The Neural Effects of Balance Versus Aerobic Training in Individuals With Degenerative Cerebellar Diseases

NCT05002218

February 21, 2025

BACKGROUND

Abstract

Exercise is the main treatment for degenerative cerebellar diseases, a group of disorders that affect cerebellar neurons causing an array of symptoms including an inability to coordinate balance, gait, and extremity movements. Studies researching the effect of balance training on degenerative cerebellar disease have found functional improvements in patient's walking.

The role of aerobic exercise in the treatment of degenerative cerebellar disease is relatively unknown. Research on rats with symptoms similar to cerebellar ataxia indicates that moderate aerobic exercise increases the rat's lifespan compared to rats that do not exercise. Studies of other neurological diseases, such as Parkinson's disease, illustrate that aerobic exercise enhances motor learning in the brain. Only one study to date has assessed the effectiveness of aerobic exercise on cerebellar ataxia in humans. Patients were given a 4-week cycling regime consisting of 15 minutes per day, 3 days per week. Results indicated that patients in the cycling group had improved ICARS scores (a scale used to monitor ataxia), but not gait speed or standing capacity compared to a control group. Other measures of balance were not tested in this study. The main objective of this project will be to compare the benefits of aerobic versus balance training in DCD. We hypothesize that both aerobic and balance training will improve function in ataxic subjects, but that the mechanisms in which these improvements occur differ.

Study Purpose and Rationale

Hereditary spinocerebellar diseases are a group of disorders in which cerebellar degradation manifests in ataxia, a neurological sign causing impaired coordination and balance.1 The diseases are devastatingly debilitating with many individuals requiring wheelchairs for locomotion after only 10 to 15 years from initial diagnoses. With no disease modifying medications currently available, balance training is recommended to improve motor skills and maintain function. Yet, recent emerging evidence from our research group shows that aerobic training is a promising treatment option. The goal of this study is to compare the impact of balance versus aerobic training on the brains of individuals with hereditary spinocerebellar diseases. Prior research has used clinical measures, such as the Scale for the Assessment and Rating of Ataxia (SARA), to determine the benefits of training. Although validated for this purpose, these scales

cannot differentiate between functional compensation of deficits versus slowing of cerebellar degradation. Thus, it is important to examine the neurological impact of different training methods to distinguish whether one training method is better able to slow disease progression than the other. Moreover, we speculate that aerobic and balance training impact the brain via different mechanisms. Two hypotheses exist regarding the neural effects of training; the degenerating cerebellum undergoes neuroplastic changes to adapt its functioning, or alternatively, other brain areas undergo neuroplastic changes to compensate for deficits. We hypothesize that balance training causes improvements for people with cerebellar degeneration by impacting brain structures outside the cerebellum whereas aerobic training induces neuroplastic changes within the cerebellum. We expect this result because:

1) A 2-week balance training program resulted in increased grey matter volume in the premotor cortex of individuals with cerebellar degeneration, but no statistically significant changes in the cerebellum.

2) Ataxic animals that regularly perform aerobic exercise have larger cerebellums with increased synapses and dendrites at death than those who are sedentary.

3) Preliminary data from our group indicates increased cerebellar volume in individuals with spinocerebellar disease who participate in a 6-month home aerobic program, but decreased

volume for those who perform balance training. Thus, if our hypothesis is true, aerobic training may have more influence on disease progression than balance training as it directly impacts the cause of deficits, the cerebellum.

Public Health Significance: There is a critical need to determine effective treatments for hereditary cerebellar diseases. Research has shown balance and aerobic training improves symptoms for individuals with these disorders, but the mechanisms of improvement are unknown. This proposal will begin to examine the impact of both training methods on the brain. By understanding how each training method impacts cerebellar volume, microstructure, and functional connectivity, future research can more precisely target training regimens with the goal of slowing the disease progression of individuals with these devastating diseases.

Research Aims & Abstracts

AIM 1) To determine the effect of training on cerebellar volume. Individuals with hereditary spinocerebellar ataxias will be randomized to either a 6-month home aerobic or balance

training program. Structural MRI scans will be taken before and after the training programs to determine the impact of training on cerebellar volume. We hypothesize that aerobic training will slow cerebellar volume loss when compared to balance training.

AIM 2) To evaluate the long-term training effects on clinical measures of ataxia and correlate changes with cerebellar volume. SARA scores will be determined before and after each training program. They will also be taken at 3- and 6-months post-training along with structural MRI scans. Consistent with our prior research, we hypothesize that improvements in SARA scores will revert back to baseline if training is halted. We further hypothesize that changes in SARA scores will correlate with cerebellar volume changes in the aerobic group, but not with changes in the balance group.

Exploratory Aim 3) To examine the effects of exercise on cerebellar microstructure and functional connectivity to the cerebellum. Diffusion weighted imaging and resting state fMRI scans will be taken before and after individuals with spinocerebellar disease participate in a 6-month home aerobic or balance training program. We will then use the cerebellum as our region of interest to analyze how training impacts cerebellar microstructure and functional cerebellar connections. Although the impact of training on the cerebellum has been investigated in healthy individuals, it is unclear how training will impact the degenerating cerebellum in our subject population. Thus, we will use this preliminary data to determine which cerebellar regions and functional networks are most impacted by training to form targeted hypotheses for future research projects.

STUDY DESIGN

This is a single-blinded randomized control trial. After initial testing, participants will be randomly assigned to either home balance or aerobic training for 6 months. After training, individuals will undergo post-training testing. At the post-training testing, individuals will be encouraged to continue training, but not required to as part of the study. Follow-up testing will then be conducted at 3- and 6-month post-training to evaluate the longevity of training effects.

The rationale for this study design is as follows:

1) Randomization between balance and aerobic training groups will balance known and unknown confounding factors that may influence changes in cerebellar volume. Individuals

conducting assessments will be blinded to group, but participants cannot be blinded given the nature of the intervention.

2) Although the use of an active control (balance training) as opposed to a placebo control may make it more difficult to detect differences between groups, our preliminary data made us comfortable that we would be able to detect differences. This design also allows us to examine the neural mechanisms underlying balance training effects on individuals with spinocerebellar disease in addition to aerobic training.

3) 6-months of training was used for this study because prior work in our laboratory on healthy individuals showed that 6-months of training was long enough to detect statistically significant changes in brain volume.

4) Follow-up testing was selected to start at 3 months post-training because our prior research showed that clinical effects were still seen at this timepoint.

Study procedures

Video Recording: We will record SARA measures in order to blind researcher to intervention. The study team will use a small hand-held recorder to video the SARA test. The video will have full facial features, but the participant's name will not be attached to the recording. Analysis of the recording will only be done by members of the research team. The recording will not be used for other purposes such as teaching or commercial purposes. The recordings will be stored in a password protected database. The recording will be destroyed upon completion of the study procedures. There is no compensation for allowing video recording. These recordings will not be used in publications. They will only be used by members of the research team for evaluation purposes.

Dynamic Gait Balance: Patients will be asked to walk 20 feet and conditions such as speed and head position will be varied as previously described. The examiner will then grade the subject's movement as detailed from Shumway-Cook & Woollacott Motor Control: Theory and Practical Applications, 1995.

Gait Speed: Participants will walk as fast as possible on a 9-m runway 3 times, and we will average the results of trials.

SARA scores: SARA is an 8-item performance based scale, yielding a total score of 0 (no ataxia) to 40 (most severe ataxia). The scores are based on patient performance of gait, stance,

sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements and heel-shin slide.

Cardiopulmonary Exercise Testing (CPET): Maximal oxygen consumption (VO_2max) will be determined by a breath-by-breath measurement of VO_2 with a Vmax Encore Metabolic System (CareFusion Corp, San Diego, CA), while participants perform a progressive ramped exercise test using an electronic-braked lower body cycle ergometer. Prior to testing, patients will be asked about prior heart conditions, joint pain, exercise intolerance, prior exercise levels, and medications. A physician will determine if the participant is eligible to participate at this time. Testing protocol includes a 3-minute warm-up at minimal resistance, and then the initial workload and individualized ramping protocol will be determined based on patient's weight, level of function, and current exercise profile. The patient will then cycle at 60-65 revolutions per minute (RPM) until achieving one of the following VO_2max criteria: respiratory exchange ratio (RER) 1.1, increases in ventilation without concomitant increases in VO_2, and/or maximum age-predicted heart rate. The test will also be terminated if the cycling cadence drops below 40 RPM for 5 seconds, or when the participant reaches volitional exhaustion. The results of this test will be used to determine initial heart rate goals of participants assigned to aerobic training.

Cerebellar Volume and Atrophy Rate: Cranial MRI will be performed in all participants using a 3-T scanner. Brain volume measurement software, FreeSurfer, will be used to calculate cerebellar volumes using Digital Imaging and Communications in Medicine (DICOM) data from T1-weighted sagittal images. We will also measure each participant's cranial anteroposterior (AP) diameter as defined by the distance in which the skull and anterior commissure-posterior commissure line intersect. For statistical analysis, the cerebellar volume will be divided by each cranial AP diameter to correct for head size differences. The difference between cerebellum volumes over a 6-month period will be used to calculate cerebellar atrophy rates.

Diffusion Tensor Imaging: This measure will be a primary outcome of Aim 3. Diffusion data will be preprocessed for motion and corrected for geometrical distortion using ExploreDTI. For each participant, the bmatrix will be reoriented to provide a more accurate estimate of diffusion tensor orientations. Diffusion tensor estimation will be performed using a non-linear least square fitting method. FA and Mean Diffusivity (MD) maps will be generated. Whole brain tractography will be performed using all brain voxels with FA 0.2 as seed region. Streamlines will be propagated using an Euler integration tractography algorithm with a step size of 0.5 mm and with an angular

and anisotropy threshold of 45 degrees and FA 0.2 respectively. Finally, diffusion tensor maps and whole brain tractography will be exported to TrackVis version 0.5.2.2 for manual dissection and quantification of cerebellar fiber tracts.

To determine cerebellar fiber tracts, we will use TrackVis to select regions of interest in the b0 images. The anatomical structure corresponding to the desired regions of interest will be initially localized in MRI atlases of the cerebellum, subsequently identified in T1 images, and then selected in the co-registered b0 dataset. The following regions of interest will be selected: 1) fastigial nucleus, 2) interpositus nucleus, 3) superior cerebellar peduncle, 4) middle cerebellar peduncle, and 5) inferior cerebellar peduncle. In order to extract clean diffusion measurements avoiding crossing and complex white matter regions, regions of interest will be selected using a manual two region approach.

Resting State Functional MRI: This measure will be a primary outcome for Aim 3. The anatomical and functional data will be pre-processed and analyzed using Statistical Parametric Mapping (SPM12) and the CONN toolbox Version 14p. Functional data will be pre-processed using a slice scan time correction, realignment (motion correction), registration to structural images and spatial normalization to Montreal Neurological Institute (MNI) standardized space, smoothing with a Gaussian filter of 5.0 mm spatial full width at half maximum value. A conventional band-pass filter over a low-frequency window of interest (0.008–0.09) will also be applied to the resting-state time series. After these preprocessing steps, we will extract signal to noise from the white matter and cerebrospinal fluid by principal component analysis without affecting intrinsic functional connectivity. These components, white matter, cerebrospinal fluid, and motion parameters, will be included in the model and considered as covariates of no-interest.

To determine the region of interest within the cerebellum, a localizer scan will be performed after resting fMRI as described in MRI acquisition. We focused on the legs because gait abnormalities are the main deficits in individuals with spinocerebellar ataxia. The coordinates of the region of interest within the cerebellum will be selected on the basis of activation peaks obtained from the block design analysis. For each subject, we will obtain the mean BOLD signal of the region of interest by defining a mask around the seed in the standard space. To ensure that distortion was not present in localizer scans, we will verify that head motion does not exceed a threshold of 1mm and run a general linear model with predictors associated with the movement conditions to ensure there is not activation of voxels outside the brain.

Aerobic training group: Participants will be given a stationary exercise bike for home use. They will be instructed to use the exercise bike five times a week for thirty-minute sessions. The exercise intensity prescription will be based on the subject's maximum heart rate based on age. The exercise program will start at 60% of max heart rate, and then will be increased by steps of 5% intensity every 2 weeks until participants reach 30 minutes of training at 80% intensity. In addition, rate of perceived exertion (Borg scale) will be assessed at each training session. Participants will be contacted weekly by e-mail or phone to answer any questions about the exercise protocol and will be instructed to log each training session. Subjects will record duration of exercise, perceived exertion, average heart rate, maximum heart rate, and distance. Subjects will be asked to use the bike for 6 months.

Balance training group: A home balance training program will be tailored for each participant based on pre-training capabilities. Subjects will be asked to perform exercises five times a week for thirty-minute sessions. Both dynamic and static exercises will be performed in sitting and standing positions. Exercises will start with stabilizing in a challenging static position and progress to dynamic arm and leg movements in the same or modified position. Participants will be contacted weekly by e-mail or phone to answer any questions about the exercise protocol and will be required to log their exercise effort in terms of frequency and level of balance challenge. Individuals will be instructed to perform more difficult exercises if balance challenge scores are low. Participants will be asked to do balance training program for 6 months.

STATISTICAL PROCEDURES

All analysis will be conducted blind to which intervention is being evaluated. SAS (version 9.4) will be used for all statistical analyses. We will use intention to treat principles. Demographic and clinical variables will be compared using the Wilcoxson's test and chi-squared analysis for continuous and categorical variables, respectively. The association between cerebellar volume change and SARA score change will be estimated with Spearman's correlation coefficient. We will use linear mixed-effect regression analysis to test whether change in cerebellar volume differed between training groups, controlling for age and other co-variates mentioned above as fixed effect. To account for within-subject correlation due to repeated measurement, we will include a random

intercept. If the assessment effect is significant ($p<0.05$), post hoc analysis will be performed using pairwise comparisons between assessments.

For diffusion tensor imaging, individual ANCOVAs will be determined for FA and MD in the middle of both hemispheres for the regions of interest, with age, gender, and disease type as covariates.

For resting fMRI analysis, the mean BOLD time course of the regions of interest will be used as a predictor in a multisubject general linear model to evaluate the functional connectivity of that seed with every voxel in the brain. In addition, to account for potential contributions of physiological noise, the time course of nuisance signals of white matter, cerebrospinal fluid, and six motion parameters will be included as predictors in the same general lineal model. The analysis will end with an activation map of all voxels in the brain that correlate with the seed of interest. We will minimize detection of false positives by using a cluster-corrected family wise error rate correction at $p<0.05$. The correction procedure will use Monte Carlo simulations to calculate the probability of having a cluster of a certain size being due to chance alone. Our z-statistic images will then be projected onto the inflated template brain. The analysis will be conducted separately for pre-training and post-training scans. For further group analysis, we will use random-effects analysis to compute comparison before and after training. To investigate the strength of connectivity changes at the single-subject level, we will calculate the values for each voxel underlying the connectivity maps in individual participants. These values will represent the strength of connectivity between the seed area and individual voxels. Analyses of the distribution of the values across subjects will be done to estimate connectivity patterns.

Sample Size Calculation: 11 subjects had completed our preliminary study with structural MRI scans before and after training. The data shows a change in cerebellar volume of -1.06% Å} 0.53 for the balance group, and a cerebellar volume increase of +1.28% Å} 1.04 for the aerobic group. The calculated effect size was 2.34. Setting = 0.05 and = 0.2 and using a conservative effect size of 1.34 and a standard deviation of 1.3 (as seen in our pilot data), we determined that we will require 16 subjects per group for this study.

Dropout and Compliance Rate: In our current study looking at 6 months of balance verse aerobic training in this population, we currently have a drop-out rate of 11.8%. Using a slightly higher drop-out rate of 20%, we will require 20 subjects per group. In addition, 85% of participants in our pilot study met training goals. Studies with similar training programs show more modest

compliance rates of around 75%.72-74 Using a compliance rate of 75%, we will need to recruit 24 subjects per group. Based on previous studies, we expect to recruit about 24 subjects per year and will plan on 2 years of recruitment.