Graded Intensity Aerobic Exercise to Improve Cerebrovascular Function and Performance in Aged Veterans: Protocol for a Randomized Controlled Trial

Medina Oneyi Bello, Kevin Michael Mammino, Mark Anthony Vernon, Daniel Wakeman, Chanse Aerius Denmon, Keith Matthew McGregor, Thomas Samuel Novak, Joe Robert Nocera, Lisa Crystal Krishnamurthy, Venkatagiri Krishnamurthy

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Medina Oneyi Bello[1*]; Kevin Michael Mammino[1*]; Mark Anthony Vernon[2*]; Daniel Wakeman[2*]; Chanse Aerius Denmon[2*]; Keith Matthew McGregor[3*]; Thomas Samuel Novak[2*]; Joe Robert Nocera[2*]; Lisa Crystal Krishnamurthy[4*]; Venkatagiri Krishnamurthy[2*]

[1]Joseph Maxwell Cleland Atlanta Veteran Affairs Medical Center Decatur US
[2]Emory University Decatur US
[3]Birmingham Veteran Affairs Medical Center Birmingham US
[4]Georgia State University Atlanta US
[*]these authors contributed equally

Corresponding Author:
Medina Oneyi Bello
Joseph Maxwell Cleland Atlanta Veteran Affairs Medical Center
1670 Clairmont Rd
Decatur
US

Abstract

Background: The growing healthcare challenges from a rapidly expanding aging population necessitates examination of effective rehabilitation techniques that mitigate age-related comorbidity and improve quality of life. To date, exercise is one of a few proven interventions known to attenuate age-related declines in cognitive and sensorimotor functions critical to sustained independence. This work aims to implement a multi-modal imaging approach to better understand the mechanistic underpinnings of the beneficial exercise induced adaptations to brain and behavior in sedentary older adults. Due to the complex cerebral and vascular dynamics that encompass neuroplastic change with aging and exercise, we propose an imaging protocol that will model exercise induced changes to cerebral perfusion, cerebral vascular reactivity (CVR) and cognitive & sensorimotor task-dependent fMRI after prescribed exercise.

Objective: Our central hypothesis is that the 12-week aerobic exercise intervention will increase basal perfusion and improve CVR as measure by increased magnitude of reactivity in areas susceptible to neural and vascular decline (inferior frontal and motor cortices) in previously sedentary older adults. To better understand the neural versus vascular adaptations in the motor and inferior frontal cortices, we will map changes in basal perfusion and CVR over target regions of interest (inferior frontal and the motor cortices) that we have demonstrated to be beneficially altered during fMRI BOLD (verbal fluency and motor tapping) by increased cardiovascular fitness.

Methods: Sedentary adults (aged 65-80) will be randomly assigned to either a 12-week aerobic-based, interval-based cycling intervention or a 12-week balance and stretching intervention. Assessments of cardiovascular fitness using the YMCA submaximal VO2 test, basal cerebral perfusion using arterial spin labeling (ASL), CVR using hypercapnic fMRI, cortical activation using fMRI during verbal fluency and motor tapping tasks, and a battery of cognitive-executive and motor function tasks outside of the scanning environment will be performed before and after the interventions.

Results: Our own studies and others show that improved cardiovascular fitness in older adults' results in improved outcomes related to both physical and cognitive health as well as quality of life. A consistent but unexplained finding in many of these studies is a change in cortical activation patterns during task-based fMRI that corresponds with improved task performance (cognitive-executive and motor).

Conclusions: To date, exercise is one of the most impactful interventions aimed to improve physical and cognitive health in aging. This study aims to better understand the mechanistic underpinnings of improved health and function of the cerebrovascular system. If our hypothesis of improved perfusion and cerebrovascular reactivity following a 12-week aerobic exercise intervention are supported, it would add critically important insight about the potential of exercise to improve brain

health in aging and could inform exercise prescription for older adults at risk for neurodegenerative disease brought on by cerebrovascular dysfunction.

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Background

The growing healthcare challenges from a rapidly expanding aging population necessitates examination of effective rehabilitation techniques that mitigate age-related comorbidity and improve quality of life. To date, exercise is one of a few proven interventions known to attenuate age-related declines in cognitive and sensorimotor functions critical to sustained independence. This work aims to implement a multi-modal imaging approach to better understand the mechanistic underpinnings of the beneficial exercise induced adaptations to brain and behavior in sedentary older adults. Due to the complex cerebral and vascular dynamics that encompass neuroplastic change with aging and exercise, we propose an imaging protocol that will model exercise induced changes to cerebral perfusion, cerebral vascular reactivity (CVR) and cognitive & sensorimotor task-dependent fMRI after prescribed exercise.

Methods

Sedentary adults (aged 65-80) will be randomly assigned to either a 12-week aerobic-based, interval-based cycling intervention or a 12-week balance and stretching intervention. Assessments of cardiovascular fitness using the YMCA submaximal VO2 test, basal cerebral perfusion using arterial spin labeling (ASL), CVR using hypercapnic fMRI, cortical activation using fMRI during verbal fluency and motor tapping tasks, and a battery of cognitive-executive and motor function tasks outside of the scanning environment will be performed before and after the interventions.

Expected Outcomes

Our central hypothesis is that the 12-week aerobic exercise intervention will increase basal perfusion and improve CVR as measure by increased magnitude of reactivity in areas susceptible to neural and vascular decline (inferior frontal and motor cortices) in previously sedentary older adults. To better understand the neural versus vascular adaptations in the motor and inferior frontal cortices, we will map changes in basal perfusion and CVR over target regions of interest (inferior frontal and the motor cortices) that we have demonstrated to be beneficially altered during fMRI BOLD (verbal fluency and motor tapping) by increased cardiovascular fitness.

Preliminary Results

Our own studies and others show that improved cardiovascular fitness in older adults' results in improved outcomes related to both physical and cognitive health as well as quality of life. A consistent but unexplained finding in many of these studies is a change in cortical activation patterns during task-based fMRI that corresponds with improved task performance (cognitive-executive and motor).

Conclusion

To date, exercise is one of the most impactful interventions aimed to improve physical and cognitive health in aging. This study aims to better understand the mechanistic underpinnings of improved health and function of the cerebrovascular system. If our hypothesis of improved perfusion and cerebrovascular reactivity following a 12-week aerobic exercise intervention are supported, it would add critically important insight about

the potential of exercise to improve brain health in aging and could inform exercise prescription for older adults at risk for neurodegenerative disease brought on by cerebrovascular dysfunction.

Introduction

The rapid growth in an aging global population presents significant healthcare and fiscal challenges due to increased prevalence of age-related neurodegenerative disease and disability. For example, of the 60 million Americans over 65 years of age, it is estimated that one in three of these older adults will be diagnosed with Alzheimer's disease (AD) or a related dementia in their lifetime. Intertwined with aging-related pathologies are physiological changes in cerebrovascular function [1]. In fact, recent epidemiological and clinico-pathological data indicate considerable overlap between cerebrovascular dysfunction in aging and AD [2,3]. While AD is an overt pathology, its "sub-clinical" progression appears to take decades before crossing a diagnostic threshold [4]. This sub-clinical stage spans a significant timeframe for targeted interventions aimed at limiting vascular dysfunction in high-risk older adults.

It has been demonstrated that of all modifiable risk factors for dementing illness, decreasing sedentary behavior is the most statistically significant and effective measure to counter disease progression and associated cognitive decline in older adults [5]. For example, nearly a quarter million cases of AD could be prevented in the US alone by improving the cardiovascular fitness profile in older adults. This staggering number is an exciting target not only for prevention during aging but also as a means to better understand aging processes and underlying mechanisms malleable to exercise. Equally significant, this number probably underestimates the total impact of increasing cardiovascular fitness due to its effects on other risk factors in aging, including hypertension and obesity [6].

This study will explore the impact of aerobic exercise on cerebrovascular health in older adults. Research over the last few decades has driven the continual promotion of exercise as one of the most impactful interventions of central nervous system health and function [7-9]. We know that older adults who are physically active have improved peripheral vascular health but the impact of an exercise intervention on cerebrovascular health is less known. We will fill this gap by examining changes in basal cerebral perfusion and CVR in older adults following a proven cardiovascular fitness intervention [10-13]. If our hypotheses of improved perfusion and CVR are supported, it would inform current intervention strategies and would add important new information about the potential of exercise to improve brain health in aging. This would have immediate implications for older adults at risk for neurodegenerative disease brought on by cerebrovascular dysfunction.

Methods

This study design follows a parallel group design where participants engaged in exercise for 12-weeks.

Participants

Older adult participants will be pseudo-randomized to one of two 12-week interventions: Interval-based, aerobic 'Spin' cycling exercise, or non-aerobic, balance and stretching exercise to serve as an active control condition. Prior to beginning any portion of this study, we must receive written approval by a qualified physician for participation in the fitness

assessment and exercise intervention. Informed consent will be provided to all participants before any testing commences. All study protocols will be in compliance with the Declaration of Helsinki and have been approved by the Emory University Internal Review Board and Atlanta VA Research and Development Office (Grant: RX002825-01).

The key inclusion criteria and final participant pool will consist of right-handed, English-speaking individuals aged 65 to 80. Participants must also self-report a sedentary lifestyle defined as not participating in at least 30 minutes of moderate-intensity physical activity on at least three days/week for at least three months. Additionally, participants will be non-demented and have no deficits in cognitive-executive function (MoCA ≥ 26). Those with severe diabetes requiring insulin will also be excluded, however, individuals with controlled diabetes that meet our inclusion criteria for sedentariness and cognitive function will be allowed to participate. Individuals with any conditions contraindicated by MRI acquisition (including but not limited to, ferrous metal implants, cardiac pacemakers or similar devices, claustrophobia, morbid obesity), and those with any history of major psychiatric disorder (including but not limited to psychosis, major depression, bipolar disorder) will also be excluded.

Measures

Pre and post evaluations of cardiovascular fitness, cognitive & motor function, and brain imaging will be conducted over 2 days (< 3 hours per day) within a 2-week timeframe.

Day 1:

Table 1 shows the span of physical, cognitive, and motor assessments performed in session 1 (both pre and post).

_____Table 1 goes here_____

Day 2: MR Environment

MRI Acquisition. MRI data will be collected on a 3T Siemens Prisma fit (Erlangen, Germany). This will consist of an anatomical T1-weighted MPRAGE scan (TE = 3 ms, TR = 2500 ms, flip angle = 7^{o}) and seven fMRI scans for each subject: One fMRI scan collected during dual-echo pseudo-continuous pCASL (TE1/TE2 = 10/25ms, TR = 4000ms, one fMRI scan collected during CVR (TE = 21 ms, TR = 1000 ms, voxel size = 3mm x 3mm x 3mm, flip angle = 50^{o}, number of volumes = 420), three runs of a language based task (TE = 25 ms, TR = 5800 ms, voxel size = 3mm x 3mm x 3mm, flip angle = 70^{o}, number of volumes = 71) and two runs of a motor based task (TE = 25 ms, TR = 2000 ms, voxel size = 3mm x 3mm x 3mm, flip angle = 70^{o}, number of volumes = 154).

Preprocessing. Preprocessing of anatomical T1w and fMRI data will be conducted utilizing fMRIPrep 22.0.22 (RRID:SCR_016216), which is based on Nipype 1.8.5 (RRID:SCR_002502). The pipeline included brain extraction, tissue segmentation and spatial normalization to MNI template space for the T1w. Regarding the fMRI data, preprocessing involved estimation of BOLD image and head-motion, slice timing correction, registration to the T1w image and resampling to MNI space (see Supplementary Materials for full preprocessing pipeline details).

Semantic Fluency: During the MRI session, participants will perform 3 blocks of a verbal fluency task programmed using via E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA)[14] (Figure 1). At the start of each block, the phrase “please wait” is projected to participants via a 20-inch HP computer display for 20s. The task is initiated when this phrase is replaced by a word corresponding to a specific semantic category. This category disappears and reappears 8 separate times, and participants are instructed to verbalize a single response corresponding to this category each time it reappears on the screen. Participants are also instructed to avoid repeating any responses from the same category. A

single task block consists of 6 separate categories (requiring 8 individuated/non-repeating responses per category). Interleaved between each semantic category is a “reading” condition. Here, participants are presented with the word “Rest” 4 separate times and instructed to verbally respond with the word “Rest” each time it appears. During these scans, verbal response will be manually recorded by an investigator, and subsequently scored based on the total number of correct (and non-repeating) responses divided by the number of response windows provided (I.e. Block Score: (# correct / 48 response windows)*100, Session Score: (# correct/ 144 response windows)*100).

_____Figure 1 goes here_____

Motor Tapping: Participants will also perform 2 blocks of a motor tapping task programmed via PsychoPy [15] and using an MR compatible 4-button box (MagConcept response unit) (figure 2.). Briefly, individuals are presented with a red dot in the center of the projected screen for 15s. The task will commence when this dot turns green, and subsequently alternates between red and green at a frequency of 1 Hz. Participants are instructed to press the button oriented to their index finger at the pace of the flashing green dot. Each block consists of five 28s tapping intervals separated by six 28s rest intervals. During these rest intervals, a solid red dot is projected, and participants are instructed to do nothing until they are presented with the next sequence of green dots.

_____Figure 2 goes here_____

Arterial Spin Labeling (ASL). The ASL sequence acquisition first magnetically labels blood water at the region of interest by applying a 180-degree radiofrequency inversion pulse. The labeled water exchanges with tissue water, which alters the tissues magnetization and the image intensity creating a "tag" image. This process is repeated without labeling blood to create a "control" image. Subtracting the control and tag images produces perfusion imaging which reflects the amount of arterial blood delivered to voxels withing a given region of interest. This difference signal is directly proportional to cerebral blood flow and can be mapped on a voxel-wise basis to obtain regional blood flow information. To convert the difference signal (=control-label) into physiological units, a single compartment model is utilized to obtain units of mL/100g/min. The ASL scan lasts approximately 7 minutes.

The aforementioned sequence parameters to be used for ASL acquisition is standard for assessing blood flow maps of the whole brain along with our regions of interest (inferior frontal and the motor cortices). The Harvard-Oxford cortical atlas developed in MNI 152 atlas space will be the starting point for the frontal region of interest. The resulting ASL with corresponding T1-weighted images will be registered into MNI 152 atlas space using the nonlinear algorithms from FMRIB Software Library (FSL) Images will be imported into AFNI for analysis.

Cerebral Vascular Reactivity (CVR). CVR will be assessed using a block-design hypercapnic response paradigm where participants alternate between breathing room air and a 5% CO_2 gas mixture during fMRI (see a detailed description in [16]). Participants will be fitted with a nose clip and mouthpiece attached to a two-way breathing valve that affords inhalation of normal room air, or CO_2 mixture filled in a 100L Douglas bag. Additional physiological parameters, including end tidal (Et) CO_2 and breathing rate will be continuously monitored and recorded using a Philips NM3 Capnograph. At the onset of this

scan, participants will inhale normal room air for 50s. A research staff member will then manually switch the valve to CO_2 air for 50s, and subsequently alternate between breathing conditions until three 50s blocks of CO_2 breathing, and four 50s blocks of room air breathing have been collected (total scan duration ~7min).

Provided Et-CO_2 is essentially the input function to the brain vasculature, it is critical to measure this trace as it is a quantitative metric for the degree of stimulation the blood vessels receive. As such, the primary outcome from this measure is BOLD change per mmHg of inhaled CO_2 in our regions of interest.

Data Analyses

For data analysis we aim to determine whether the two groups (Spin and Control) have different responses of cerebral perfusion in the regions of interests following the intervention. Our *a priori* hypothesis is that individuals in the aerobic group will show increased perfusion in both the right and left inferior frontal gyri and motor cortices when compared to those in the Control. The primary outcome is cerebral blood flow in units of mL/100g/min within each region of interest. We will test each mL/100g/min region of interest value jointly using a mixed effects linear model to determine whether the mean change of the groups is significantly different across the time points (pre and post). Fixed effect will be group (Spin vs. Control) and the random effect will be time (Pre vs. Post). We expect that modeling the outcomes jointly will allow for some gains in power. This model will enable us to estimate the overall effects of time and the interventions, and most importantly, how the effects of the interventions differ with time. Additional analyses will use multiple regressions to describe the effect of participant demographics (gender, race, age, and hypertensive status) or by pre-intervention cognitive status (MoCA). A false discovery rate (FDR) of q=0.05 will be calculated and used to correct for multiple tests and effect sizes will be computed.

Next, we aim to determine the impact of an aerobic intervention on CVR. Our *a priori* hypothesis is that individuals in the aerobic group will show increased CVR in both the right and left inferior frontal gyri and motor cortices when compared to those in the control condition. Similar to our analyses specific to perfusion, we will test each region of interest BOLD change value jointly using a mixed effects linear model to determine whether the mean change of the groups is significantly different across the time points (pre and post). Fixed effect will be group (Spin vs. Control) and the random effect will be time (Pre vs. Post). Additional analyses will use multiple regressions to describe the effect participant demographics (gender, race, age, and hypertensive status) or by pre-intervention cognitive (MoCA). A false discovery rate (FDR) of q=0.05 will be calculated and used to correct for multiple tests and effect sizes will be computed.

After the aforementioned preprocessing steps are performed on ASL and CVR, the images will be scaled to accurately determine the relative percent signal change in BOLD induced by the task. Finally, task-induced BOLD changes (ΔBOLD) from pre- to post-aerobic intervention and corresponding hemodynamic response functions are quantified using deconvolution technique.

Since the goal of this aim is to quantify the impact of baseline physiologic measures (i.e. resting blood flow and CVR on task-induced BOLD changes, we plan to accomplish this task by modeling the contributions of CBF and CVR to ΔBOLD responses. The equations below describe our simple modeling approach using linear regression:

$$\Delta BOLD_{i,ROI} = A + B \cdot CBF_{i,ROI} + C \cdot CVR_{i,ROI} + D \cdot \left(CBF_{i,ROI} \times CVR_{i,ROI}\right)$$

Where subscript i=pre or post session, ROI refers to the regions of interest, and coefficients A is the modeled intercept, B and C are modeled slopes for perfusion and CVR contributions, and D is modeled slope for the interaction between perfusion and CVR respectively. We will compare the slopes obtained for pre- and post-exercise to explore (a) how each of the baseline measures (i.e. CBF and CVR) change in response to exercise, and (b) within each condition (pre or post), disentangle perfusion and vascular influence on task-induced BOLD change. Also, modeling for the interaction will account for the coupling effect which by itself can provide insightful information in terms of exercise-induced perfusion-CVR coupled effects. We plan to carry out the above processing and modeling at the ROI level as it renders more detection power and is computationally less intensive. From statistics standpoint, we will compute the F score to test the significance of overall fitting of the model, and we will also obtain the t score for each predictor (perfusion and CVR) to test the significance of their association with change in measured variable (ΔBOLD).

Average AUC will be taken from the right and left inferior frontal gyri ROI's during semantic fluency for both pre- and post-sessions. AUC will be averaged from the right and left inferior frontal gyri and treated as a single ROI for this analysis. The base analyses for this aim will be 2 analyses of variance (ANOVAs), 2 groups X 2 times (pre- vs. post-AE).

The analysis plan for behavioral performance will include the following dependent variables: VO2, in-scanner verbal fluency performance, the motor task, as described above as well as our cognitive battery. Paired t-tests will be performed to test for a pre to post effect. Spearman's correlations (r) will be used to correlate behavioral performance to primary outcomes and a mixed regression will be used to assess the influence of session (pre and post) on outcomes.

Potential Outcomes

Decreased vascular health because of aging, and particularly sedentary aging, fosters both cognitive and motor dysfunction [17] which has implications for neurodegenerative disease. Task-based fMRI and the resultant BOLD map is currently a dominant method of neurocognitive investigation, particularly related to documenting the beneficial changes demonstrated with rehabilitation. At the forefront of much of this research is the use of task-based fMRI BOLD to quantify beneficial changes in cortical function following aerobic exercise [11,18,19]. While transformative, the true impact of this research is limited in scope until we can define the influence of cerebrovascular function on the well-documented beneficial change in BOLD response. Because the BOLD signal reflects the health and function of the cerebrovasculature [20,21], we believe the changes brought on by exercise are at least partially mediated by improved perfusion and CVR. No single imaging technique can resolve the complexities of imaging neural plasticity in brain systems; therefore, we propose a solution of combining imaging techniques and modeling the impact of perfusion and CVR on the BOLD response. We will model the hypothesized change in perfusion and CVR to the BOLD response following the intervention to quantify the percentage of variance both perfusion and CVR account for in the task-induced BOLD signal. This will allow us to

understand the degree to which change in perfusion and CVR impacts the well-documented beneficial change in task-induced BOLD following exercise.

Limitations

We have considered the following potential weaknesses. First, the length of the intervention (12-weeks) is not sufficient to induce change in cerebrovascular function. Of note, we encourage all of our research participants to maintain a lifelong commitment to physical activity and hope that our 12-week intervention is the beginning of behavioral change. We do believe, however, that the 12-week timeline is sufficient to significantly change both perfusion and reactivity based on, 1) the significant change demonstrated in cardiovascular fitness and BOLD response in 12-weeks utilizing the proposed Spin intervention, and 2) the numerous studies demonstrated change in perfusion and reactivity in the periphery with 12-week interventions. Further, it is known that acute bouts of moderate-intensity aerobic exercise reduces both central and peripheral femoral artery stiffness [22] while increasing endothelial function [23,24] is also anti-inflammatory.

An additional potential weakness is that older adults will not be compliant and adherent to the intervention. Compliance in our studies generally has been at or above 90% with retention consistently being above 85%; however, long-term success of interventions will depend on accessibility and sustainability. Community exercise programs that increase accessibility are obtaining good results[25], but sustainability is still an issue. Dealing with these issues in later stage clinical trials is in our long-term goals once we know the full extent of the intervention and it is consistent with our long-term goals. In line with this, we are currently working with two local YMCA's and have implemented an exercise intervention within their facilities. We are also currently developing and deploying tele-exercise interventions that are disseminated with wearables. We believe this will allow us to impact a much larger pool of Veterans including those in rural areas.

Acknowledgments

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Conflicts of Interest

None declared.

Abbreviations

ASL: arterial spin labeling
BOLD: Blood Oxygen Level Dependent
CVR: cerebral vascular reactivity
FDR: false recovery rate
HR: heart rate
fMRI: functional magnetic resonance imaging

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Supplementary Files

Multimedia Appendixes

Untitled.
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