Bridging animal and human models of exercise-induced visual rehabilitation

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Specific Aim: Assess visual outcomes and serum BDNF **in human subjects** before, during, and after an aerobic exercise training program that includes progressive increases in exercise. **Hypothesis:** Circulating BDNF will increase and visual outcomes will change with increasing exercise intensity or interval.

Objectives: To assess changes in visual acuity (primary outcome) and contrast sensitivity (secondary outcome) and to determine the feasibility of and to develop expertise in measuring BDNF in human blood samples (tertiary outcome). **Rationale:** Animal and human studies examining the effects of exercise on cognition and peripheral nerve regeneration demonstrate that circulating BDNF levels vary with outcome; whether BDNF varies with exercise levels is less well studied. If amounts of exercise and circulating BDNF levels similarly co-vary in humans and in mice, BDNF may be useful as a biomarker for testing exercise regimens as interventions in human studies. Additionally, no human studies have monitored exercise, BDNF, and retinal and visual outcomes. **Design:** The study is comprised of a 12-week exercise portion with one return visit 3 months after the end of the exercise portion. Participants will be recruited from our volunteer database, which includes elderly individuals (65-89 years old) who are not visually impaired and who report being sedentary (defined as engaging in structured physical activity for 30 minutes or less over the last 3 months) and who meet other inclusion criteria previously established for our exercise studies. Participants will be divided into a group that will exercise and a group that will remain sedentary. Exercising participants will train three times a week for 12 weeks on a stationary bicycle ergometer ("spin" training). Exercise intensity will begin at low levels (50% of maximal heart rate reserve) and will be increased by 5% every week (as tolerated by the participant) to a maximum of 80% of maximal heart rate. Exercise time will progress from an initial 20 minutes per session to a maximum of 45 minutes by increasing 5 minutes each week. A CPR-certified fitness specialist will monitor each session. We will follow the guidelines provided by the American College of Sports Medicine for optimizing cardiovascular fitness. Blood draws and visual assessments will be taken at one week prior to the 12-week regimen, at the 3-month follow-up, and at weeks 1, 4, 8, and 12 of the 12-week regimen. Blood will be drawn by a certified phlebotomist in the rest period before the exercise, immediately following the exercise, and after a recovery period of 10 min. Visual assessment will include visual acuity and contrast sensitivity (CSV-1000E). Control (non-exercising) participants will have blood drawn and undergo other assessments identically to the exercised participants. To control for potential benefits of the spinning program that are unrelated to aerobic exercise, they will participate in group balance training. All participants will be instructed to otherwise continue with their daily routines and will be contacted bi-weekly to track self-reported levels of physical activity outside of the study. All participants will be asked to return to their pre-study routines following the 12-week exercise portion of the study. All procedures involving human subjects have been reviewed and approved by an Institutional Review Board (IRB). Sample remainders will be archived for analyses that are beyond the scope of a SPiRE support. **Expected outcomes and Significance:** If functional changes differ between exercised versus control cohorts across the study period, we will conclude that even relatively short-term aerobic exercise can be beneficial to visual health. Such an outcome would also suggest that effects are due to physiological mechanisms rather than test-specific psychological confounds. Circulating levels of BDNF will be measurable and will increase in exercised versus unexercised subjects, indicating that circulating BDNF levels correlate with exercise activity. **Potential difficulties and alternative approaches:** **(1)** It may be that changes in BDNF levels are not observed. Human studies demonstrate that many forms of aerobic exercise, including "spin" ergometer training, increase circulating BDNF levels. However, the temporal relationship between an exercise session and its effects on BDNF may vary. If we do not observe changes in BDNF with the proposed sampling regimen within the first week of the 12-week training portion of the study, we will add a draw at the midway point of the spin session. Additional draws during the recovery period at 5 min intervals may be attempted (we have institutional approval, though these would require cannulation, which increases complexity and increases the probability of participant drop-out). Additions will be iterative and kept to a minimum based on assaying for BDNF concentration the day of the spin sessions. **(2)** It may be that that BDNF levels do not vary with exercise volume changes. If so, similar to the suggested alternative in Aim 1, additional circulating growth factors will be assessed. Candidates include insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), and leukemia insulin factor (LIF), nerve growth factor (NGF), and Neurotrophin-4/5.

Methods

Visual function testing:

Visual acuity: The visual acuity of the subjects will be measured according to a standard procedure developed and used by many multi-center clinical trials. An Early Treatment Diabetic Retinopathy Study (ETDRS) Chart and a 3 meter testing lane providing standardized chart illumination (80 to 120 cd/m^2) are used to test visual acuity. Testing is done at a distance of 3 meters (20 feet) or (for subjects with sufficiently reduced vision) a distance of 1 meter. The 3 meter distance should be marked clearly and permanently while the 1 meter distance must be measured with a 1 meter string. Subjects should be prevented from seeing the chart until the visual acuity testing actually begins.

The subject is first positioned at 3 meters in a chair with his or her back firmly touching the back of the chair. The head of the subject should not move forward or backward during the test so that the subject's eyes remain at the specified distance. The subject is instructed to slowly read with the study eye(s) each letter of each line at a rate not faster than about one letter per second. If the subject is unable to correctly identify all the letters of the top two lines, then position the subject at 1 meter and again instruct the subject to read each letter of each line beginning again with the top line. If the subject loses his or her place the examiner may point to a line (but outside the line at the edge of the chart) or below the letter (at a distance equal to the inter-letter spacing in a line) with a long pointer. The testing procedure for visual acuity is based on the principle that the objective is to test resolution ability and not the ability to find each letter on a line.

The subject's responses are recorded on the visual acuity recording sheet. Each wrong response is scored by putting an X through the letter and writing the incorrect response above the letter. Once a subject has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response before s/he has read aloud the next letter, then the change should be accepted. When the subject has missed at least 3 letters on the previous line and can make no further meaningful guesses, despite urges to read or guess, the examiner should stop the test for that eye. The examiner records the number of letters correctly read and from this number computes the Snellen Equivalent and LogMAR values from the table provided.

Script: **This is a visual acuity test like you might have seen at your doctor's office. This chart shows letters that become smaller toward the bottom. I want you to stop at the end of each row and wait until I ask you to continue. Please try your best to read all the letters. If you are unsure, I will ask you to take a guess even if it is very difficult for you to see. Any questions?**

Statistical analysis: The number of correct ETDRS responses from a subject assessed prior to start of the first session of the the 12 week study is subtracted from the number of correct responses elicited at the end of the last session of the study. The means of these differences for each study group (Balance Training vs Aerobic Exercise) is compared by two-tailed t-test.

Contrast sensitivity: The contrast sensitivity of the subjects will be measured with the Pelli-Robson Chart following the instructions provided with the chart. The two sides of the Pelli-Robson Chart have different letter sequences but are otherwise identical. The chart should be illuminated as uniformly as possible, so that the luminance of the white areas is between 80 and 120 cd/ m^2 with no glare. The patient should sit directly in front of the chart at a distance of 1 meter (use the same 1 meter string as for visual acuity testing to measure the eye-to-chart distance). Subjects should be prevented from seeing the chart until the contrast sensitivity testing actually begins. Subjects should wear their best distance correction.

As in visual acuity testing, the subject is instructed to slowly read with their study eye(s) each letter of each line at a rate not faster than about one letter per second. If the subject loses his or her place the examiner may point to a line (but outside the line at the edge of the chart) or below the letter (at a distance equal to the inter-letter spacing in a line) with a long pointer. The testing procedure for contrast sensitivity is also based on the principle that the objective is to test threshold contrast sensitivity and not the ability to find each letter on a line.

The subject's responses are recorded on the contrast sensitivity recording sheet. Each wrong response is scored by putting an X through the letter and writing the incorrect response above the letter. Once a subject has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response before s/he has read aloud the next letter, then the change should be accepted. When the subject says s/he cannot read a letter, s/he should be encouraged to guess. If the subject identifies a letter as one of two or more letters, s/he should be asked to choose one letter. When the subject has missed at least 2 letters of the previous triplet and can make no further meaningful guesses, despite urges to read or guess, the examiner should stop the test for that eye.

The examiner records the number of letters correctly read and from this number computes the Contrast Sensitivity from the table provided.

Excerpt containing one possible script (per Pelli Robson instruction manual): *Explaining the test.* This test will be unfamiliar to most of your patients, and they may cooperate more readily if they understand why it is being performed. Here is one possible set of instructions. **In everyday life we do not look at small black objects. Contrast sensitivity is a more realistic assessment of how well we see large faint objects around us. This chart is a little different from the regular eye chart. With this chart letters are all uniformly large, and they fade out towards the bottom of the chart. The top line has high-contrast letters, black on white. The letters below them are grey and more difficult to see, very much like looking through fog or dirty glasses. What you must do is read as many letters as you can. The letters at the bottom of the chart are difficult for everyone to read, so do not be discouraged.** When the patient begins to have trouble, it may be useful to provide some strategies to help him or her make the best attempt at seeing the letters. **Try reading just one letter at a time. Try blinking, or viewing the letter a little eccentrically, moving your head from side to side.** Indicate (without touching the chart) the particular letter you want the patient to concentrate on. **Try reading this one. Do you see something against the white background? Is there a smudge? Is it round or square? Does it have corners or lines you can see? Keep trying. The whole letter may suddenly appear to you. Go ahead and guess.**

Serum BDNF analysis: Blood is collected into 2 ml microtubes containing serum separation gel. The blood is allowed to clot for 30 min. Serum is then separated by centrifugation. Enzyme linked immusorbant assay (ELISA) is used to quantify BDNF in a set volume of serum from each sample. Briefly, highly specific antibodies against BDNF are used to bind BDNF to a 96 well plate surface and to link horseradish peroxidase (HRP) to the bound BDNF. The quantity of BDNF is indirectly measured by the activity of the HRP that is bound to the plate surface using a HRP substrate that produces a blue dye when catalyzed. A plate reader is used to measure absorbance at 450 nm (BioTek ELx808), and absorbance values were compared with an internal standard curve on the same plate.