Report

Current Biology

Physical Exercise Performed Four Hours after Learning Improves Memory Retention and Increases Hippocampal Pattern Similarity during Retrieval

Highlights

- Performing aerobic exercise 4 hr after learning improved associative memory
- Exercise at this time also increased hippocampal pattern similarity during retrieval
- Exercise performed immediately after learning had no effect on memory retention
- Exercise could have potential as a memory intervention in educational settings

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In Brief

van Dongen et al. show that physical exercise performed 4 hr, but not directly, after learning improves long-term memory in humans. Such exercise was also associated with higher consistency in hippocampal activation during memory recall. Together, these findings suggest that correctly timed exercise holds promise as a memory intervention.

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Report

Physical Exercise Performed Four Hours after Learning Improves Memory Retention and Increases Hippocampal Pattern Similarity during Retrieval

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SUMMARY

Persistent long-term memory depends on successful stabilization and integration of new memories after initial encoding [1, 2]. This consolidation process is thought to require neuromodulatory factors such as dopamine, noradrenaline, and brain-derived neurotrophic factor [3–7]. Without the release of such factors around the time of encoding, memories will decay rapidly [3, 5, 6, 8]. Recent studies have shown that physical exercise acutely stimulates the release of several consolidation-promoting factors in humans [9–14], raising the question of whether physical exercise can be used to improve memory retention [15–17]. Here, we used a single session of physical exercise after learning to exogenously boost memory consolidation and thus long-term memory. Three groups of randomly assigned participants first encoded a set of picture-location associations. Afterward, one group performed exercise immediately, one 4 hr later, and the third did not perform any exercise. Participants otherwise underwent exactly the same procedures to control for potential experimental confounds. Forty-eight hours later, participants returned for a cued-recall test in a magnetic resonance scanner. With this design, we could investigate the impact of acute exercise on memory consolidation and retrieval-related neural processing. We found that performing exercise 4 hr, but not immediately, after encoding improved the retention of picture-location associations compared to the no-exercise control group. Moreover, performing exercise after a delay was associated with increased hippocampal pattern similarity for correct responses during delayed retrieval. Our results suggest that appropriately timed physical exercise can improve long-term memory and highlight the potential of exercise as an intervention in educational and clinical settings.

RESULTS

Seventy-two participants were randomly assigned to one of three age- and gender-matched groups; all learned 90 picture-location associations over a period of approximately 40 min (Figure 1; for visualization of the experimental trials, see Figure S1; for sample demographics, see Table S1). In each group, half of the participants started at 9 a.m. and half at 12 p.m. to control for time-of-day effects. Following a baseline cued recall test (test 1), participants in the immediate exercise (IE) group performed a 35-min interval training on an ergometer at an intensity of up to 80% of their maximum heart rate (see Supplemental Experimental Procedures and Figure S2). IE participants subsequently moved to a separate quiet environment for a 3-hr delay period, where they watched nature documentaries, before returning to the exercise lab for a control session. This control session did not involve exercise but used the same context otherwise. For the delayed exercise (DE) group, the protocol was identical but with the order of the exercise and control session reversed; for the no exercise (NE) group, both sessions before and after the delay period were control sessions. Participants returned to the lab 48 hr after initial encoding and performed a second cued recall test (test 2) in the magnetic resonance (MR) scanner. With this design, we could investigate whether post-learning physical exercise affected memory retention, whether its effects were time dependent, and whether our intervention influenced the neural substrate of memory retrieval as measured using fMRI. The study was approved by the local ethics committee (CMO Region Arnhem-Nijmegen, the Netherlands).

Response to Exercise

Our exercise intervention was successful in raising our participants' heart rates and subjective ratings of exercise intensity, in line with the intended schedule (see Supplemental Experimental Procedures and Figure S2), indicating that participants experienced the expected physiological consequences of the interval training.

Behavioral Performance

Memory performance on test 1 was well above chance level for all experimental groups (one-sample t test versus chance level [16.67%]; percentage of correct responses ± SEM: μ_{NE} = 79.1 ± 3.8%, μ_{IE} = 79.3 ± 2.7%, μ_{DE} = 85.2 ± 2.4%;

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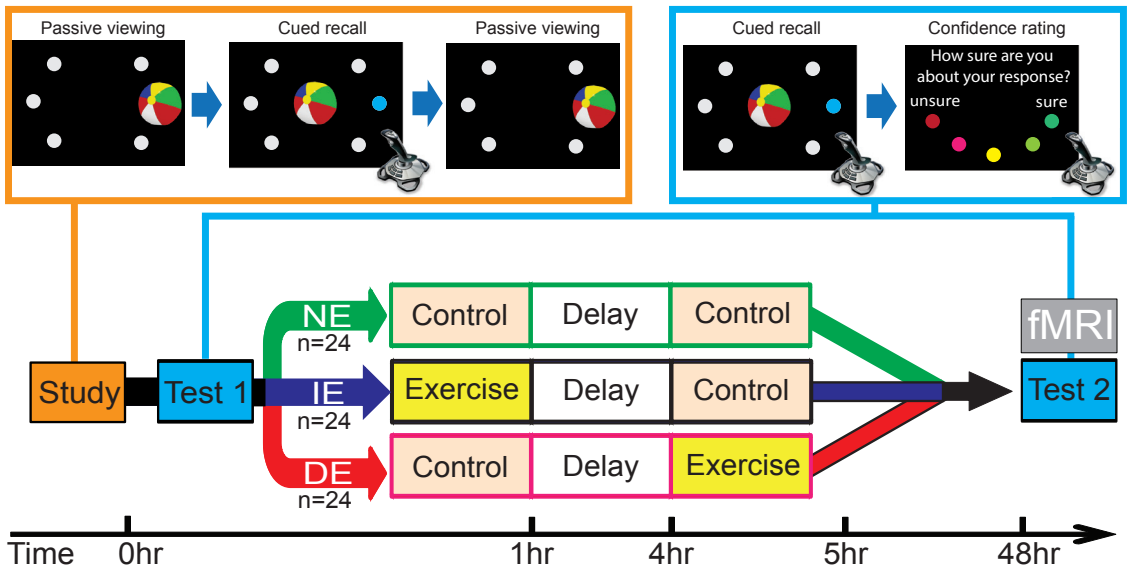

Figure 1. Experimental Design

IE, immediate exercise group; DE, delayed exercise group; NE, no exercise group. Participants first learned 90 picture-location associations and completed a baseline memory test (test 1) before undergoing two control sessions (NE) or a control session and an exercise session (IE and DE) separated by a 3-hr delay period. 48 hr after initial learning, a delayed memory test (test 2) was administered in the magnetic resonance scanner. See also Figure S1 for a visualization of the experimental trials and Figure S2 for the exercise protocol and measures of heart rate, exercise load, and ratings of exercise intensity. See also Table S1.

t_{NE} = 16.56, t_{IE} = 23.00, t_{DE} = 28.46; all $p < 0.001$; see also Figure S4), indicating that all groups successfully learned a substantial number of picture-location associations. Performance at test 1 was not significantly different between groups (F_{Group} = 1.48, p_{Group} = 0.236) nor dependent on starting time or gender (F_{Time} = 0.235, p_{Time} = 0.630; F_{Gender} = 1.74, p_{Gender} = 0.192).

To find out whether exercise influenced the consolidation of picture-location associations, and thus the retention of information learned on day 1, we used memory retention as our primary memory measure. This measure was defined as test 2 performance divided by test 1 performance and thus corrected for baseline performance differences between participants. Memory retention was significantly different between groups (μ_{NE} = 0.800, μ_{IE} = 0.795, μ_{DE} = 0.866; F_{Group} = 4.83, p_{Group} = 0.011; see Figure 2). Post hoc pairwise comparisons showed that retention in the DE group was higher than in the IE and NE groups, with no difference between the latter two groups (DE-IE: $p_{TukeyHSD}$ = 0.031; DE-NE: $p_{TukeyHSD}$ = 0.045; IE-NE: $p_{TukeyHSD}$ = 0.986). Raw performance scores for test 1 and test 2 can be found in Figure S3 and Table S1.

In addition, memory retention was higher in female than male participants (mean ± SEM: μ_{Female} = 0.84 ± 0.015, μ_{male} = 0.78 ± 0.021, F_{Gender} = 6.32, p_{Gender} = 0.019), but this effect did not interact with the observed retention difference between groups ($F_{Group \times Gender}$ = 0.639, $p_{Group \times Gender}$ = 0.531). Similarly, no main effect of participants' starting time nor interaction between group and starting time was observed (F_{Time} = 3.21; p_{Time} = 0.078; $F_{Group \times Time}$ = 2.31, $p_{Group \times Time}$ = 0.108). Memory retention was not correlated with participants' weekly exercise duration or frequency (Pearson's $r_{duration}$ = 0.057, $p_{duration}$ = 0.636; Pearson's $r_{frequency}$ = 0.031, $p_{frequency}$ = 0.799; see also Table S2).

To investigate whether exercise additionally modulated retrieval time and/or subjective measures of memory strength, we also analyzed the reaction times and confidence ratings during recall. Both reaction times and confidence ratings during test 1 and test 2 were not significantly different between groups (all $p > 0.05$; for the raw values, see Table S1). Across the sample, confidence was higher for correct versus incorrect responses at both test 1 and test 2 (paired-samples t tests, test 1: $\mu_{correct}$ = 4.41, $\mu_{incorrect}$ = 2.20, t_{Test1} = 22.95, p_{Test1}<0.001; test 2: $\mu_{correct}$ = 4.18, $\mu_{incorrect}$ = 2.24, t_{Test2} = 26.14, p_{Test2}<0.001). Similarly, reaction times were shorter for correct than incorrect responses (paired-samples t tests, test 1: $\mu_{correct}$ = 2,134 ms, $\mu_{incorrect}$ = 2,711 ms, t_{Test1} = 8.15, p_{Test1}<0.001; test 2: $\mu_{correct}$ = 2,646 ms, $\mu_{incorrect}$ = 3,012 ms, t_{Test2} = 6.23, p_{Test2}<0.001). Reaction times could not be directly compared between test 1 and test 2 since the MR scanner environment of test 2 was substantially different from test 1's experimental lab setting. However, confidence levels for correct responses were lower at test 2 versus test 1 (paired-samples t tests, $\mu_{Test1correct}$ = 4.41, $\mu_{Test2correct}$ = 4.18, t = 7.85, $p < 0.001$).

Together, these results suggest that performing physical exercise 4 hr after encoding promoted the retention of associative memory, without differentially affecting participants' reaction times or confidence levels.

Functional Neuroimaging Results

Using functional imaging, we found that blood oxygenation level dependent (BOLD) activation was increased in a wide range of brain regions during correct recall relative to a fixation baseline (see Figure 3A). Moreover, our analyses showed a significant difference in BOLD activation during correct and incorrect

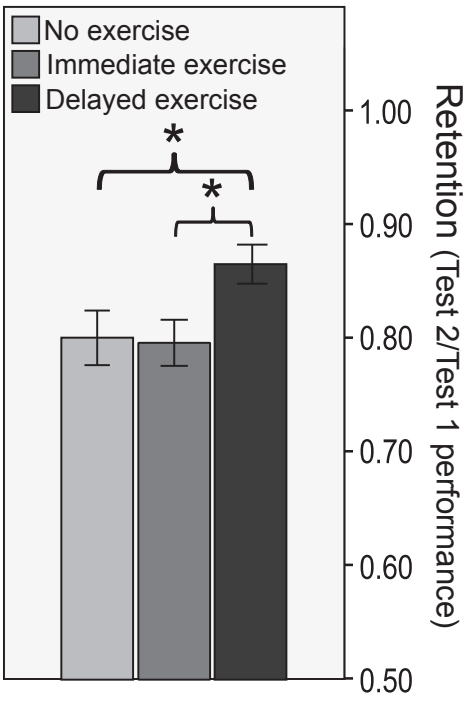

Figure 2. Memory Retention—Test 2/Test 1 Performance

Error bars denote SEMs. Asterisks denote significant differences at $p_{TukeyHSD} < 0.05$. See also Figure S3 for raw performance scores. See also Table S2.

responses in bilateral hippocampus, the striatum, and prefrontal, occipital, and parietal areas (see Figure 3B and Table S3). However, we observed no significant effect of experimental group for either contrast (for analytic details, see Supplemental Experimental Procedures).

Based on previous research demonstrating the relevance of consistent neural processing (i.e., pattern similarity) for memory retention and its reported utility in investigating differences in neural representations between experimental conditions and groups, we then conducted a hippocampal pattern similarity analysis [18–22]. We speculated that exercise-related physiological effects (e.g., dopamine and/or noradrenaline) could have neuromodulatory effects and thus alter the neural representations of recently encoded memories [23, 24]. In this way, exercise might produce differences in the neural response patterns observed during recall instead of differences in regional BOLD amplitude.

Using regions of interest in left and right hippocampus (Supplemental Experimental Procedures), we found that hippocampal pattern similarity was significantly different between groups during correct trials (Figure 4). A three-way repeated-measures ANOVA with the factors group, correctness, and hemisphere (left/right) indicated a main effect of group and correctness and a significant group × correctness interaction ($F_{Group} = 5.35$, $p_{Group} = 0.007$; $F_{Correct} = 3.97$, $p_{Correct} = 0.050$; $F_{Group \times Correct} = 5.43$, $p_{Group \times Correct} = 0.007$, all other effects and interactions $p > 0.05$). Post hoc pairwise comparisons indicated that hippocampal pattern similarity during correct (versus incorrect) trials was higher for the DE group than both IE and NE groups and not different between IE and NE participants (DE-IE: $p_{Sidak} = 0.012$; DE-NE: $p_{Sidak} = 0.003$; IE-NE: $p_{Sidak} = 0.967$). Pattern analyses in other brain regions showed that significant group differences were limited to the hippocampus only (Figure S4). Pearson's correlations between hippocampal pattern similarity and memory retention showed that across the sample, higher hippocampal pattern similarity was weakly but significantly associated with better memory retention (Pearson's $r = 0.287$; $p = 0.015$).

DISCUSSION

Together, these results indicate that performing physical exercise after learning can improve the retention of associative memories and modulates the consistency of hippocampal activation patterns during retrieval.

Considering that the exercise intervention took place after learning, delayed exercise most likely affected memory retention through an impact on memory consolidation. As such, it seems likely that one or more of the physiological consequences of aerobic exercise facilitated consolidation. Although we did not measure this directly in our study, previous research suggests that exercise triggers the release of BDNF, plasticity-related products (PRPs), noradrenaline, and dopamine, among other substances that promote neural plasticity. Such factors are critical for the consolidation of synaptic potentiation, as proposed in the synaptic tagging and capture (STC) hypothesis [3, 8], and are also important for later stages of memory consolidation [25, 26]. One possibility is that the release of PRPs at a time where naturally lower levels of PRPs would be available (i.e., several hours after learning) could have mediated the facilitation of memory retention in our study. Alternatively, exercise-dependent release of dopamine and noradrenaline could have facilitated consolidation similar to previously described effects of novelty and arousal [4, 5, 7, 14, 24, 27, 28].

We found no evidence for any effect of physical exercise immediately after learning, suggesting that the physiological response to exercise did not benefit memory consolidation at this stage. This finding is not predicted by consolidation theories such as the STC hypothesis. One explanation for this result could be that the neural context at this time was already optimal following initial learning and recall and could not be further improved through an additional influx of consolidation-promoting factors. Indeed, the good performance in all three groups at test 1 suggests that the study procedure itself enabled high levels of recall initially. Alternatively, the time course of synaptic consolidation might be different in humans compared to animals. Our experimental design does not allow us to directly investigate these explanations, however, so they should be considered as speculative until supported by other studies. In addition, even though our results do not seem to directly support the simplest STC prediction, the lack of current knowledge about the time course and mechanisms of STC in humans warrants caution in interpreting our findings this way.

We used a declarative memory task. However, previous studies using procedural tasks have provided evidence that in those settings the close proximity of exercise maximizes its effects on memory [29–31] (for an exception, see [32]). For this reason, it seems that the effect of exercise on memory is not only modulated by timing but also by the type of memory investigated. Several studies using declarative tasks have also shown

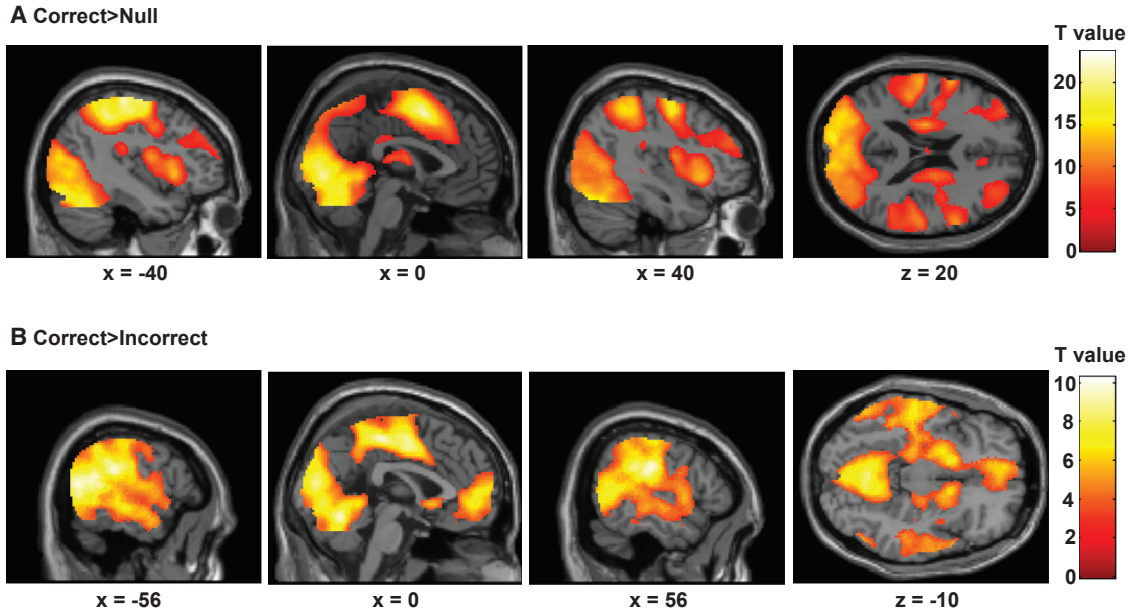

Figure 3. BOLD Activation during Test 2

(A) BOLD contrast between correct trials and null events.

(B) BOLD contrast between correct trials and incorrect trials.

Results from these group analyses include the full sample of participants. Activation shown on the SPM8 MNI template at $p_{voxel} < 0.001$ and $p_{cluster} < 0.05$(familywise error corrected). MNI coordinates are given for the relevant axis. See also Table S3 for statistics.

effects of exercise conducted immediately after acquisition, suggesting that experimental parameters such as task, type of learning, type of stimulus material, and subject population could be important for the net effect of exercise on memory retention [12, 14, 33, 34]. It remains a challenge for future research to determine the specific parameters that modulate the impact of exercise on memory.

Univariate analyses of BOLD fMRI activity during test 2 showed no effects of exercise. Although contrasts between correct and incorrect responses did provide evidence that brain regions associated with memory recall were recruited during our task, they did not distinguish between experimental groups. This finding suggests that cued recall after delayed exercise does not involve different brain circuits compared to no or immediate exercise. Moreover, delayed exercise was apparently not related to an overall modulation of BOLD signal amplitude in the correct versus incorrect responses contrast. Instead, our pattern similarity analysis points to delayed exercise maybe having caused a qualitative change in the activation patterns associated with correct recall of the picture-location associations.

As far as we know, between-group differences in hippocampal pattern similarity during retrieval in regards to acute exercise have not been reported previously. They could represent differential efficiency or coherence during memory retrieval and might relate to differences in memory strength [19]. The effect of exercise on pattern similarity could alternatively be interpreted as an increase in the signal-to-noise ratio, which is intriguing considering the neuromodulatory roles of dopamine and noradrenalin and their known association with exercise [9, 10, 13, 23, 24]. Interestingly, although pattern similarity was, across our sample, higher for correct compared to incorrect responses in hippocampus, striatum, and medial prefrontal cortex, it was specifically increased for the DE group in hippocampus only. This finding could imply that the hippocampus is particularly sensitive to the acute effects of exercise and thus important in mediating its cognitive benefits. The correlation between hippocampal pattern similarity and memory retention seems in line with this prediction, but more research is needed to substantiate this claim.

The results of the current study should be seen in the context of some limitations. First, we did not measure any peripheral or central measures of BDNF, dopamine, noradrenalin, or other factors released during aerobic exercise and thus cannot conclude with certainty that such factors mediated the behavioral and neural effects of our exercise intervention. Related, we did not measure cardiovascular fitness explicitly by, e.g., using a $V0_2$max test and therefore cannot rule out that the fitness level of our participants could modulate the effects of exercise we report here. Future studies should ideally include such measures or specific experimental manipulations to gain more insight into the molecular mechanisms of exercise-related memory improvement.

Second, based on the current data, we cannot yet determine the exact time window in which delayed exercise is effective in promoting memory retention. Future studies should include experimental groups that perform exercise at time points beyond 4 hr after learning to better delineate the critical time period for these effects.

Third, it is not possible to determine whether the observed effects of exercise require sleep and/or prolonged consolidation or could already have been observed during or shortly after exercise. Future research should further investigate to what degree

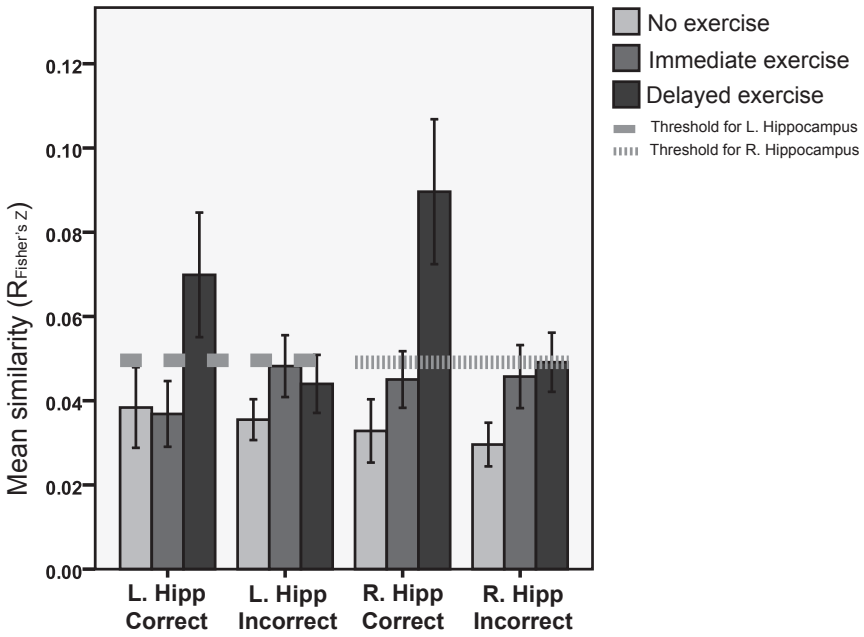

Figure 4. Hippocampal Pattern Similarity during Test 2

Thresholds are based on the 95th percentile of the computed distribution of random permutations; similarity above this threshold is higher than expected by chance (given a p_{chance} of 0.05). Error bars denote SEMs. L, left; R, right. See also Figure S4 for pattern similarity in other regions of interest.

sleep and time contribute to the mnemonic effects of acute aerobic exercise. Related to this, it is not yet clear how exercise affects memory retention beyond 48 hr after learning. Follow-up research should include longer retention periods to see whether or not positive effects of delayed exercise persist beyond 2 days.

Finally, we would like to stress that much is yet unknown about the molecular mechanisms of consolidation in humans. The timing of early consolidation processes is as yet poorly understood, and we do not know whether the molecular factors critical in animal models play similar roles in humans. In addition, by necessity, human studies generally use correlational analyses and peripheral measures of the physiological effects of exercise when investigating the mnemonic impact of exercise. It remains unclear how serum levels of, e.g., BDNF, dopamine, and noradrenaline relate to local changes in consolidation factors in the neural circuits important for long-term memory. As such, our speculations on possible mechanistic explanations of our findings should be interpreted with caution.

Regardless of these limitations, our results provide initial evidence that properly timed physical exercise can alter mnemonic processes at delayed retrieval and improve memory retention over a period of at least 48 hr. This finding is in line with previous studies reporting beneficial effects of physical exercise (for a review, see [15]) and highlights its potential as a memory intervention in humans. The economic, healthy, and practical nature of exercise makes it ideal for interventions in educational and clinical settings. Our experiment thus serves as a proof of principle study that could inspire future applications of exercise to boost long-term memory in various populations.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, and three tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.04.071.

AUTHOR CONTRIBUTIONS

E.V.v.D., R.G.M.M., and G.F. designed the experiment. E.V.v.D. and I.H.P.K. acquired the data. E.V.v.D. and I.H.P.K. analyzed the data. I.C.W. created an analysis toolbox for the pattern similarity analyses and assisted with this part of the analysis. E.V.v.D., I.H.P.K., I.C.W., R.G.M.M., and G.F. wrote the paper.

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