. It is a novel concept that aims to quantify how individuals cope while operating in dynamic and complex task environments. It also incorporates complex physiological systems of baseline reserve, stress detection, and adaptation capabilities. Resilience also results from the speed and appropriateness of responses, including the ability to heal and recover, that enable the body to return to homeostasis following disruptions. Current assessments of dynamic resiliencearebased on subjective questionnairesthat may not quantify the physiological responses accompanying stress events. **Objectively understanding the physiological mechanisms of dynamic resilience among older adults offers valuable insights into aging that may actively promote human health and life expectancy**.

We can now harness our ability to induce a real-life physiological stress event in the laboratory to detect dynamic prognostic markers associated with human resilience. Novel in vitro platforms allow us to construct human-derived systems of physiological relevance to evaluate human responses to laboratory-induced stress events. The PI, Prof. Melzer, has developed a novel motion platform, the **B**alance **M**easure & **Per**turbation (BaMPer) system, which can simulate unexpected loss of balance while the participant walks on the BaMPer system. Our data shows that after exposure to unexpected balance loss, the sympathetic nervous system is triggered even among young adults. Interestingly, some participants show high resilience to this event, whereas others show lower resilience (see section **5.2.2 Pilot data). This data provides the basis for this ISF proposal, where our overall goal is to understand the physiological mechanisms of dynamic resilience among older adults by simulating a stress event.** Through our Hypotheses, Objectives, and Specific Aims (see section **3.1 Primary Hypothesis and Objective of the Proposal**), we will use the BaMPer system to induce an unexpected stressful event, identify objective markers for a dynamic resilience and construct a multivariate model that will result in a dynamic resilience prediction score (*dRePS)*.

**The primary goal of this proposal is to identify personalized** **physiological and functional biomarkers indicative of resilience**. A major output of the proposal will be identifying and validating causal measures and models of dynamic resilience that are sufficiently predictive to inform clinical decision-making and intervention. Notably, a 25% reduction in the progression to frailty among individuals over age 65 would safeguard the well-being of up to 87 million people globally[2]. This aspiration is entirely within the realm of possibility, as frailty has demonstrated potential for arrest and even reversal.

Our Objectives below will provide the foundation for enhancing the capacity for measurement, modeling, and testing critical for innovative methodologies to enhance holistic well-being. We will address the following key questions: How can we effectively gauge and identify individuals at the highest risk of experiencing health deterioration following a stress-inducing event? That is, can we identify individuals with “fragile dynamic resilience”? What factors underlie the variability of dynamic resilience, where some individuals maintain fragile dynamic resilience and others do not? In particular, what underlies instances where individuals exhibit frailty levels using static measurements disparate from their dynamic resilience responses?

**1.1 Objective and primary hypothesis of the proposal**

***The primary objective of our proposal is to identify physiological, biological, medical, functional, and emotional markers associated with adaptive behavior and dynamic resilience.* Our primary hypothesis is that older adults with poor resilience to an acute stress event, a laboratory-induced unexpected balance loss, will be less adaptable compared to older adults who are highly resilient*.***

**2. Scientific Background**

**2.1. Epidemiological rationale for the proposal**

As we age, most individuals experience a decline in baseline reserves and a gradual deterioration of biological maintenance systems, culminating in a significant burden of age-related chronic conditions, often manifesting as multimorbidity. Approximately 50% of adults aged over 65 suffer from at least two age-related chronic conditions, a figure that escalates to nearly 80% among those over 80[3]. Furthermore, our capacity to cope with stress diminishes with age, rendering us susceptible to sudden and severe health deterioration upon encountering acute illness or injury. In clinical terminology, this diminished resilience or vulnerability is termed “frailty” and afflicts around **10%** of people over 65 years, rising to between 25% and 50% of those over 85[4]. As a result, our “health span”, the period of good health we experience, is significantly shorter than our entire lifespan. This fact underscores the profound consequences of reduced resilience with age[5].

Escalating global aging has brought frailty to the forefront as a pressing and burgeoning health issue. Notably, the proportion of adults over 65 has reached 11.8% in Israel, 16% in Singapore, 17% in the US, 19% in the UK, and 30% in Japan[6]. Projections indicate that by 2050, over 1.5 billion individuals will surpass age 65, with the oldest over 85 expected to triple[7]. Alarming statistics reveal that 25-30% of adults over 65 experience falls annually, with 50% of frail older adults reporting to have fallen in the previous year. Frailty-induced falls are associated with a greater risk of fractures, hospitalization, and institutionalization [8]. Similarly, frailty accounts for 70% of unplanned hospital admissions and contributes to 20% of hospital bed occupancy in the UK[9]. Frailty also notably amplifies the risk of death by eight to ten-fold following emergency hospital admissions[10]. For frail patients, surgical interventions heighten risks, leading to prolonged hospital stays, adverse outcomes, loss of independence, discharge to long-term care, or even death[8,11]. The detrimental impact of frailty and age-related health issues on older individuals, their families, caregivers, and societies is unsustainable[12], necessitating urgent attention and proactive interventions to address this global health crisis.

**2.2. Resilience as a new framework to promote healthy aging**

Knowledge concerning biological aging is well-established[13]. The knowledge is underscored by a growing acceptance that age-related ailments, multimorbidity, and frailty result from inherent cellular and molecular alterations instigated by aging[14]. Focusing on a resilience perspective is a novel framework for comprehending health dynamics during aging. The framework reinstates static and dynamic resilience to limit the erosion of homeostatic equilibrium, which reduces frailty and age-associated multimorbidity. Anti-aging therapies have attracted multi-billion-dollar investments[15] as researchers worldwide develop interventions to enhance health during aging. There is a pressing need to establish quantitative, predictive, and robust metrics to expedite this scientific endeavor to elucidate the mechanisms that maintain the physiological steady state. Markers of dynamic resilience are imperative, particularly in response to stress-inducing events. Frailty scores and indices offer reasonably accurate predictions regarding aggregate statistical outcomes of stress events, such as recovery, debilitation, or mortality. However, the efficacy of such tools to predict individual outcomes is limited[16]. Even precise techniques like methylation or immune-based aging clocks[17] primarily gauge an individual’s physiological state at a specific moment without assessing dynamic resilience, namely the capacity to adapt to and recuperate from stress events.

**Our critical goal is to identify and quantify parameters associated with resilience among older adults and overall health within complex biological systems. In conjunction, we seek to understand the intricate biological processes and factors underpinning the preservation and restoration of homeostasis.** The parameters may encompass enhancements in immune responses, improved energy regulation, or robust stress-coping mechanisms, as demonstrated among centenarians[18]. Rigorously validated models incorporating the identified parameters and spanning scales from organ-level to system examinations, and ultimately the entire human body, can be instrumental tools for unraveling causal mechanisms. Moreover, these tools may aid in the identification of individuals at risk of health deterioration from stress-event-induced factors. Significantly, such models may expedite clinical investigations of interventions to sustain or reinstate resilience. Accurate prediction of individual dynamic resilience and the ability of older adults to return to homeostasis after disruption, health challenges, and stress events is scarce and insufficient. **We propose to identify predictors and causes of human resilience by utilizing a unique experimental design integrating data from physiological and biological systems, physical performance measures, brain imaging, and emotional markers to investigate dynamic resilience, which is the ability to recover after a significant stress event.**

**2.3. Frailty and dynamic resilience**

bythrive by ing Dynamic resilience is crucial in preventing or delaying the onset of frailty in older adults[19]. Poor dynamic resilience is a major contributor to frailty and disability, which may increase the risk of death in older adults[19]. Dynamic resilience and frailty are two related concepts when considering the well-being of older adults. Notably, frailty increased from 4.2% of community-dwelling older adults in 2015 to 6.7% in 2020[20]. The prevalence of pre-frailty was 36.4%, being higher in hospital settings (39.3%) and lower in nursing homes (20%)[21], with higher rates among females[20]. While frailty and dynamic resilience appear contradictory, they can coexist and influence each other. There are five key points regarding their relationship.

**2.3.1. Prevention and delay of frailty**. Frailty can be prevented or delayed by regular physical activity[24], maintaining a healthy diet[25], staying socially active[26], and participating in mentally stimulating activities[27]. Older adults can enhance physical, cognitive, and social functioning to reduce the risk of frailty[28].

**2.3.2. Recovery from frailty**. Dynamic resilience is essential for frail older adults with health challenges in their daily lives. Interventions promoting functional independence can improve overall well-being in frail older adults by helping them regain physical and cognitive function[23].

**2.3.3. Adaptation to changing circumstances**. Frailty can limit an older adult’s ability to respond and adapt to new circumstances and stressful events[29]. Dynamic resilience can help overcome these limitations by utilizing available resources and support systems to promote adaptive strategies and emotional well-being.

**2.3.4. Intervention**. Dynamic resilience is a crucial factor in intervention programs for older adults with frailty[30,31]. They can build resilience and regain functional independence to the best of their abilities through interventions tailored to improve physiological, biological, medical, nutritional, functional, and emotional well-being.

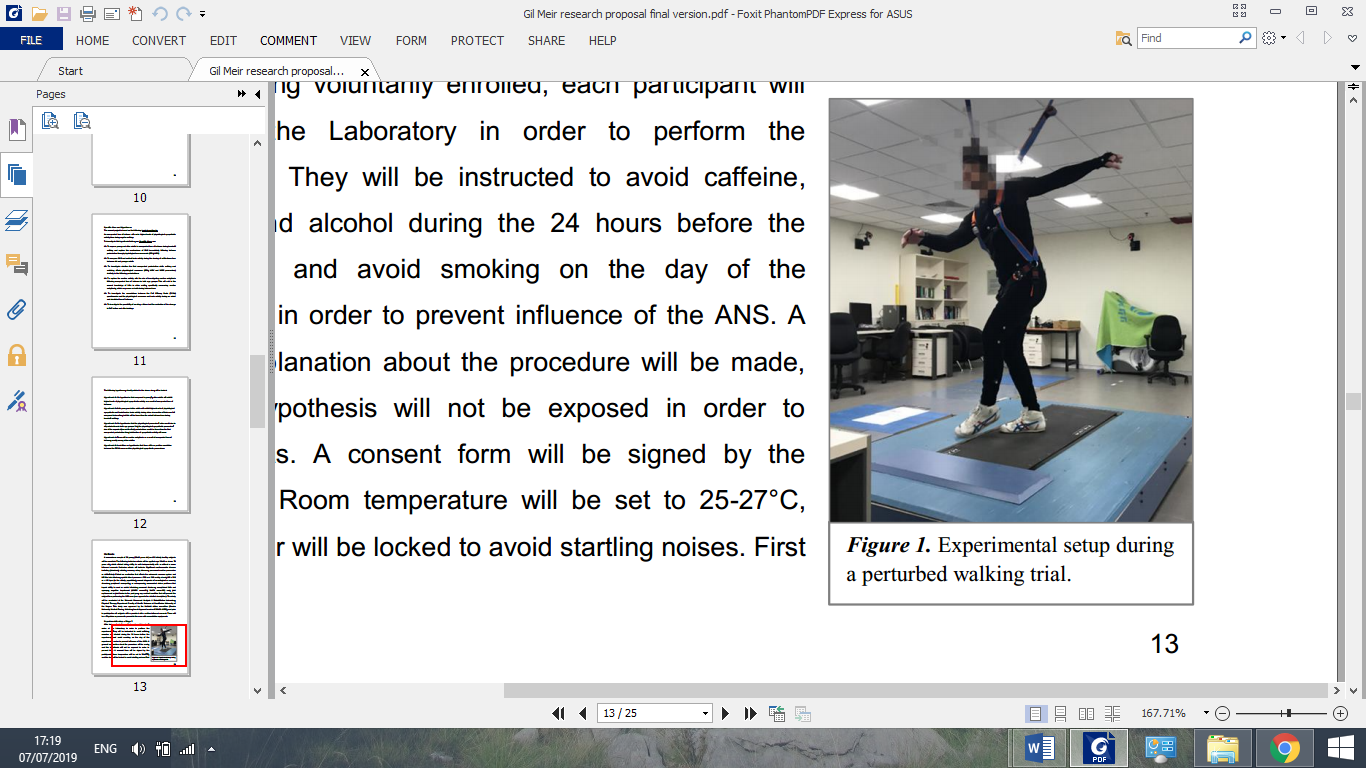
**2.3.5. Supportive Environments**. Creating supportive environments for frail older adults is crucial to foster their dynamic resilience[32]. The support includes accessible infrastructure, social support networks, healthcare services, and community programs that promote engagement, empowerment, and well-being.

**2.4. Proposal goal**

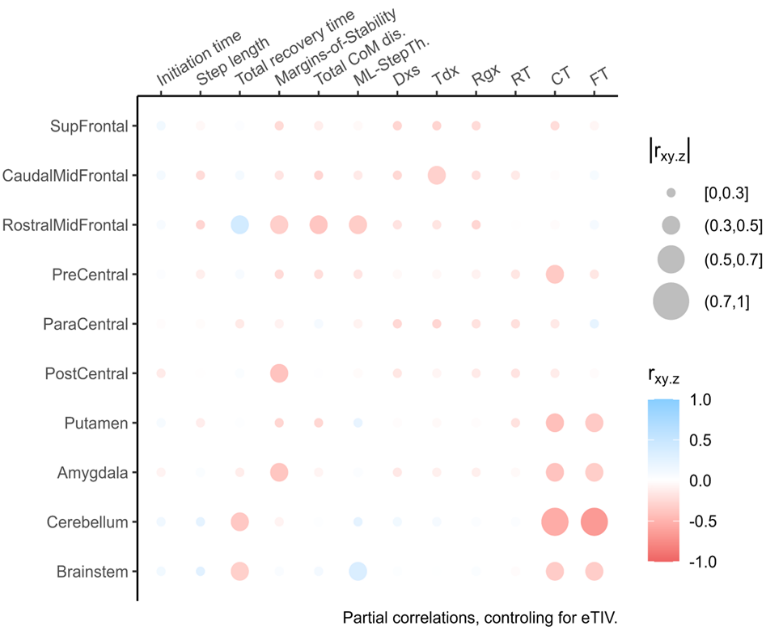
It is crucial to understand the mechanism underlying dynamic resilience to maintain and improve the health of our aging population. How can some older adults cope with physical and psychological stress, whereas others cannot? Investigating dynamic resilience can mitigate the impact of frailty and enhance the overall well-being of older adults. Dynamic resilience may achieve this by providing a framework for directing interventions with the greatest impact toward slowing or reversing frailty, leading to extended periods of health and activity. **We propose to understand the physiological mechanisms of dynamic resilience by identifying dynamic prognostic biomarkers of resilience in older adults with the goal of predicting and detecting risk factors for frailty years before onset**.

**2.5. Previous relevant work**

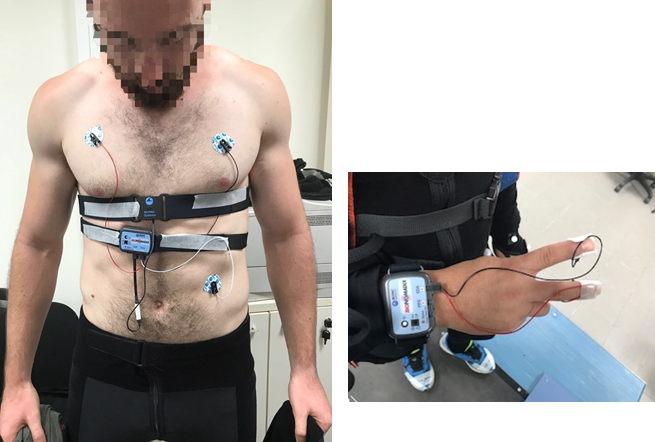
**2.5.1. Basic work.** During the past 20 years, PI Melzer’s team developed novel examinations and testing protocols that measure balance function among older adults. Specifically, these examinations provide information about mechanisms of gait and balance function during the stress of an unexpected loss of balance event. We developed and built a novel motion platform, the Balance Measure & Perturbation (BaMPer) system, patent PCT/IB2010/ 052079)[44], which provokes loss of balance while walking, simulating a real-world fall event (Figure 1). We can characterize responses following unexpected balance loss among older adults[45]. We found that older adults (mean age 79.8 years) reporting a recent fall have impaired reactive balance responses and cannot effectively recover from unexpected balance loss as they fall into the harness system. In contrast, we found that non-fallers show effective balance recovery[45-54]. In a different study, we found a significant increase in the total spectral power of lower-limb muscles immediately after perturbation[49], indicating fast-twitch muscle fiber use during recovery. In addition, we exposed 30 people and their stroke and age-matched control subjects to perturbations while standing. People with stroke demonstrated significantly lower fall and multiple-step thresholds, with 24 of 30 falling into the harness system during the experiment and most falls occurring toward the paretic side[50-52]. We further investigated responses to unexpected balance loss while concurrently performing a dual-task in 20 adults 70 years and older[53] and 30 adults 20-30 years old[54]. In both groups, balance recovery parameters are similar in single-task versus dual-task conditions, indicating that when the postural threat is substantial, such as unexpected balance loss during walking, recovery reactions are automatic and unaffected by a concurrent cognitive task. Recently, we completed an MRI study (Figure 2, manuscripts in preparation) and found a negative association between gray matter volume in these brain areas and balance recovery. The negative association demonstrates that as the cerebellum and brainstem shrink, the total time to recover balance is impaired among older adults. We also found a positive association between Rostral frontal area volumes and total time to recover balance. The changes indicate the involvement of cognitive higher brain areas in balance recovery and less involvement of deep brain areas. Thus, slowness in reactive balance response may indicate a less automatic motor response.



***Figure 1:*** *Experimental setup. An example of balance recovery response during perturbed walking.*

***Figure 2.*** *Partial correlation analysis between the gray matter volume of regions of interest (ROI; y-axis) and balance control parameters (x-axis) in older adults.* ***Note:*** *The circle sizes represent the correlation size, and the color represents positive (blue) or negative (red) correlations.*

**2.5.2.** **Sympathetic nervous system response to unexpected balance loss - Pilot data.** In a different recent study (manuscript in preparation), 34 young adults (27.2±2.3 years) were exposed to six unexpected perturbations during walking, an unanticipated stressful event (Figure 1). We examined the skin conductance level (SCL) before and immediately after each perturbation by galvanic skin response or electrodermal activity (EDA) as a direct measure of the sympathetic nervous system (SNS) activity during a stress event. We also measured electrocardiogram (ECG) and heart and respiratory rates (Figure 3). We calculated the skin conductance response (SCR), defined as the change (delta) in the absolute value of the SCL measured in microsiemens (μS) before and after perturbations. An SCR was determined to be event-specific if it was a direct outcome of the stimulus, where the increase started during a time window of two to five seconds after the perturbation. Predictably, we found that unexpected balance loss elicited a dramatic and significant rise in SNS response (Figure 4A-C). Interestingly, three different behaviors of ANS were observed: 1) **Steady-level behavior** - This most common type of EDA behavior (58%) was characterized by a transient increase (phasic raise) of SNS activity immediately after each perturbation, followed by an immediate recovery to pre-perturbation level (Figure 4A), indicating **moderately resilient behavior**; 2) **Ascending behavior** - Thirty percent of participants experienced increased EDA immediately after each perturbation, followed by an EDA decrease; however, EDA remained greater than the pre-perturbation level, possibly indicatingless adaptive **poorly** **resilient behavior** (Figure 4B); and 3) **Descending behavior** - Twelve percent of participants experienced increased EDA immediately after each perturbation, followed by an EDA decrease to a lower level compared to the pre-perturbation level indicating **highly resilient behavior** (Figure 4C).



***Figure 3:*** *Demonstration of electrode placement. Left photo – the 3-lead ECG placement, with the respiratory strap. Right Photo– Electrodermal activity electrodes placed on the distal phalanx.*

|  |  |
| --- | --- |
| A |  |
| B |  |
| C |  |
| ***Figure 4.*** *(A) The steady-level wave-shaped graph, characterized by a steady SCL with transient peaks which are SCRs post–pre-perturbations, (B) The ascending step shape. These graphs present an ongoing increase in SCL following perturbations, (C) The descending step shape where the SCL constantly decreases.* | |

Our results show that unexpected loss of balance while walking is a stressful event, even for young, healthy adults. Moreover, the results emphasize the need to conduct similar experiments with older adults. For this proposal, we will define highly resilient behavior as demonstrating steady- and ascending-level behavior in older adults. In contrast, descending behavior will be defined as poor resilience in older adults. We predict unexpected balance loss will be a stressful event triggering SNS activity in older adults. The proposed experiments will explore the resilient behavior of older adults in a laboratory setting.

The work presented in this section provides unpublished preliminary results that provide the basis for this proposal to explore physiological, biological, medical, functional, and emotional markers of dynamic resilience among non-frail, pre-frail, and frail older adults. In this more extensive investigation of older adults, we propose to study resilient behavior, which is the ability to cope with stressful laboratory-based events. To investigate dynamic resilience in older adults, we will recruit 75 adults, 75-90 years and older, with an equal number of frail, pre-frail, and non-frail (25 each). To the best of our knowledge, this is the first investigation that will identify the physiological ANS response, biological (cortisol level), medical (The Charlson Comorbidity and Fried Frailty Indexes), physical (gait and balance), dynamic resilience (MiC questionnaire), Nutritional (Mini Nutritional Assessment) and emotional markers of dynamic resilience. ***The ISF program provides an opportunity to investigate and identify physiological biomarkers of resilience in older adult populations to accurately predict dynamic resilience underpinning the loss of human resilience at multiple scales.*** This empirical work will be the basis for future intervention studies to improve resilience among older adults.

**3.** **Objectives and Specific Aims**

Our proposal is structured around two Objectives.

**Objective 1.** We will expose 75-year-old adults (n=75) to the laboratory-induced stress event of unexpected loss of balance while walking. ***Hypothesis 1: Thirty percent of older adults will show fragile dynamic resilience, namely less adaptive physiologically dynamic resilient behavior.***

**Objective 2.** We will develop a multivariate model to construct a dRePSbased on markers from our proposed investigation. ***Hypothesis 2: A “signature of resilience” can be identified after a laboratory-induced stress event that will be particularly valuable for the elderly population***. The identification score will be a weighted summary of identified biomarkers determined by the model coefficients, including SNS and cortisol responses, functional markers, and brain markers. ***Hypothesis 3: We further predict that markers from discovery cohorts will demonstrate that resilience markers associate significantly with (p<0.05) and predict immediate recovery from a laboratory-induced stress event of unexpected perturbation and a loss of balance during walking.***

**Specific Aims**

We will achieve our Objectives through three specific aims.

1. **Behavior and resilience in non-frail adults.** We will assess whether non-frail older adults possess higher levels of adaptive behavior and dynamic resilience compared to frail and pre-frail older adults.
2. **Correlation between behavior and resilience.** We will examine whether a significant positive correlation exists between human adaptive behavior to an induced stress event and dynamic resilience in older adults, as measured by laboratory physiological, biological, and functional markers.
3. **Predicting dynamic resilience.** We will build a multivariate model estimating the contribution of each laboratory marker in predicting dynamic resilience and construct a weighted dynamic prediction score using advanced statistical methods.

**4. Research Design and Methods**

Recruitment will be as in our previous studies[45-54]. Seventy-five community-dwelling older adults (25 frail, 25 pre-frail, and 25 non-frail) from the Beer Sheva area and retirement housing facilities in the Beer Sheva area will be recruited based on the Fried frailty phenotype[69] (see section 4.2.10. Fried frailty phenotype). The adults aged 75-90 will undergo a Mini Mental State Examination and medical history interview for exclusion. Our exclusionary criteria are being younger than 75 years old, being 91 years old or older, CNS trauma, including loss of consciousness for greater than 30 min, seizures, neurodegenerative disease, and severe medical conditions, including stroke, Parkinson’s disease, ALS, and other neurogenetic diseases. Also excluded will be subjects with an active malignancy within 24 months prior to examination or metastatic cancer, severe cognitive impairment (Mini Mental State Examination <20), or any medical reason such as a known or suspected inability to comply with the protocol. After signing a written informed consent according to the Declaration of Helsinki and the ethics committees, we will administer the following examination for research purposes only.

**4.1. Experimental** **protocol**

**4.1.1. Preparation**

According to participant preference, we will set the laboratory room temperature at a comfortable level between 20–22°C (68–72°F) and close the door to avoid startling noises. The skin of the participants’ 2nd and 3rd distal phalanx of the right hand will be cleaned using cotton and alcohol. Dermal electrodes will then be placed for EDA recording (Figure 3) using the Biopac system (Biopac Systems Inc. Goleta, CA, USA). For the ECG recording, we will place three electrodes with a three-lead (I, II, III) configuration on both sides of the upper chest and the left side of the lower abdomen. The respiratory strap will be placed gently on the xiphoid process line, allowing the participant to breathe normally. We will affix all loose cables to prevent mechanical noise. Participants will rest in a comfortable seated position for five minutes for baseline recording. The lab will be quiet with dim light.

**4.1.2. Perturbed standing and walking tests**

We will conduct a total of 12 unexpected perturbation trials on the BaMPer for each participant in two task conditions: 1) six perturbed standing trials and 2) six perturbed walking trials. The participants will be strapped into a harness hung from the ceiling and designed to allow free joint motion during the walking trials. The harness permits balance loss trials but prevents ground contact and injury in case of a fall. We will instruct the participants to stand five minutes (1st task condition) or walk five minutes (2nd task condition) on the BaMPer system. No handrails are mounted on the BaMPer perturbation system, so arms and hands movements are unconstrained (Figure 1). During the standing trials, the participants will stand in a narrow base stance, with their feet placed together. During the walking trials, a habitual self-selected comfortable walking speed will be chosen for participants while wearing their own comfortable shoes. During the five-minute standing and walking tests, the participants will be exposed to six unexpected perturbations with 30- to 45-second intervals between perturbations. A research student familiar with system activation will sit at a computer in front of the BaMPer system and manually document the time of each perturbation online for future analysis. Another student will stand near the participant for the safety assurance of the participants. We will instruct participants “to try to avoid a fall in case you lose your balance” without further instructions for either task condition.

**4.2.** **Proposed outcome parameters**

**4.2.1. ANS response to stress after unexpected balance loss**

We will collect physiological measurements of EDA, ECG, and respiratory rate with the Biopac system (Biopac Systems Inc. Goleta, CA, USA) using the MP160 Data Acquisition System (DAQ). Two Bionomadix wireless transmitter + receiver pairs will be used for 1) ECG + Respiratory and 2) EDA. In addition to the Bionomadix respiration transducer, we will use EL507 electrodes (0.5% chloride salt) for EDA measurements and EL503 pre-gelled electrodes for ECG (Biopac Systems Inc. Goleta, CA, USA) (Figure 3). During both the standing and the walking tests, 60 seconds before the first perturbation, the subjects will stand/walk without external perturbations. This protocol will allow us to examine the effect of unperturbed standing and unperturbed walking on the physiological parameters. The participants will do the six perturbed standing trials and six perturbed walking trials and rest in a comfortable seated position for five minutes between two task conditions.

For baseline assessment, we will collect physiological measurements of EDA, ECG, and respiratory rate in a comfortable seated position. We will then measure 60 seconds before the first perturbation for the perturbed standing and perturbed walking tests and before and after each of six perturbations using the MP160 DAQ. This data will allow us to examine the three adaptive/resilient behaviors: 1) steady-level behavior, 2) descending behavior, and 3) ascending behavior. ***For this proposal, we define resilient behavior as participants who show steady-level behavior and descending behavior.*** We will collect data during all experiment stages using the Biopac system. We will then extract from the raw data graphs of physiological parameters over time as an EDA graph (Figures 4A-C) of absolute values of microSiemens (μS) and ECG as a standard strip (mV).

### 

### **4.2.2. EDA parameters**

1. We will measure SCL by the tonic component of skin conductance, which represents the basic autonomic nervous system arousal level.
2. We will determine SCR, the delta of the absolute value of the SCL change following the perturbation. An SCR will be determined as an event-specific, direct outcome of the perturbation stimulus if the rise starts two to five seconds after the event[55].
3. We will measure the SCL value at the beginning and the end of the rise (μS) (Figure 4A-C).
4. We will determine the relative rise of SCL, calculated as the ratio percent of SCR/SCL. We will use log transformation to reach normal distribution based on our previous experiments (see **2.5.2. Sympathetic nervous system response to unexpected balance loss - Pilot data**). The physiological meaning of the ratio is the magnitude of the stress response compared to the basal stress level during each of the standing or walking test conditions prior to the stimulus. This parameter is particularly valuable because it normalizes the significance of between-subject differences in EDA levels.

**4.2.3. ECG activity**

#### **4.2.3.1. Heart rate values**

1. We will calculate heart rate (HR) delta post-perturbation as the absolute delta (beats/min) between the single lowest value in the three seconds preceding perturbation (pre-perturbation HR) and the highest single value (HR Peak) within two to 20 seconds from the time of perturbation.
2. The time to peak is the time (s) between perturbation and the following HR peak.
3. The HR delta of means is the change between the mean HR ten seconds prior to the perturbation (the last window pre-perturbation) and the greatest mean value of the ten-second window five to 30 seconds post-perturbation.
4. Time to recovery is the time (s) between the peak HR and the HR decrease to the pre-perturbation HR (or 0.5 BPM above).

#### **4.2.3.2. Heart rate variability values**

We will calculate heart rate variability (HRV) parameters using ten-second sliding windows, the minimal time range for HVR parameters. All calculations will use the normal and interpolated beats.

1. **The root mean square of standard deviation (RMSSD).** This parameter is often considered reliable for short and ultra-short measurements[56] and is highly associated with the parasympathetic tone[57,58].
2. **The standard deviation of normal-to-normal beat intervals (SDNN).** This parameter is reliable under specific conditions for short-term measurements and is linked to sympathetic and parasympathetic divisions[58,59].

**4.2.4. Stress biomarkers**

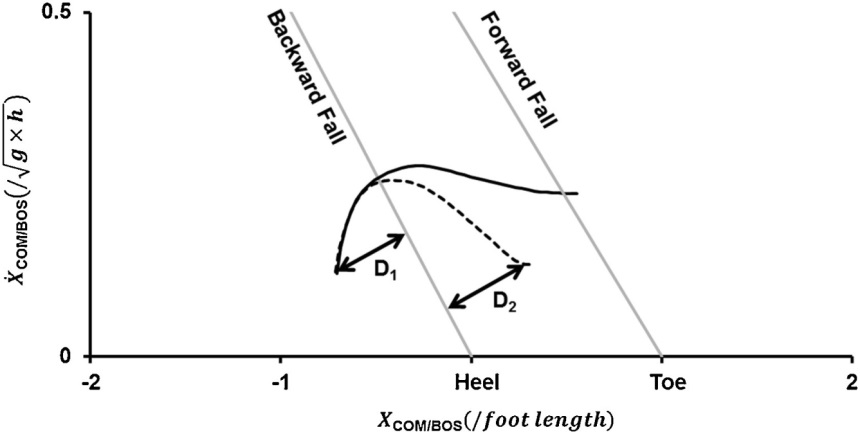
We will test whether unexpected loss of balance affects stress system activity, namely the hypothalamus-pituitary-adrenal (HPA) axis and low-grade inflammation. We will examine the concentration of the stress biomarkers cortisol and alpha-amylase, the inflammatory markers C-reactive protein and interleukin (IL)-6, and tumor necrosis factor TNF-alpha before and immediately after perturbed standing and walking conditions. We will conduct 1) six perturbed standing trials and 2) six perturbed walking trials. Stress system activitywill be assessed by HPA axis activity using non-invasive saliva samples measuring salivary cortisol[60]. We will determine IL-6 and TNF-a levels using commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA). We hypothesize that unexpected perturbations will cause a significant increase in cortisol levels immediately after the perturbation.

**4.2.5. Proxy** **biomechanical measures of fall risk**

Numerous measures have been proposed to evaluate reactive balance control for effective balance response[61]. We will use 3D motion analysis (Vicon system Ltd.) to determine the center of mass (COM) relative to the base of support (BOS) during and immediately following perturbations. The margin of stability (MOS) will be selected to qualify individual balance status in gait[61]. The MOS will be calculated using the below equation[61,62]:

**.**

Here, the xCOM indicates the COM position in the anterior-posterior (AP) direction, and vCoM indicates the COM velocity in the AP direction. The body COM kinematics is calculated using a 13-segment rigid body model using the 3D motion data. *g* is the gravitational acceleration, and *l* represents the leg length calculated with markers attached to the greater trochanter of the femur. BOS represents the area beneath a person encircled by points of contact a foot or feet make with the supporting surface. BOSpos is the posterior edge of BOS, calculated using heel marker position. A negative MoS indicates the extrapolated COM exceeds the posterior boundary of BOS, leading to a backward balance loss (BLoB), whereas a positive MOS represents a no BLoB. We will further normalize the MOS by the length of BOS, which is the foot length in a single stance phase. This length is the distance between a leading foot toe marker and a trailing foot heel marker in a double stance phase. For example, in the normalized MOS, a value greater than one indicates the extrapolated COM exceeds the anterior boundary of the BOS as a forward loss of balance. A negative value indicates the extrapolated COM exceeds the posterior BOS boundary as a BLoB, and any value between zero and one indicates no BLoB (Figure 5).

***Figure 5. Proposed proxy measures of stability.*** *The normalized COM velocity is on the y-axis, and the normalized COM displacement is on the x-axis. The solid black line shows stability during unperturbed walking, and the dashed line shows stability when experiencing a slip perturbation. Stability is defined as the perpendicular distance to the posterior boundary of the lead, slipping foot (at the heel, gray line). D1 represents stability at the heel strike, and D2 represents stability at the end of slip acceleration. Stability shifts posteriorly during the unexpected slip compared to unperturbed walking, as noted by a shorter perpendicular distance to the posterior boundary. (Figure from Huntley et al. [[62](#_ENREF_29" \o "*Huntley, 2019 #26)])*

We will also measure single-step and multiple-step fall thresholds, identifying older adults who have recently reported a fall[45-54]. The single-step threshold level is defined as the minimum perturbation magnitude that consistently elicits a single compensatory step for at least two consecutive perturbation magnitudes. In contrast, the multiple-step threshold is defined as the minimum perturbation magnitude that consistently elicits a sequence of recovery steps.

**4.2.6. Gait speed**

Gait speed is the best predictor of survival among older adults[63]. We will measure gait speed with a digital stopwatch using a ten-meter walking path with a five-meter measurement section bordered on each side by three-meter preparation sections. At the start of measurement, we will verbally instruct subjects to “Please walk normally”, and their walking speed will be measured (m/s) using the recorded time (s).

**4.2.7. Brain markers**

Our recent study is described in section **2.5.1. Basic work** shows that aging is associated with brain structural changes related to balance control function. MRI studies report that whole brain structural changes and brain atrophy are associated with normal aging, including loss of volume of the frontal lobe, temporal lobe, and hippocampus[64,65]. We will use similar neuroimaging techniques to explore structural differences between older adults with high and poor dynamic resilience scores based on the Making it CLEAR (MiC) questionnaire, a gold standard questionnaire that measures dynamic resilience (see details in section **4.2.8**). Additionally, we will explore structural differences between older adults with high and low resilience based on our proposed laboratory physiological dynamic resilience stress test and examine how dynamic resilience corresponds to age-related changes, namely brain shrinkage. We propose investigating differences in whole brain volume and regions of interest (ROI) among high and poor resilience groups. We propose to conduct resting state MRI as well as diffusion tensor imaging (DTI), which will characterize the magnitude, degree of anisotropy, and orientation of directional diffusion and white matter pathologic features, such as ischemia, myelination, axonal damage, inflammation, and edema, among the groups with differing dynamic resilience.

**Questionnaires to be utilized**

**4.2.8. Making it CLEAR (MiC) questionnaire for dynamic resilience.** The MiC questionnaire[66] contains 34 items addressing a variety of factors influencing resilience in older adults(QMU and NHS Lothian)[68]. The items are split into two distinct subscales, one assessing the individual determinants of resilience (IDoR), consisting of 21 items, and one assessing the environmental determinants of resilience EDoR, consisting of 13 items. Participants rate their level of agreement with each item on a four-point scale, namely strongly agree, agree, disagree, or strongly disagree. For each item, zero to three points are given, with higher scores indicating stronger agreement. The IDoR subscale has a maximum score of 63, and descriptive score interpretation is as follows: 0-21 = poor IDoR, 22-42 = moderate IDoR, and >43 = high IDoR[65]. The EDoR subscale has a maximum score of 39, and scores are interpreted as follows: 0-13 = poor EDoR, 14-26 = moderate EDoR, and >27 = high EDoR[66]. The questionnaire grades will serve as our gold standard measurement for resilience.

**4.2.9. Charlson Comorbidity Index (CCI)**. The CCI is a simple and widely used index for assessing comorbidities. It is administered in five to ten minutes and most commonly predicts mortality[67]. The CCI scale[68] will be used to calculate the comorbidities of subjects at enrollment.

**4.2.10. Fried frailty phenotype.** The Fried frailty phenotype[69] is the most popular measurement of frailty. The index considers frailty by its physical characteristics or “phenotype.” The index defines frailty as the presence of shrinking (self-reported unintentional weight loss of 4.5kg or more in the last year), weakness (low grip strength), exhaustion (self-reported), slowness (slow walking speed), and low physical activity. Older people without the five indicators are characterized as non-frail. Those with one or two indicators are hypothesized to comprise intermediate or pre-frail people, whereas those with three or more indicators are considered frail[70].

**4.2.11. Mini Nutritional Assessment-Short Form (MNA-SF).** The MNA-SF[71] will evaluate the nutritional status of the subjects with three classifications: 0–7 points = malnourished, 8–11 points = risk of malnutrition, and 12–14 points = well-nourished[72]. For our analyses, we will divide participants according to MNA-SF score into well-nourished and malnourished or at risk of malnutrition.

**4.2.12. Dundee Stress State Questionnaire (DSSQ).** The DSSQ[73] is a self-reported measure of individual stress levels. It consists of 15 items capturing different aspects of stress, including perceived stress, physical symptoms, and negative emotions[73]. Respondents rate each item on a four-point scale indicating the extent to which they experience stress-related feelings or symptoms.

**4.3. Statistical analyses**

Our primary statistical analyses will be conducted in three phases.

1. We will investigate the association between poorly, moderately, and highly resilient behavior as measured by our experimental protocol (see section **4.1.2. Perturbed standing and walking tests**) and levels of frailty by using several general linear models with interactions for each laboratory parameter, specifically ANS, cortisol-based stress biomarkers, biomechanical measures, gait speed, and brain imaging markers. Overall grades on the MiC, Fried frailty phenotype, DSSQ, and MNA questionnaires will be dependent variables, whereas age group and sex will be independent variables. Non-normally distributed dependent variables will be transformed to achieve normality. P-values will be adjusted for multiplicity using the Benjamini and Hochberg false discovery rate (FDR) controlling procedure[74].
2. We will assess the association between laboratory resilience measurements and dynamic resilience using the overall MiC questionnaire grade. We will initially do univariate analysis using the Spearman correlation coefficient and test with FDR adjustment for multiplicity. Next, we will use a multivariate generalized linear model with resilience as a dependent variable and adaptive behavior measurements, frailty level, and age as independent variables to identify resilience-associated markers. The link function for the generalized model will be selected in accordance with the distribution of the resilience variable.
3. We will use the multivariate model to construct the dynamic dRePS.The score will be defined as a weighted summary of the biomarkers identified by the model, which are ANS and cortisol responses to the stress event, balance, gait speed, and brain markers. We will determine weights by the model coefficients and then use statistical model selection methods such as forward selection, backward elimination, least absolute shrinkage, and selection operator (lasso)[75,76] to refine the prediction model.

**4.4. Sample size**.

We will include a total of 75 participants to achieve a statistical power of 0.93 at a significance level of 0.05, based on two-way ANOVA utilizing six combinations, represented by three frailty groups by the two task conditions of standing and walking.

**5. Expected Results and Pitfalls.**

To our knowledge, this proposal will be the first laboratory-based study to detect ANS activity as an indirect measure of an acute stress event, specifically a laboratory-induced unexpected balance loss during walking. **After a series of perturbations, the measured adaptive behavior may identify a *“signature of resilience.”*** We recognize that the five-minute perturbed walking protocol may be too difficult for relatively more balance-impaired frail older adults. Thus, we added the alternative experimental approach with a five-minute perturbed standing protocol, probably allowing even frail older adults to complete the test. We know recruiting 75 older adults (25 frail, 25 pre-frail, and 25 non-frail) is challenging. However, our strong ties with community providers and dwelling centers in the Beer Sheva area will enable participant recruitment[45-54]. Another challenge may be the relatively large number of parameters used in the current investigation. However, based on our past experiments, three to four stress parameters will allow the multivariate model to construct the dynamic dRePS. The parameters are 1) adaptive/resilient behaviors based on EDA with high resilience, poor resilience, and moderate resilience, 2) pre-post perturbation cortisol concentrations, 3) Fried frailty phenotype, and 4) the DSSQ questionnaire to be used in regression models to identify people with high resilience based on their MiC score.

Our results will leverage future grant applications, particularly for our long-term goals of 1) prospectively investigating the ability of the dRePS score to predict survival among older adults and 2) developing an intervention program to improve resilience nationally based on the results of this proposal. We will present the results of this project at national and international meetings and through peer-reviewed journals. We predict that the proposal will result in at least four peer-reviewed articles: one focusing on rehabilitation and prevention, one on autonomic nervous system response to stress, one on brain markers, and one about the predictive model to identify resilience of older adults.

**6. Lab Resources and Facilities**

The Motion Analysis and Rehabilitation Laboratory, directed by **Prof. Itshak Melzer,** focuses on increasing knowledge of balance control, falls, and injury prevention in older adults. The following equipment will be available at the Lab: 3D Vicon system 16-infrared cameras, a 3D ZED2 camera, an eight-channel Myo-EMG system, two Kistler Force plates systems, and the BaMPer perturbation system. Several collaborators will consult on this project: 1) **Prof. Yan Press**, head of the Geriatric Department at Soroka Medical Center, has years of experience working with the elderly population. His contribution is essential for medical screening and the selection criteria required for the proposed work. 2) **Prof. Abed Azab** is the Director of the Clinical Pharmacology Laboratory. In recent years, he has investigated the involvement of inflammation in pathophysiology. One of his areas of expertise is the influence of stress events on inflammatory processes. In this proposal, he will analyze biological biomarkers of stress. 3) **Prof. Amir Shapiro** is the Director of the Robotics Laboratory. His interests include the locomotion of multi-limbed mechanisms in unstructured, complex environments. For the proposed research, Prof. Shapiro will supervise a research engineering student responsible for the maintenance of the BaMPer system, and 4) **Dr. Moti Salti** is the Scientific Director of the Brain Imaging Research Center (BIRC) at Ben-Gurion University of the Negev and will be responsible for the imaging aspects of the proposal.

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