Supplemental Information
Exercise and hippocampal memory systems

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I. Methodologies used to measure aerobic exercise intensity and cardiorespiratory fitness

Aerobic exercise can be defined as exercise to improve cardiorespiratory fitness that is fueled primarily on aerobic metabolism, which converts inspired oxygen to physical work. Aerobic physical activity (PA) intensity can be measured subjectively ["how hard are you working?" with answers on the Ratings of Perceived Exertion (RPE) scale on 6-20] or objectively based on heart rate in comparison to a personalized maximum heart rate (HR_{max}) [2]. A given intensity can be specified as a proportion of one's maximum heart rate (HR_{max}) (e.g., intensity = 0.60 could indicate 60% of HR_{max} in the following equation, Target Heart Rate = intensity* HR_{max}). HR_{max} can be estimated based on age (e.g., a common equation used to estimate age-predicted HR_{max} is 220 - age), but this formula will not work well for everyone [3]. Rather, ideally HR_{max} is determined during a maximal exercise test that pushes you to exhaustion. When this is not possible, a modified equation of HR_{max} = 208 - (0.7*age) is preferable for estimating maximum heart rate [4]. Additionally, when participants are on medications that could affect exercise effects on HR, such as beta blockers, or if they have a heart condition affecting HR monitor readings (e.g., arrhythmia), then subjective measures are particularly informative. By comparison, Heart Rate Reserve (HRR) also takes into account resting heart rate ($HR_{resting}$) [%HRR= intensity*(HR_{max} – $HR_{resting}$) + $HR_{resting}$). For instance, this table shows a typical description of different aerobic exercise intensities:

Table S1. Aerobic intensity levels

Intensity category	Objective measures	Subjective measures (e.g., Borg's RPE 6-20)	Qualitative description*
Sedentary/Resting	< 40% HR_{max} < 20% HRR	RPE < 8	- Sitting or lying down
Light	40 < 55% HR_{max} 20 < 40% HRR	RPE 8-10	- No noticeable change in breathing rate or sweating - Can be sustained for an hour or more
Moderate	55 < 70% HR_{max} 40 < 60% HRR	RPE 11-13	- Slight changes in breathing, but can be done comfortably while holding a conversation - Can be sustained for 30 minutes to an hour
Vigorous	70 < 90% HR_{max} 60 < 85% HRR	RPE 14-16	- Heavier breathing than moderate, cannot sustain conversation without interruption - Can be sustained for up to 30 minutes
High	≥ 90% HR_{max} ≥ 85% HRR	RPE ≥ 17	- Can be sustained for up to 10 minutes - Heavy breathing, cannot sustain conversation without interruption

Table S1. Modified version of Table 1 in [2]: Norton, K., Norton, L., Sadgrove, D., 2010. Position statement on physical activity and exercise intensity terminology. J Sci Med Sport 13(5), 496-502. HR_{max}, maximum heart rate; HRR, heart rate reserve; RPE, ratings of perceived exertion. Similar training zones have been published by the American College of Sports Medicine [5]. *There is some variability among adults on how their objective measures relate to RPE, and training status will affect their ability to exercise at for a given intensity at the estimated duration. However, generally the ability to hold a conversation (i.e., the "talk test") is a useful qualitative indicator of the transition between moderate and vigorous intensity.

II. Aerobic training paradigms utilized to evaluate cognition and brain in older adults

Exercise training protocols from representative studies cited in our main text are here examined in more detail. Note that because participants were inactive when they started the intervention, (1) their pre-training cardiorespiratory fitness is quite low (typically in bottom 10^{th}% of their age and sex matched peers), and (2) there is a "ramping" period where duration and/or intensity is gradually increased to a target training zone. Below, we summarize training intensity based on the peak intensity zone targeted during each intervention [1, 6-11]. The training intensities listed for each study refer to zones of minimum and maximum target heart rates for a given target intensity during training sessions. Ideally, as described above, each participant will have completed a supervised exercise test to determine their personalized maximum heart rate. With this value, personalized target heart rate zones can be determined, and even adjusted during training if exercise tests can be repeated.

Accordingly, it is best practice for participants to wear HR monitors during the intervention so that HR data can be monitored and used for feedback during training, and the validity of the intervention manipulation can be verified.

Figure S1. Average change in fitness from representative studies

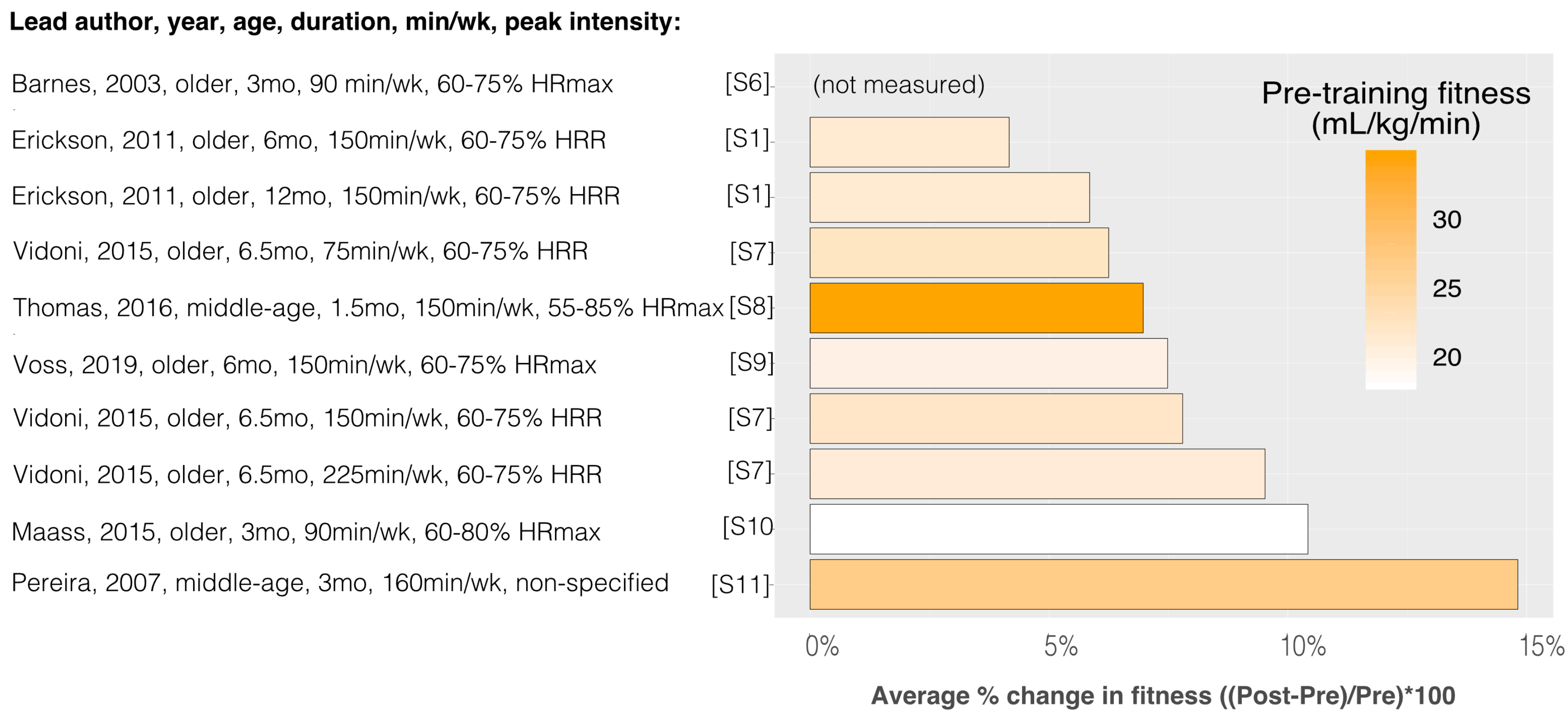

Figure S1. Range of changes in cardiorespiratory fitness (mL/kg/min) across representative training studies. Pre- and post-training fitness are measured with supervised maximal graded exercise tests. The x-axis indicates how much on average the aerobic walking group improved fitness following the intervention, and y-axis indicates different studies ordered from least to most change in fitness. The color coding indicates the average pre-training fitness level, which is a relevant factor in considering %change and shows participants in reviewed studies start with relatively low fitness (see discussion below). HR_{max}, maximum heart rate; HRR, heart rate reserve; mo, months; wk, week; min, minutes.

Specifically, Erickson et al., 2011 [1] measured fitness at 6 months and 12 months over a 12 month intervention, showing that longer training will lead to greater fitness gains. In addition, Vidoni et al., 2015 [7] examined the effect of increasing the duration of training per week, and also found a dose-response effect with the longest training time of 225 min/week resulting in the largest fitness gains. It is also worth highlighting that average cardiorespiratory fitness declines about 2% per year [12] from the sixth decade onwards, and an average fitness level for a 60-year-old male is 36 mL/kg/min and for a female it is 30 mL/kg/min (for an online calculator, see http://www.kumc.edu/fitness-ranking.html). By comparison, the typical pre-training average fitness in intervention studies described above with older adults is around 20 mL/kg/min, which is below the 10th percentile for 60 to 75 year-old males and females. Results from most training studies with cognitive and brain outcomes thus generally include primarily individuals that are well below average in their age and sex-predicted fitness, and yet still qualify to participate in the intervention (i.e., have not experienced major health problems or psychiatric disease).

This is important to keep in mind when applying the results to the general population. Further, much less is known about the additional benefits of improved fitness for older adults with an already active lifestyle and high fitness levels.

III. Individual differences in training response

In addition to the variability in fitness gains across studies, there are large individual differences in training responses within studies. For example, the plot below summarizes individual participant changes in fitness (mL/kg/min) for those in the walking group in the Erickson et al., 2011 study [1], which showed relatively smaller group changes (see Figure S1). Further, greater changes in fitness were related to greater increases in hippocampal volume for the walking but not the stretching group, suggesting that greater changes in fitness indicate greater benefit for hippocampal structure.

Variation in fitness change can be partly explained by attendance to exercise sessions (shown here), and other factors, such as genetics, age, and measurement error. However, studies often see a correlation between change in fitness and hippocampal brain or memory outcomes even when controlling for a range of known factors. Thus, more research is needed to

Figure S2.

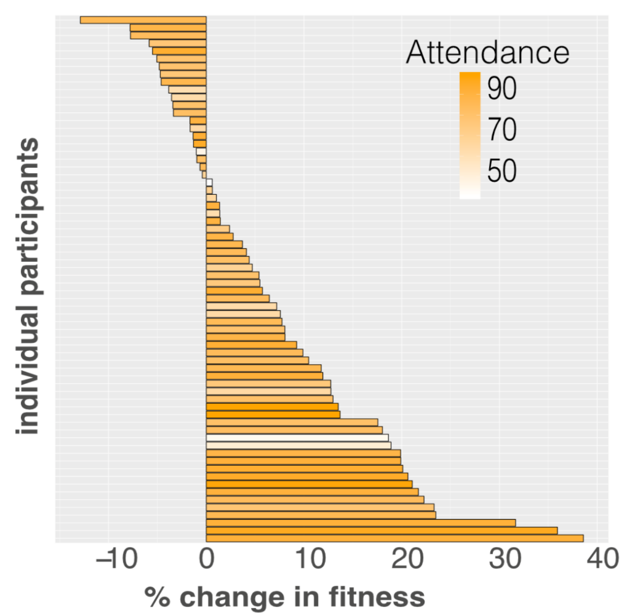

Figure S2. Variability within a given study [1] for the participants in the aerobic (walking) group. Attendance represents percentage of exercise sessions completed over the year-long intervention (3 sessions/week).

understand the mechanistic significance of change in fitness in relation to predicting improved hippocampal system memory outcomes.

IV. Cognitive constructs examined in meta-analyses on training studies

Recently, a number of meta-analyses have summarized the effects of aerobic exercise training on different aspects of cognition. Meta-analyses summarize results of different cognitive tasks across multiple studies. However, in these analyses different cognitive tasks are grouped together as reflecting a common cognitive construct. While this can be useful, it can result in classification of similar tasks under different constructs. For instance, a word list memory task may go under “declarative memory”, “memory”, or “verbal memory” – with varying degrees of precision in what other tasks are included within the domain of “memory.” Below we summarize in a table the different constructs of recent meta-analyses [13-23] with memory terms highlighted (yellow), including “visuospatial ability” which commonly includes configural memory tasks:

Table S2. Summary of recent meta-analytic effect sizes of exercise training effects on cognition

Meta-analysis	Population	Cognitive Status	Cognitive Construct Grouping Term	Exercise effect	Exercise SE	Control effect	Control SE	Std Mean Diff (SMD)	SMD SE
Barha2017	Older	Normal	Executive Function					2.064	0.249
Barha2017	Older	Normal	Episodic Memory					0.045	0.205
Barha2017	Older	Normal	Processing Speed					0.468	0.117
Barha2017	Older	Normal	Verbal Fluency					0.351	0.078
Barha2017	Older	Normal	Visuospatial Ability					0.645	0.259
Colcombe2003	Older	Normal	Controlled	0.461	0.035	0.12			
Colcombe2003	Older	Normal	Executive Function	0.68	0.05	0.1			
Colcombe2003	Older	Normal	Spatial	0.426	0.06	0.08			
Colcombe2003	Older	Normal	Cognitive Speed	0.274	0.05	0.08			
Forbes2015	Older	MCI	Cognition					0.21	0.2
Heyn2004	Older	Dementia	Cognition					0.57	0.07

Kane2017	Older	Normal	Executive-Attention-Processing Speed					Insufficient	
Kane2017	Older	Normal	Memory					Insufficient	
Law2014	Older	Mixed	Qualitative					Qualitative	
Northey2018	Older	Normal	Attention					0.27	0.07
Northey2018	Older	Normal	Executive Function					0.34	0.07
Northey2018	Older	Normal	Memory					0.36	0.07
Northey2018	Older	Normal	Working Memory					0.29	0.08
Panza2018	Older	Dementia Risk	Cognition					0.47	0.11
Roig2013	Adults	Normal	Long Term Memory					0.07	0.1
Roig2013	Adults	Normal	Short Term Memory					0.15	0.06
Smith2010	Adults	Normal	Attention Proc-Speed					0.158	0.05
Smith2010	Adults	Normal	Declarative Memory					0.128	0.06
Smith2010	Adults	Normal	Executive Function					0.12	0.05
Smith2010	Adults	Normal	Working Memory					0.03	0.07
Young2015	Older	Normal	Auditory Attention					0.15	0.28
Young2015	Older	Normal	Cognitive Inhibition					-0.06	0.12
Young2015	Older	Normal	Cognitive Speed					0.12	0.11
Young2015	Older	Normal	Executive Function					0.38	0.27
Young2015	Older	Normal	Motor Function					0.08	0.15
Young2015	Older	Normal	Perception					-0.01	0.25
Young2015	Older	Normal	Verbal Memory Delayed					0.1	0.13
Young2015	Older	Normal	Verbal Memory Immediate					0.08	0.24
Young2015	Older	Normal	Visual Attention					0.22	0.12
Young2015	Older	Normal	Visual Memory Immediate					-0.26	0.36
Young2015	Older	Normal	Working Memory					0.1	0.13

Table S2: Column for group "effect" denotes effect size as provided in the original meta-analysis. SMD, standardized mean difference between groups, which is an effect size estimating how much the effect favored a training group compared to a control group. SE, standard error of effect sizes. MCI, Mild cognitive impartment.

V. Summary of results from meta-analyses at the task-level

This section describes our method for summarizing results from aerobic training effects on different memory tasks (see Figure 1A in main text). We focused on standardized neuropsychological tasks that can predict accelerated age-related cognitive decline, cognitive impairment, and risk of progressing to dementia. These include delayed recall on word list learning (e.g., Rey Auditory Verbal Learning Task, Hopkins Verbal Learning Task, California Verbal Learning Task), delayed recall of details from stories (e.g., logical memory), and visuospatial configural memory (e.g., complex figure).

Additionally, cognitive experimental tasks designed to tap into subtle decline of hippocampal function may be fruitful for early detection of physical activity effects on the deterioration process. Therefore, we also summarized results from tasks which have been proposed to specifically tap into processes that require the hippocampus (e.g., pattern separation, spatial navigation, relational memory). Although the meta-analyses included some populations with cognitive impairment, because we are interested in prevention and the preclinical phase, our summary of outcomes only includes cognitively normal middle age and older adults. Note also, a new quantitative meta-analysis would be beyond the scope of our review, so our aim was to simply count how often memory tasks showed statistically significant change from training (see Figure 1A in main text).

Table S3. Hippocampal memory tasks evaluated for summary in Figure 1A

Task label	Task versions	Search terms
Visuospatial	Rey-Osterrieth Complex Figure (ROCF), alternative versions of the complex figure task	“ROCF”, “Rey-Osterrieth Complex Figure (ROCF)”, “rey-osterrieth”, “rey osterrieth complex figure”
Word List Learning	Auditory Verbal Learning task, California Verbal Learning task, Hopkins Verbal Learning task, List learning unspecified, Rey Auditory Verbal Learning task	RAVLT, “rey auditory”, “verbal learning”, CVLT, “california modified (CVLT)”, “california modified”, “california verbal”, “california learning”, HVLT, hopkins, “hopkins verbal”
Story Recall	Logical memory, Story Recall tasks unspecified	“logical memory”
Relational	Verbal or spatial paired associates tasks, face-name memory, face-place memory, any variant of memory for relations, spatial reconstruction.	“Paired associate”, “relational memory”
Wayfinding	No standard task exists	allocentric, “spatial navigation”, wayfinding,
Mnemonic discrimination	No standard task exists	“pattern separation”, “object discrimination”, “mnemonic discrimination”

Table S3. Alternative versions of tasks that were included in the summary of training effects by memory tasks.

A full database of studies, task outcomes, and a notebook showing the code used for creating the graph in Figure 1A are available here: https://github.com/mwvoss/physical-activity-outcomes

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