Bike Extend

Exercise effects on brain connectivity and learning from minutes to months

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Overall Data Analysis Approach

The primary analysis concerns the difference in functional connectivity among the chronic treatment groups of moderate intensity (M) and light intensity (L) at the single terminus (last visit) of the 6-month RCT. Multiple regression will be used to regress functional connectivity (FC) on dummy coded group membership, and the stratification variables of age and sex. Suppose that FC for the i^{th} participant at the end of the study is denoted as y_i ($i = 1, \dots, N$) and group is coded as grp_i = 1 if M and grp_i = 0 if L. Then the multiple regression model for the primary analysis is

$$y_i = \beta_0 + \beta_1 grp_i + \beta_2 sex_i + \beta_3 age_i + e_i.$$

Under the typical assumption that e_i is normally distributed, the coefficients can be estimated using ordinary least squares. The null hypothesis of interest is that there is no group difference, $H_0: \beta_1 = 0$, which can be evaluated with a *t*-test. In order to account for missing data, multiple imputation will be used, and the null hypothesis of interest will be evaluated based on pooled estimates using Rubin's rules (1). In order to ensure maximal statistical power for the primary aim, the first analysis will have a single outcome, which is the average FC between the posterior hippocampus, posterior cingulate cortex, and the ventral medial prefrontal cortex. Additional exploratory analysis will be performed on individual connections with adjustment for multiple testing (i.e., adjustment for false discovery rate within a region of interest).

We will use a similar approach to examine intervention effects on learning rate in the hippocampal-dependent learning tasks compared to the non-hippocampal tasks. The final analysis of *Aim 1* will examine the relationship between changes in hippocampal-cortical FC and learning rate by adding hippocampal-cortical FC as an independent variable to the regression predicting learning rate. Secondary analysis for chronic effects on learning will evaluate mediation models that treat change in CRF as a continuous variable. The purpose of this analysis is to test the model proposed in *Aim 3* whereby change in CRF acts as a critical mediator leading to change in hippocampal-cortical FC and hippocampal-dependent learning. The α-adjustment for the secondary analysis will be more stringent than the primary analysis.

The secondary aim examines whether acute increases in FC that are specific to moderate intensity exercise are related to improvement in FC and learning at the end of the 6-month RCT. Specifically, we will test the prediction proposed in *Aim 2* that greater acute increases in FC to the M compared to L condition will be associated with a greater effect in the chronic M group. Acute increases will be computed for each participant based on a fitted linear mixed model (LMM) from the acute phase. The LMM models change from M to L accounting for the cross-over in conditions. A type of difference score will be computed for each participant based on the fixed and random effects estimates representing the acute M – L difference (2). Positive values indicate an increase in FC for M compared to L (and negative values indicate a decrease; 0 indicates no change). A multiple regression model will be used to regress FC on chronic group, the acute M – L difference, and their interaction. Suppose that the acute M – L difference for the i^{th} participant is denoted as $diff_i$. Then the regression model for the second aim is

$$y_i = \gamma_0 + \gamma_1 grp_i + \gamma_2 diff_i + \gamma_3 (grp_i)(diff_i) + e_i.$$

The interaction term allows the effect of the acute M – L difference to vary by chronic group. When $\gamma_3 \neq 0$, the acute difference has a different effect for the chronic M group. Therefore, the null hypothesis of interest for the second aim is $H_0: \gamma_3 = 0$. Missing data will again be handled with multiple imputation. The first test will consist of the same hippocampal-cortical outcome described above, and additional exploratory analysis will be performed adjusting for multiple testing.

The main analysis for all three aims will be conducted under the intent-to-treat (ITT) principle. A participant will be counted as a member of their group at the time of re-randomization in the chronic phase. Participants will be analyzed in their initial group assignments in a blinded manner, regardless of dropout or adherence. Fidelity will be assessed by separate regression models in which CRF is the outcome with the goal of examining if the treatment caused a sufficient difference in CRF. A small number of participants will be allowed to enroll as a couple with the couple being the unit for random assignment. One member of the couple will be randomly assigned for analysis and the other member's data will not be considered for analysis in the primary aim (data might be inspected for exploratory purposes).

Due to its importance in achieving our objectives, the power analysis is based on preliminary data for the relationship between aerobic exercise training change in learning rate on one of the learning tasks. Based on the effect size observed from a multiple linear regression of training group and additional covariates as predictors, our power analysis maintains an allowance of 10 predictor variables including training group. Based on these considerations, a sample size of 120 older adults, randomized to one of two training groups (N=60 per group), would ensure 95% power. If we further account for up to ~15% (N=18) missing data due to factors such as (a) motion or drop-out during scanning, (b) missing post-test due to drop-out during training, or (c) co-enrollment with spouse, we would still have a final sample size of ~N=100, which would achieve ~90% two-tailed power and still result in larger group sizes than our published results of hippocampal-cortical FC following exercise training. We do not have plans for formal interim analyses and there is no predefined interim statistical analysis or result that would cause termination of the trial.

Dealing with missing data: The primary analysis will be conducted according to the ITT principle, in which participants are analyzed in their assigned group at randomization. Multiple imputation will be used for pooled estimation, which provides unbiased estimates under the ignorable mechanism. It is not possible to determine if a missing data mechanism is ignorable or non-ignorable. In order to address the possibility of a non-ignorable mechanism, a sensitivity analysis using pattern mixture modeling with multiple imputation will be conducted under the framework discussed by Little and colleagues (3).

Assessing effects of adherence and training context: ITT analysis is recognized as the best approach for making sound inferences regarding the treatment effect (4). However, ITT focuses on the effect of treatment assignment rather than on the effect of the treatment for participants who experienced the treatment as defined in the protocol. For example, ITT analysis does not adjust for potential non-adherence (variations in session attendance) or treatment cross-over (exposure to the treatment intended for another group). In exercise trials both of these issues are theoretically important to examine because (a) mechanistically exercise effects are expected to be strongest in a dose-response manner relative to the prescribed exercise program, and (b) there is significant variability in the extent to which participants achieve the prescribed exercise intensity during their training. For example, the latter issue can occur if participants in the M group have difficulty consistently getting their heart rate up to higher intensities due to physical or motivational constraints; or, in contrast, if participants in the L group enrolled in the study with expectations to work harder and in turn get their heart rate up above the prescribed lighter intensity zone when they are exercising at their home sessions.

Therefore, in a series of un-blinded exploratory per-protocol analyses (5), we will test the extent to which adherence and training context affects training-induced change in primary outcomes of hippocampal-cortical FC and learning. Based on the issues outlined above, analyses will initially be based on pre-planned definitions of context and adherence. First, we will test the extent to which training heart rate (HR) differed in the lab compared to home sessions as a function of intervention group. Based on preliminary descriptive data, we predict that HR will be higher during home sessions for both groups, but there will be no average group differences in this context effect. Second, we will test all training group effects described above with an additional continuous interaction term for %sessions completed. We predict that greater sessions attended will have a weak to moderate effect on the benefit of M compared to L intensity training. Third, we will test the

same group interactions with a continuous interaction term for %sessions in the prescribed HR zone. We predict this will have a moderate to strong effect on primary outcomes, as adhering to the intensity prescription is predicted to have a stronger effect than attendance alone. A final analysis will further unpack the direction of intensity adherence, with negative values indicating the percent of sessions below the prescribed HR zone and positive values indicating the percent of sessions above the prescribed HR zone. This final intensity adherence analysis will test both *whether* and *how* gains in benefits were associated with variations in adherence to prescribed HR intensity.

References

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