The Effects of Physical Exercise and Cognitive Training on Memory and Neurotrophic Factors

Jennifer J. Heisz, Ilana B. Clark, Katija Bonin, Emily M. Paolucci, Bernadeta Michalski, Suzanna Becker, and Margaret Fahnestock

Abstract

■ This study examined the combined effect of physical exercise and cognitive training on memory and neurotrophic factors in healthy, young adults. Ninety-five participants completed 6 weeks of exercise training, combined exercise and cognitive training, or no training (control). Both the exercise and combined training groups improved performance on a high-interference memory task, whereas the control group did not. In contrast, neither training group improved on general recognition performance, suggesting that exercise training selectively increases high-interference memory that may be linked to hippocampal function. Individuals who experienced greater fitness improvements from the exercise training (i.e., high responders to exercise) also had greater increases in the serum neurotrophic factors brain-derived neurotrophic factor and insulin-like growth factor-1. These high responders to exercise also had better high-interference memory performance as a result of the combined exercise and cognitive training compared with exercise alone, suggesting that potential synergistic effects might depend on the availability of neurotrophic factors. These findings are especially important, as memory benefits accrued from a relatively short intervention in high-functioning young adults. ■

INTRODUCTION

Physical exercise potently stimulates brain function (Heisz, Gould, & McIntosh, 2015; Heisz, Vandermorris, Wu, McIntosh, & Ryan, 2015; Hillman, Erickson, & Kramer, 2008), and its positive effects may be enhanced when combined with cognitive training. In animal models, exercise promotes the proliferation of new neurons within the dentate gyrus of the hippocampus whereas cognitive training promotes the survival and integration of those new neurons within the network (Fabel et al., 2009; Olson, Eadie, Ernst, & Christie, 2006; Gould, Beylin, Tanapat, Reeves, & Shors, 1999), suggesting that these synergistic pathways improve hippocampal function. Therefore, an intervention that combines the two may have a greater impact on hippocampal function than exercise alone. This study examined the impact of exercise training versus combined exercise and cognitive training to determine whether there are synergistic effects on memory in humans. Neurotrophic factors that support the survival and function of hippocampal cells were also examined as a potential mechanism for the observed memory changes.

If exercise promotes hippocampal function, it is important to determine the specific cognitive benefits. The hippocampus plays a pivotal role in the formation and retrieval of memories for complex events and episodes, and its subregions subserve different aspects of memory processing (Olsen, Moses, Riggs, & Ryan, 2012). The cornus ammonis 3 subregion (CA3) is critical for associative memory formation and retrieval, such as object–place and odor–place associations (Gilbert & Kesner, 2003) as well as novel place learning (Stupien, Florian, & Roullet, 2003). In contrast, the dentate gyrus is critical for the finer details of memory and is believed to play an important role in resolving interference between highly similar contexts, such as learning to discriminate nearby spatial locations (Hunsaker & Kesner, 2008). One potential mechanism for interference reduction in the dentate gyrus is sparse coding, which can orthogonalize and decorrelate incoming information through a process known as "pattern separation" (Rolls, 2013). However, sparse coding does not necessitate better memory. Instead, the opposite has been observed: behavioral discrimination of similar contexts is predicted by the degree of recruitment of overlapping populations of dentate gyrus neurons (Marrone, Adams, & Satvat, 2011), suggesting that less pattern separation predicts better memory. Newly generated neurons in the dentate gyrus (4–6 weeks old) may reduce pattern separation. These neurons are hyperexcitable, highly plastic, and recruited preferentially into novel memory traces relative to fully mature dentate gyrus neurons (Marín-Burgin, Mongiat, Pardi, & Schinder, 2012; Schmidt-Hieber, Jonas, & Bischofberger, 2004; Snyder, Kee, & Wojtowicz, 2001; Wang, Scott, & Wojtowicz, 2000). Furthermore, computational models suggest that

McMaster University, Hamilton, Ontario, Canada

Journal of Cognitive Neuroscience 29:11, pp. 1895–1907
doi:10.1162/jocn_a_01164

these hyperactive young neurons generate highly distributed and overlapping codes that decrease pattern separation but nonetheless help to reduce interference and improve memory (Becker, 2017; Finnegan & Becker, 2015; Aimone, Deng, & Gage, 2011).

Regular physical exercise enhances the structure and function of the hippocampus (Maass et al., 2014; Erickson et al., 2011; Pereira et al., 2007) and may have differential effects on younger versus older brains. Although exercise increases dentate gyrus neurogenesis in both younger and older animal models, exercise in older animals also has broader effects on the hippocampus, increasing dentate gyrus and CA3 synaptic density and reversing age-related degradation of hippocampal network efficiency (Siette et al., 2013). Critically, the up-regulation of neurogenesis in younger animals is accompanied by selective benefits on high-interference memory tasks such as contextual fear conditioning, discriminating similar spatial locations, and discriminating similar contexts (Nakashiba et al., 2012; Sahay et al., 2011; Creer, Romberg, Saksida, van Praag, & Bussey, 2010; Wojtowicz, Askew, & Winocur, 2008). On the basis of these data, exercise is expected to impart a selective benefit on high-interference memory tasks in younger humans (Déry et al., 2013). Consistent with this prediction, younger adults who had a greater aerobic fitness adaptation to 6 weeks of high-intensity interval aerobic exercise (i.e., high responders to exercise) increased performance on a high-interference memory task, but not on a general recognition task (Déry et al., 2013). Other cross-sectional studies have found that aerobic fitness predicts better memory performance on tasks of delayed free recall (Pereira et al., 2007), relational memory (Monti, Hillman, & Cohen, 2012; Chaddock et al., 2010), and spatial learning (Holzschneider, Wolbers, Röder, & Hötting, 2012).

The association between higher aerobic fitness and better memory performance may be enhanced by increases in neurotrophic factors (Maass et al., 2016; Whiteman, Young, Budson, Stern, & Schon, 2016; Whiteman et al., 2014; Griffin et al., 2011). Specifically, insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic factor (BDNF) may underlie the effect of exercise on hippocampal function by promoting the survival, maturation, and maintenance of new cells in the hippocampus (Fahnestock et al., 2012; Fahnestock, 2011; Schmidt & Duman, 2010; Carro, Trejo, Busiguina, & Torres-Aleman, 2001; Trejo, Carro, & Torres-Alemán, 2001; Carro, Nuñez, Busiguina, & Torres-Aleman, 2000). IGF-1 and BDNF are both known to influence neurogenesis and plasticity through similar signaling pathways (Cotman, Berchtold, & Christie, 2007; Cotman & Berchtold, 2002). Exercise increases IGF-1 levels—a potent stimulus for angiogenesis—and this is believed to act as an upstream mediator to increase the production of BDNF in the hippocampus (Cotman et al., 2007). BDNF regulates synaptic plasticity, which is essential for high-interference memory (Vaynman, Ying, & Gomez-Pinilla, 2004), and thus, both IGF-1 and BDNF are believed to play key roles in exercise-induced cognitive effects (Cotman et al., 2007).

Up to 1 hr postexercise, acute aerobic exercise increases IGF-1 and BDNF and the cascade of reactions they trigger (Knaepen, Goekint, Heyman, & Meeusen, 2010; Cotman & Berchtold, 2002). A dose–response relationship exists between the intensity of the aerobic exercise and BDNF levels, such that higher intensity exercises induce greater increases in BDNF, with greater increases for interval exercises compared with continuous exercises (Afzalpour, Chadorneshin, Foadoddini, & Eivari, 2015; Marquez, Vanaudenaerde, Troosters, & Wenderoth, 2015). Likewise, with chronic training, aerobic exercise increases resting-state levels of BDNF (Dinoff et al., 2016). Interestingly, these acute (Knaepen et al., 2010) and chronic effects (Dinoff et al., 2016) of exercise on BDNF have only been observed for aerobic exercise but not for resistance exercise. Moreover, chronic increases in resting-state IGF-1 and BDNF are related to aerobic fitness, but only BDNF levels are also related to memory performance (Whiteman et al., 2014).

The effect of exercise on high-interference memory may be enhanced if combined with memory training. Although cognitive training does not typically transfer to other cognitive domains or even to other untrained tasks within the same cognitive domain (Makin, 2016; Jaeggi, Buschkuehl, Shah, & Jonides, 2014; Kelly et al., 2014; Melby-Lervåg & Hulme, 2013; Owen et al., 2010), exercise may help to facilitate transfer effects: In animal models, high-interference memory training increases the survival of newborn cells within the dentate gyrus (Gould et al., 1999), and this may be complementary to the increased newborn cell proliferation induced by exercise (Curlik & Shors, 2013). Moreover, in neurogenesis-ablated mice, the combination of environmental enrichment and exercise partially rescues neurogenesis and restores memory (Sakalem et al., 2017). Few studies have examined the combined effects of exercise and cognitive training in humans, and these have been limited to older adult populations (Ngandu et al., 2015; Law, Barnett, Yau, & Gray, 2014; Linde & Alfermann, 2014; McDaniel et al., 2014; O'Dwyer, Burton, Pachana, & Brown, 2007) or individuals with neurological impairment (Evans, Greenfield, Wilson, & Bateman, 2009). In one study, older adults who engaged in combined exercise and memory training showed greater memory improvements than those who engaged in exercise training alone. However, only one of the eight memory training sessions in their program focused on high-interference memory, and so it is unclear whether this aspect of training was driving the observed change (Fabre, Chamari, Mucci, Masse-Biron, & Prefaut, 2002). Furthermore, given that hippocampal neurogenesis declines with age (Voss, Vivar, Kramer, & van Praag, 2013) and may be less crucial for memory in the older adults, the effects of combining exercise with cognitive training may be more robust in younger adults. It remains unclear whether combining exercise with cognitive training would

elevate basal levels of BDNF and IGF-1 to strengthen the interplay between aerobic fitness, BDNF, and memory to a greater extent than exercise alone.

This study is the first to examine the combined effect of exercise and cognitive training on memory and neurotrophic factors in young adults. Participants completed 6 weeks of exercise training, combined exercise and cognitive training, or no training (control). The transfer of cognitive training was assessed using a memory task that provided an index of high-interference memory and general recognition. The impact of training on aerobic fitness and serum neurotrophic factors was also assessed. We hypothesized that both training protocols would increase aerobic fitness, high-interference memory performance, and neurotrophic factor levels compared with the no-training group and that combining exercise with cognitive training would result in even greater increases in high-interference memory and neurotrophic factor levels than exercise alone. Furthermore, given that exercise-induced brain plasticity may depend on the individual's fitness improvements from exercise training (Déry et al., 2013), we hypothesized that individuals with greater fitness gains from exercise training (i.e., high responders to exercise) would also show greater increases in both high-interference memory and neurotrophic factors, relative to individuals with lower fitness gains (i.e., low responders to exercise).

METHODS

Participants

The 95 healthy young adults (58 women, 37 men; age *M* (*SD*) = 21 (±3) years, range = 17–30 years) who participated in the study provided written informed consent and met the inclusion criterion of ≤1 hr/week of vigorous exercise (see Table 3 for baseline physical activity). Sixteen additional participants dropped out of the study (14%), of whom seven were assigned to the control group, three were in the exercise group, and six were in the combined exercise and cognitive training group. Participants were recruited through posters distributed to McMaster University students on campus and online. All participants received an honorarium for their participation in the study.

Intervention Training

Participants were assigned to one of three groups: (1) exercise training group, (2) combined exercise and cognitive training group, or (3) no-training control group. Exercise and cognitive training sessions were all conducted in a laboratory setting under direct supervision by a research assistant and were performed in a group.

Exercise training consisted of 20 min of high-intensity interval training (HIT; Heisz, Tejada, Paolucci, & Muir, 2016) ~3 times a week for 6 weeks (mean number of training sessions for the exercise group: 17 ± 1 *SD*, range = 16–18; combined exercise and cognitive training group: 17 ± 1 *SD*, range = 14–20). We created individualized exercise protocols based on the results of preintervention VO_2 peak tests using the maximum workload that each individual was capable of exerting and his or her heart rate at that peak wattage. Participants completed HIT on stationary cycle ergometers (Lifecycle 95Ci). The protocol consisted of a 3-min warm up with a resistance of 50 W, followed by 10 alternating high-intensity (60-sec high-intensity intervals at ~80% maximum wattage and ~90–95% peak HR) and recovery (60-sec active recovery intervals at ~30% of their maximum wattage, ≥50 W) intervals, and then a 2-min cool down at 50 W. Heart rate was monitored using Polar RS300X heart rate monitors. Workload for the high-intensity intervals was increased every week to maintain a desired target heart rate of 90% peak heart rate as assessed at baseline. Participants progressed through the levels at an individualized pace for the duration of the intervention.

Combined exercise and cognitive training consisted of the exercise training (as described above) plus cognitive training completed on the same day, during the same session (mean number of training sessions reported above). Cognitive training consisted of 20 min of training on a computerized version of the Concentration Memory Task (a.k.a. Pelmanism [Makin, 2016], Match, Pairs or Pexeso, adapted from Goldstein, Déry, Pilgrim, Ioan, & Becker, 2016), ~3 times a week for 6 weeks. Participants played the game at different levels of difficulty with different numbers of cards to be remembered. All participants began training at Level 1, with the presentation of a 4 × 3 array of 12 facedown cards. Two identical copies of images of six different faces were hidden beneath the cards. All faces were the same size, grayscaled, and without hair to maximize the interpattern similarity and create a high-interference memory task. Participants first completed an incidental learning phase in which they were instructed to learn the locations of the faces with the aim of finding matched pairs. During each trial, participants selected two cards to reveal the faces below. Regardless of whether they successfully uncovered a matched pair of faces, each card returned to a facedown position upon the completion of each trial. Correctly matched pairs of faces were displayed on the side. Once participants found all the matched pairs of faces, their memory for the face pair locations was tested both immediately and following a 5-min delay from the immediate test. Performance was based on the number of mismatches made on the memory test following the 5-min delay, with fewer mismatches indicating better memory performance. If three or fewer mismatches were made on the delayed memory test, the array of cards increased by two face pairs to increase difficulty to the next level, up to a maximum of 44 cards (Level 9). The maximum level reached by the participant by the end of a session was the level they started at for the next training session. Participants progressed through the

levels at an individualized pace for the duration of the intervention. Eighteen participants performed each cognitive training session before each exercise training session, whereas 11 participants performed each exercise training session before each cognitive training session. Preliminary ANCOVA with Training order entered as a between-subject factor, Posttest values of memory or neurotrophic factor as the dependent variable, and their pretest values entered as covariates revealed no effect of the order of training on dependent variables. This was true regardless of whether exercise training response was entered as a between-subject factor, and so we collapsed across training order for all subsequent analyses.

Control participants did not perform either training protocol and were asked to remain sedentary for the 6 weeks.

Pre-/Posttesting

The experimental procedure included pre- and posttesting that was typically completed over 2 days: Day 1 always started with a 12-hr fasted blood draw, followed by something to eat and then cognitive testing. On Day 2, participants completed aerobic fitness testing. The pre- and posttesting sessions were separated by the 6-week intervention, and posttesting was done within 48 hr after completing the intervention.

Neurotrophic Factors

Twelve-hour fasted blood samples were collected in the morning into BD Vacutainer SST tubes (BD, Franklin Lakes, NJ). Immediately following blood collection, the tubes were chilled on ice for 30 min and then centrifuged at 4000 rpm for 10 min at 4°C. The supernatant was then collected to obtain serum and aliquoted into cryovials for storage at −80°C until analysis. Serum BDNF was measured using the human BDNF DuoSet ELISA kit (R&D Systems, Minneapolis, MN), and serum IGF-1 was measured using the human IGF-1 Quantikine ELISA kit (R&D Systems). Serum samples measured by the BDNF ELISA were diluted 75×, whereas serum samples measured by the IGF-1 ELISA were pretreated and diluted 100× according to the manufacturer's instructions (R&D Systems). Samples and standards for each ELISA were run in duplicate. Absorbance was measured at 450 nm, with a reference at 540 nm, using a Multiskan GO UV/Vis microplate spectrophotometer and SKANIT 3.2 software (Thermo-Fisher Scientific, Waltham, MA).

Memory Task

Kirwan and Stark's mnemonic similarity task (MST; Yassa & Stark, 2011; Bakker, Kirwan, Miller, & Stark, 2008; Kirwan & Stark, 2007) was used to assess memory function pre- and postintervention. MST is a test of memory for images of everyday objects; importantly, the task includes high-interference trials on which highly similar lures must be distinguished from previously studied items. The correct discrimination of these high-interference lures preferentially engages the CA3/dentate gyrus (Kirwan & Stark, 2007), correlates negatively with stress and depression scores (Déry, Goldstein, & Becker, 2015; Déry et al., 2013; Shelton & Kirwan, 2013) and heavy alcohol consumption (Goldstein et al., 2016), and declines with aging (Toner, Pirogovsky, Kirwan, & Gilbert, 2009). Conversely, exercise is associated with enhanced performance on these items (Déry et al., 2013). In rodents, stress, heavy alcohol exposure, and aging are all factors that reduce neurogenesis (Nixon & Crews, 2002; Gould, McEwen, Tanapat, Galea, & Fuchs, 1997; Kuhn, Dickinson-Anson, & Gage, 1996), whereas exercise enhances neurogenesis (Van Praag, Kempermann, & Gage, 1999). Furthermore, rodents with reduced neurogenesis perform more poorly on a wide range of high-interference memory tasks including tasks that test memory retention after a long time delay (Ben Abdallah et al., 2013; Pan, Chan, Kuo, Storm, & Xia, 2012; Snyder, Hong, McDonald, & Wojtowicz, 2005); tasks that require the association of stimuli across time (Shors et al., 2001) or the discrimination between similar spatial locations, objects, and contexts (Kheirbek, Tannenholz, & Hen, 2012; Nakashiba et al., 2012; Niibori et al., 2012; Clelland et al., 2009); tasks that create retroactive interference between current and previously learned information (Luu et al., 2012); tasks that create proactive interference between overlapping stimulus sets learned at different times (Winocur, Becker, Luu, Rosenzweig, & Wojtowicz, 2012); and tasks that create interference due to reversal learning (Kalm, Karlsson, Nilsson, & Blomgren, 2013; Burghardt, Park, Hen, & Fenton, 2012; Pan et al., 2012; Garthe, Behr, & Kempermann, 2009) and extinction (Cleva, Wischerath, & Olive, 2011; Noonan, Bulin, Fuller, & Eisch, 2010). Taken together, these findings support the hypothesis that, in humans, the MST is sensitive to the unique coding properties of the CA3 and dentate gyrus including neurogenesis.

The MST involves differentiating between previously learned images and novel images, some of which are highly similar, generating a high degree of memory interference (Figure 1). Following an incidental learning phase during which participants were asked to classify a sequence of 60 images of objects as indoor or outdoor, the recognition phase asked participants to judge whether each test image was an exact copy of an image already seen (30 repeat images; correct response = "Old"), highly similar but not identical to an image already seen (30 lure or decoy images; correct response = "Similar"), or completely new (30 foil images; correct response = "New"). A different stimulus set was used in the pre- and posttesting sessions.

A correction factor based on responses made to new items was applied to correct for response bias. "High-interference memory" was defined as the bias-corrected ability to correctly identify lure items as "similar"

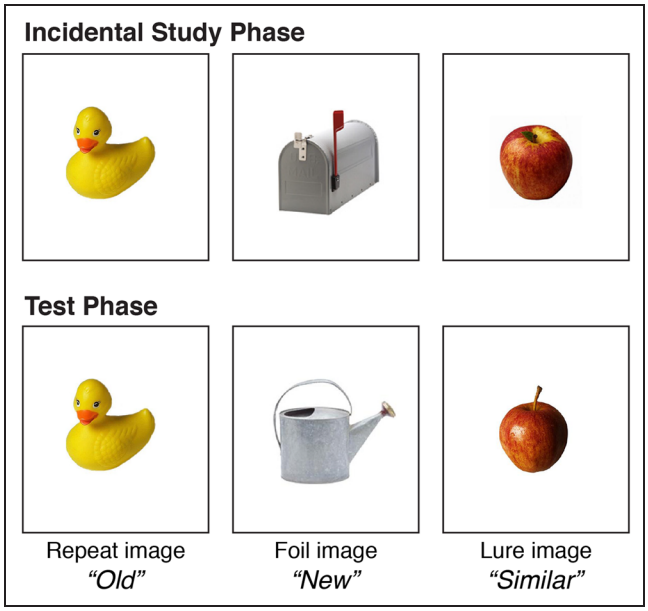

Figure 1. Mnemonic similarity task. MST involves differentiating between previously learned images and novel images, some of which are highly similar, and this generates a high degree of memory interference. Following an incidental learning phase during which participants were asked to classify a sequence of 60 images of objects as indoor or outdoor, the recognition phase asked participants to judge whether each test image was an exact copy of an image already seen (30 repeat images; correct response = "Old"), highly similar but not identical to an image already seen (30 lure or decoy images; correct response = "Similar"), or completely new (30 foil images; correct response = "New"). A different stimulus set was used in the pre- and posttesting sessions.

[p("Similar"|Lure image) − p("Similar"|Foil image)] × 100. "General recognition" was defined as the bias-corrected ability to correctly identify a repetition as "old" [p("Old"|Repeat image) − p("Old"|Foil image)] × 100. Inspection of the data revealed that several participants did not follow task instructions (i.e., did not use all target buttons; number of participants: pretest, 8/95; posttest, 4/95), and their data were removed from the memory analysis.

Aerobic Fitness

To confirm that exercise training improved aerobic fitness, peak oxygen consumption (VO_2 peak) was measured. All participants completed a maximal aerobic fitness test on a cycle ergometer using a metabolic cart to determine VO_2 peak.

Statistical Analysis

The data were initially screened for missing cells; 1% of the data were missing, and those cells were left empty for the analyses. The data were also screened for extreme outliers (Q1 − 1.5 × IQR; Q3 + 1.5 × IQR); 2.9% of the data met these criteria and were excluded from subsequent analyses. All data were normally distributed except for recognition memory performance scores, which were transformed to normal for subsequent analyses.

Manipulation checks for potential group differences in preintervention scores were conducted using separate univariate ANOVAs with a between-subject factor of Group (control, exercise, combined). Moreover, to check that exercise and cognitive training improved performance on the trained tasks, repeated-measures ANOVAs were conducted on the average workload of the high-intensity intervals for the exercise training and, on the average game level, completed for the cognitive training, with a within-subject factor of Time (1–6 weeks). The ANOVA for the average workload also included a between-subject factor of Group.

Group Effects

To test our main hypotheses regarding the effects of training on memory, neurotrophic factors and aerobic fitness, we conducted univariate ANCOVAs with the Posttest value as the dependent factor, Group (control, exercise, combined) as the between-subject factor, and the pretest value as the covariate. This was done separately for aerobic fitness, high-interference memory performance, general recognition memory performance, and BDNF and IGF-1 levels.

Individual differences in response to exercise training were assessed by dichotomizing participants by aerobic fitness into high versus low responders using a median split to characterize the interaction between exercise training response and group. The median aerobic fitness was calculated by collapsing the exercise and combined training groups. We conducted ANCOVAs of memory scores and neurotrophic factor levels with the Posttest value as the dependent factor, Exercise training response (high vs. low responder to exercise) and Group (exercise, combined) as between-subject factors, and the pretest value as the covariate. This was done separately for high-interference memory performance, general recognition memory performance, and BDNF and IGF-1 levels. If a significant interaction between exercise training response and group was observed, post hoc analyses of the simple main effects were assessed for high and low exercise responders separately using ANCOVAs with the Posttest value as the dependent factor, Group as the between-subject factor, and the pretest value as the covariate.

As a secondary analysis, all significant associations between our key measures and exercise training response were evaluated using Pearson's correlation (one-tailed) with aerobic fitness (i.e., VO_2 peak) as a continuous variable, with posttest values entered as the dependent variables and pretest values entered as covariates. Post hoc hierarchical linear regression analyses were used to evaluate whether interactions between memory scores and aerobic fitness were modified by BDNF or IGF-1 levels. Post-minus-pre change scores for all variables were used.

Table 1. Mean (*SD*) Pre and Post Outcome Measures for the Control Group, Exercise Training Group, and Combined Exercise and Cognitive Training Group

	Control		*Exercise*		*Combined*	
n	32		34		29	
Age	20.5 (2.8)		20.9 (2.7)		21.7 (3.6)	
Sex (female/male)	21/11		21/13		16/13	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
VO_2 peak (ml/kg/min)	30.9 (6.8)	30.5 (8.1)	34.3 (8.2)	39.1 (9.3)	31.5 (7.0)	35.7 (7.7)
High-interference memory (%)	48.9 (15.2)	46.6 (17.3)	48.4 (23.1)	59.6 (13.8)	41.3 (20.5)	55.0 (18.1)
General recognition memory (%)	81.5 (7.5)	83.2 (8.6)	84.3 (11.9)	84.9 (8.3)	84.9 (12.9)	86.9 (9.2)
BDNF (ng/ml)	31.9 (8.3)	33.2 (7.3)	33.5 (7.9)	31.3 (7.6)	27.9 (8.8)	29.0 (7.0)
IGF-1 (ng/ml)	177.9 (43.5)	177.1 (37.9)	178.0 (55.1)	174.0 (48.4)	176.0 (53.0)	167.1 (51.9)

Memory was entered as the dependent variable. Aerobic fitness was entered as an independent variable in Step 1 of the model, and BDNF and IGF-1 were entered (stepwise) as independent variables in Step 2 of the model.

RESULTS

Manipulation Checks

Table 1 reports baseline levels of key variables. There were no group differences at baseline in aerobic fitness, $F(2, 91) = 1.92$, $p = .15$, memory performance (high-interference memory: $F(2, 79) = 1.15$, $p = .32$; recognition memory: $F(2, 81) = 1.76$, $p = .18$), or IGF-1 levels, $F(2, 90) = .02$, $p = .99$; BDNF values were significantly lower in the combined group than the exercise only group (main effect of group: $F(2, 88) = 3.66$, $p = .03$). There were no significant Pearson correlations between any of the variables at baseline (all ps $> .1$).

Across the 6 weeks of training, performance increased linearly with respect to the average workload attained by the exercisers (Table 2; main effect of Time: $F(5, 305) = 166.92$, $p < .001$, $\eta_p^2 = .73$), and there were no significant differences in workload attained by the exercise group and the combined exercise and cognitive training group (main effect of Group: $F(1, 61) = 0.18$, $p = .67$; Group × Time interaction: $F(5, 305) = 1.54$, $p = .22$). There was also a linear increase in the game level attained by the cognitive trainers (main effect of Time: $F(5, 140) = 120.67$, $p < .001$, $\eta_p^2 = .81$; Table 2).

Group Effects

For the high-interference memory task, there was a main effect of Group, $F(2, 70) = 5.12$, $p < .01$, $\eta_p^2 = .13$. High-interference memory improved more for the exercise ($p = .006$) and the combined ($p = .008$) training groups than the control Group (Table 1; Figure 2). There was also a main effect of Group for aerobic fitness, $F(2, 87) = 8.53$, $p < .001$, $\eta_p^2 = .16$, with greater fitness gains for the exercise ($p < .001$) and the combined ($p = .002$) training groups than the control group (Table 1). No group differences were observed for BDNF levels, $F(2, 76) =$

Table 2. Linear Increases in Mean (*SD*) Difficulty of the Exercise Training (Watts) and Cognitive Training (Level) across the 6 Weeks for the Exercise Training Group and Combined Exercise and Cognitive Training Group

	Week 1	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*
Exercise Training Watts						
Exercise	154 (47)	159 (48)	171 (54)	178 (58)	189 (62)	195 (67)
Combined	154 (45)	166 (47)	175 (48)	186 (52)	195 (56)	204 (59)
Cognitive Training Level						
Combined	1.4 (0.5)	2.2 (0.9)	2.7 (1.0)	3.1 (1.1)	3.7 (1.1)	4.1 (1.2)

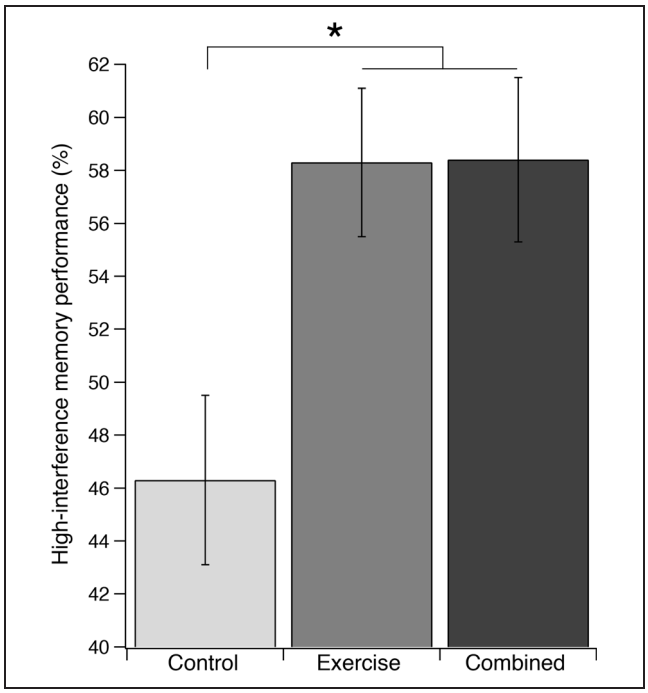

Figure 2. High-interference memory performance following 6 weeks of no training (control), exercise training, or combined exercise and cognitive training. Both the exercise and combined training groups had better high-interference memory performance than the control group. This was supported by an ANCOVA, which revealed a main effect of Group. Pretest values were entered as covariates in the models at the following values: 47%. Error bars represent *SEM* for each group. *$p < .05$.

1.14, $p = .33$; IGF-1 levels, $F(2, 90) = 1.01$, $p = .37$; or recognition memory scores, $F(2, 70) = .39$, $p = .68$ (Table 1). For recognition memory, bootstrapped one-sample t tests revealed that untransformed pretest ($p = .001$, 95% CI [−18%, −13%]) and posttest ($p = .001$, 95% CI [−18%, −14%]) recognition scores were significantly lower than 100%, suggesting that the lack of significant effect of Group on recognition memory was not due to a ceiling effect.

Individual Differences

Using a median split, exercisers in the combined and the exercise training groups were split into high (>4.6 ml/kg/min) versus low (<4.6 ml/kg/min) responders to the exercise training based on their post-minus-pre change in VO_2 peak; 42% of the high responders were from the combined group, and 48% percent of the low responders were from the combined group. Three participants were missing a VO_2 peak score and were excluded from the following analyses.

Manipulation checks confirmed that high and low responders did not significantly differ in the number of training sessions that they attended (independent samples t test: $t(58) = 0$, $p = 1$; Table 3) or in their progression through the cognitive training for those in the combined group (ANOVA, main effect of Exercise response: $F(1, 25) = 0.89$, $p = .36$; Week × Exercise response interaction: $F(5, 125) = 0.65$, $p = .54$). They also did not differ at baseline with respect to age, physical activity level, aerobic fitness, memory performance, or neurotrophic factors (all ps > .1). The only exception was the ratio of women to men, which was higher for low responders than high responders, $t(58) = 2.15$, $p = .035$ (Table 3); however, including sex as a covariate did not affect the results reported below. Furthermore, baseline aerobic fitness (evaluated as a continuous variable) did not significantly correlate with changes in memory (high-interference memory, $r(51) = -.11$, $p = .22$; general recognition, $r(50) = .13$, $p = .19$) or neurotrophic

Table 3. Mean (*SD*) Pre and Post Outcome Measures for Low versus High Responders to Exercise Training from Both the Exercise Group and the Combined Exercise and Cognitive Training Group

	Low Responder		*High Responder*	
n	30		30	
Age	21.4 (3.3)		21.3 (3.1)	
Sex (female/male)	22/8		14/16	
Baseline PA level (hr/week)	0.22 (0.34)		0.17 (0.21)	
Training sessions completed	17 (1)		17 (1)	
	Pre	*Post*	*Pre*	*Post*
VO_2 peak (ml/kg/min)	33.3 (7.5)	34.1 (6.9)	32.3 (8.1)	41.1 (9.0)
High-interference memory (%)	44.3 (23.4)	55.1 (19.1)	46.3 (21.9)	60.7 (12.1)
General recognition memory (%)	87.4 (8.7)	88.3 (5.8)	82.5 (14.7)	84.1 (10.0)
BDNF (ng/ml)	31.3 (9.1)	28.4 (8.3)	30.8 (8.7)	31.7 (6.2)
IGF-1 (ng/ml)	182.5 (54.6)	166.5 (46.3)	170.4 (49.3)	172.1 (49.1)

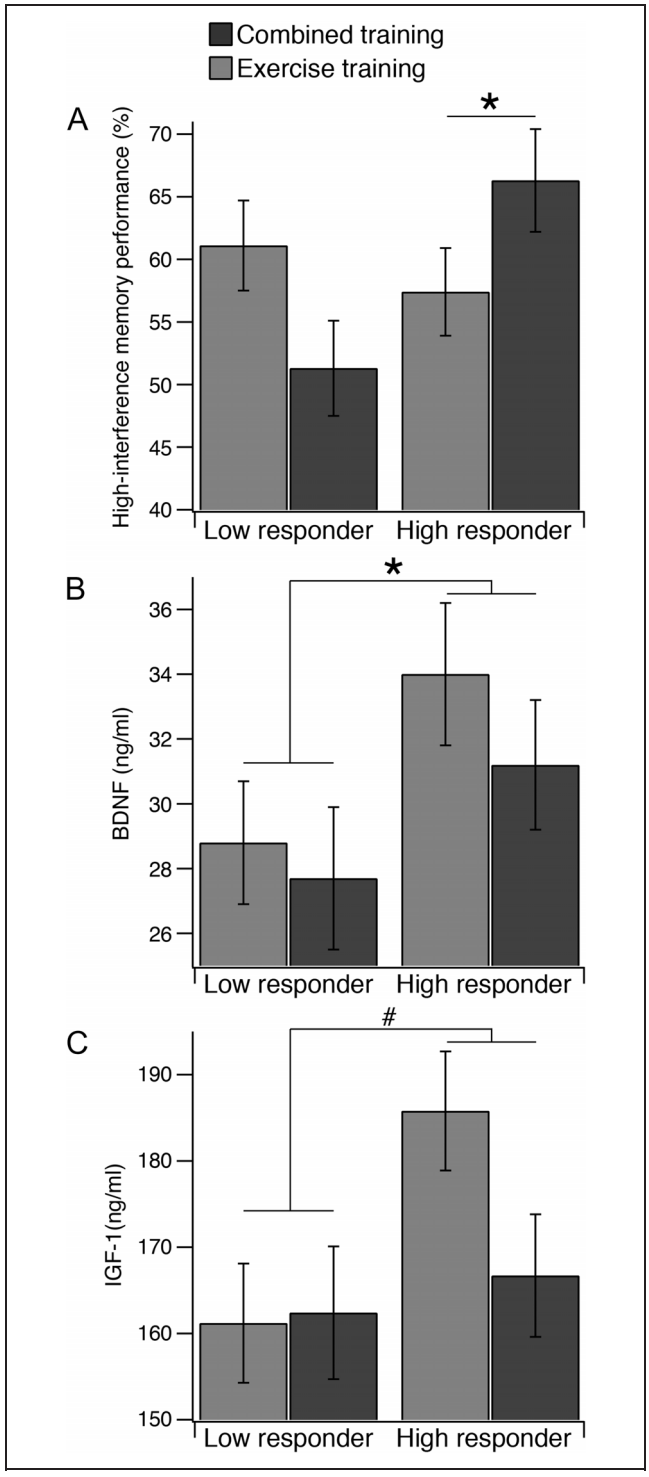

Figure 3. The effect of response to exercise on high-interference memory, BDNF, and IGF-1 following 6 weeks of exercise training or combined exercise and cognitive training. For high-interference memory, the ANCOVA revealed a significant interaction between Group and Exercise training response, in which high responders to exercise had better performance following combined training than exercise training alone. For BDNF and IGF-1, the ANCOVA revealed a main effect of Exercise training response, such that high responders to exercise had greater concentrations of neurotrophic factors in the serum regardless of training group. Pretest values were entered as covariates in the models at the following values: high-interference at 47%, BDNF at 31 ng/ml, and IGF-1 at 172 ng/ml. Error bars represent *SEM* for each group. $^{\#}p = .05$, $^{*}p < .05$.

factors (BDNF, $r(49) = .01$, $p = .49$; IGF-1, $r(58) = -.051$, $p = .35$).

For high-interference memory performance, there was a significant interaction between Training response and Group, $F(1, 44) = 6.23$, $p = .016$, $\eta_p^2 = .12$. Post hoc analyses revealed better high-interference memory for high responders in the combined training group compared with the exercise only group ($p = .037$); there was no effect of Group among the low responders ($p = .16$; Figure 3A). These results were further supported by Pearson's correlations demonstrating that aerobic fitness (as a continuous variable) correlated with high-interference memory for the combined group ($r(18) = .52$, $p = .01$) but not for the exercise only group ($r(23) = -.14$, $p = .26$). In contrast, exercise training response had no effect on general recognition performance (all ps $> .1$).

For both BDNF and IGF-1, there was a main effect of Exercise training response, such that high responders had higher BDNF and IGF-1 levels than low responders (BDNF: $F(1, 42) = 4.40$, $p = .04$, $\eta_p^2 = .10$; IGF-1: $F(1, 51) = 4.04$, $p = .05$, $\eta_p^2 = .07$; Figure 3B and C). There was no main effect of Group or interaction between Group and Exercise response (all ps $> .05$). The effect of Training response on neurotrophic factors was further supported by Pearson's correlations demonstrating that aerobic fitness (as a continuous variable) correlated with levels of BDNF ($r(43) = .25$, $p = .046$) and IGF-1 ($r(52) = .26$, $p = .03$).

Hierarchical linear regression analyses were used to evaluate the interaction between memory, aerobic fitness, and neurotrophic factors (Table 4). Critically, the relation between high-interference memory performance and aerobic fitness for the combined group ($R^2 = .16$; $F(1, 20) = 3.80$, $p = .066$) was strengthened when BDNF was entered into the model ($R^2 = .33$; $\Delta F(1, 19) = 4.93$, $p = .039$).

DISCUSSION

This is the first study to examine the synergistic effects of physical exercise and cognitive training on memory function and neurotrophic factors in young adults. Synergistic effects were predicted by prior animal work showing that exercise and cognitive training enhance hippocampal function through overlapping but somewhat distinct pathways: Exercise predominantly increases the proliferation of newborn cells in the dentate gyrus (Van Praag et al., 1999) but also increases the survival of newborn cells (Van Praag et al., 1999), whereas cognitive training and environmental enrichment primarily support the survival and integration of those cells into the hippocampal network (Gould et al., 1999; Van Praag et al., 1999). In our examination of young adults, the combined intervention improved performance on a high-interference memory task to a similar extent as the exercise training alone, suggesting that the results from rodent models may not directly translate to human subjects. However, there were important individual differences. High responders

Table 4. Hierarchical Linear Regression Analyses Revealed that for the Combined Group the Relation between High-interference Memory Performance and Aerobic Fitness Was Strengthened When BDNF Was Entered into the Model

Dependent Variable	*Group*	*Model*	*Independent Variable*	*B (SE)*	*Beta*	*t*
High-interference memory	Combined	1	ΔVO_2 peak	.02 (.01)	.40	1.95
		2	ΔVO_2 peak	.03 (.01)	.44	2.33*
			ΔBDNF	.009 (.004)	.42	2.22*
	Exercise	1	ΔVO_2 peak	−.01 (.01)	−.38	−1.78
General recognition memory	Combined	1	ΔVO_2 peak	.001 (.007)	.02	0.10
	Exercise	1	ΔVO_2 peak	−.004 (.005)	−.19	−.87

For each dependent variable, aerobic fitness was entered as an independent variable in Step 1 of the model, and BDNF and IGF-1 were entered (stepwise) as independent variables in Step 2 of the model.

*$p < .05$.

to exercise in the combined training group had better high-interference memory performance than high responders to exercise who only received exercise training, and this pattern of results is consistent with rodent models. Critically, high responders also had higher levels of BDNF and IGF-1, suggesting that the additional memory benefit from cognitive training in humans may require the availability of neurotrophic factors. However, the exercise protocols used in human versus rodent studies are very different, so the translation of findings from rodents to humans must be interpreted with caution. Typically rodents in a running condition are given continuous access to a running wheel for a period of several weeks, whereas control animals are housed individually with no running wheel and no other form of exercise.

In this study, exercise training and combined exercise and cognitive training increased correct identification of similar items (high-interference memory); however, the training had no impact on recognition performance for old items (general recognition). This is consistent with our hypothesis that exercise training favors the formation of high-fidelity memory traces. It is theorized that turnover and regeneration of neurons in the dentate gyrus contribute to the creation of event-specific memory traces that reduce interference and increase distinction between the memory traces of highly similar events (Sahay et al., 2011; Deng, Aimone, & Gage, 2010; Clelland et al., 2009; Becker, 2005). If increased neurogenesis is indeed a mediating factor in the training-induced changes in cognition observed here, it could be that greater levels of neurogenesis contribute to the distinctive encoding of both similar and repeat items during the recognition memory test.

An alternative explanation for why exercise training did not improve recognition memory performance is that increased neurogenesis may have promoted clearance of the previous memories, as predicted by several computational models (Weisz & Argibay, 2009, 2012; Chambers, Potenza, Hoffman, & Miranker, 2004; Deisseroth et al., 2004). Evidence supporting the memory clearance hypothesis comes from rodent studies demonstrating that, when neurogenesis is induced after memory formation has occurred, there is enhanced forgetting of the previously learned memory (Akers et al., 2014). However, there are important differences between the setup used in these previous studies and our experiment: In this study, the original study items and tested items (repeats and lures) were always seen within the same session, and more importantly, the exercise (and presumed increase in neurogenesis) occurred before memory formation.

Serum levels of neurotrophic factors BDNF and IGF-1 were not impacted by the exercise or combined interventions at the group level. This may be surprising, given that exercise training consistently up-regulates these growth factors in animal models (Voss et al., 2013). However, the effect of exercise training on neurotrophic factors in humans is not as consistent (Maass et al., 2016) and often does not elicit basal changes in BDNF or IGF-1 in young adults (Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014). Our results point to individual differences in response to exercise training that may mask an effect at the group level. Specifically, we found that high responders to exercise (i.e., those who had greater fitness improvements from exercise training) also had greater postintervention BDNF and IGF-1 serum levels compared with low responders to exercise. We hypothesize that this may reflect individual differences in the ability to effectively adapt to repeated bouts of acute exercise stress. Exercise is a physiological stressor that triggers an increase in cortisol (Hackney & Viru, 1999); little to no fitness improvements from exercise training were seen for the low responders, and may be indicative of a general deficit in their ability to adapt to the exercise stress (Webb et al., 2013). Critically, with training, this would cause elevated cortisol, which binds to glucocorticoid receptors in the hippocampus (McEwen, 2007) and reduces the expression of neurotrophic factors in the dentate gyrus (Schaaf, Hoetelmans, de Kloet, & Vreugdenhil, 1997). Ultimately, this would result in lower BDNF and IGF-1 concentrations for low versus high responders to exercise.

In addition to exhibiting greater levels of neurotrophic factors, the high responders to exercise who also received cognitive training had better high- interference memory than those who exercised only. Furthermore, for participants who received combined exercise and cognitive training, there was a significant correlation between the change in high-interference memory performance and aerobic fitness that was strengthened when BDNF was entered into the regression model. In contrast, there were no synergistic effects of combining cognitive training with exercise for low responders, and there was no significant correlation between the change in high-interference memory performance and aerobic fitness for those who only received exercise training. Taken together, these results suggest that the potential for synergistic effects of combining exercise and cognitive training may depend on aerobic fitness gains and the availability of neurotrophic fac- tors. Outside the exercise literature, cognitive training protocols usually do not control for neurotrophic factors or fitness level, and these may be important factors contributing to the individual differences associated with previously reported cognitive training effects (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). That said, most cognitive training protocols target executive functions and working memory (Olesen, Westerberg, & Klingberg, 2004) rather than hippocampal-dependent long-term memory, and aerobic fitness may only affect cognitive training when the cognitive training relies on the integrity of the hippocampus.

This study makes an important contribution but is not without limitations. It is not easy to create a nonexercise control. Part of the problem is that we do not fully understand the key exercise components that are driving memory changes. Although this study highlights the importance of aerobic fitness adaptations, this is only one of the many different physiological adaptations that take place during exercise training that could contribute to the memory effect. Prior research has used a "strength and stretching" control group (Erickson et al., 2009); however, this assumes that the adaptations from these exercises do not play a role in promoting memory, and we know that this is not true. Indeed, prior work has shown cognitive benefits from strengthening (Liu-Ambrose et al., 2010; Liu-Ambrose & Donaldson, 2009; Cassilhas et al., 2007) and stretching (Gothe, Keswani, & McAuley, 2016; Luu & Hall, 2016) protocols, suggesting that this may not be the best control.

Consistent with prior research in humans (Déry et al., 2013), the type of memory that benefited from exercise was restricted to the high-interference trials of the MST, whereas the general recognition memory trials of this task were not affected. An important contribution of this article is that it extends these previous findings by demonstrating a synergy between exercise and cognitive training. The cognitive training task was another high-interference task, the concentration memory task. Both the MST and concentration memory task create interference by testing memory for visually similar items studied within a single session. Future research is needed to determine whether training on other hippocampal-dependent memory tasks would impart similar benefits, whether other types of interference would result in similar transfer to the MST, and what is the optimal type, intensity, frequency and duration of exercise that is ideal for evoking these memory changes. Future research examining the potential synergistic effects of exercise and cognitive training should include a cognitive training only group. Finally, given that the effects of training on memory and neurotrophic factors were highly variable across individuals, future research is needed to explore the factors driving these individual differences and how to induce greater benefits for nonresponders.

In summary, exercise training selectively enhanced performance on an untrained high-interference memory task—the MST. Serum BDNF and IGF-1 levels increased significantly in individuals who exhibited a larger aerobic adaptation to exercise training (i.e., high responders to exercise), suggesting important individual differences. Critically, the high responders to exercise who also received cognitive training had better high-interference memory than those who exercised only. Taken together, the results suggest that the potential for synergistic effects of combining exercise and cognitive training may depend on individual differences in the availability of neurotrophic factors induced by exercise. These findings are especially important, as memory benefits were found from a relatively short intervention in high-functioning young adults.

Acknowledgments

This research was supported by the Natural Sciences and Engineering Research Council of Canada Discovery grant no. 296518 to J. J. Heisz and a grant from the Alzheimer Society of Canada to M. Fahnestock.

Reprint requests should be sent to Jennifer J. Heisz, Department of Kinesiology, McMaster University, 1280 Main St W, Hamilton, ON, Canada, L8S 4K1, or via e-mail: heiszjj@mcmaster.ca.

REFERENCES

Afzalpour, M. E., Chadorneshin, H. T., Foadoddini, M., & Eivari, H. A. (2015). Comparing interval and continuous exercise training regimens on neurotrophic factors in rat brain. *Physiology & Behavior, 147,* 78–83.

Aimone, J. B., Deng, W., & Gage, F. H. (2011). Resolving new memories: A critical look at the dentate gyrus, adult neurogenesis, and pattern separation. *Neuron, 70,* 589–596.

Akers, K. G., Martinez-Canabal, A., Restivo, L., Yiu, A. P., De Cristofaro, A., Hsiang, H. L., et al. (2014). Hippocampal neurogenesis regulates forgetting during adulthood and infancy. *Science, 344,* 598–602.

Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science, 319,* 1640–1642.

Becker, S. (2005). A computational principle for hippocampal learning and neurogenesis. *Hippocampus, 15,* 722.

Becker, S. (2017). Neurogenesis and pattern separation: Time for a divorce. *Wiley Interdisciplinary Reviews: Cognitive Science, 8*.
Ben-Abdallah, N. M., Filipkowski, R. K., Pruschy, M., Jaholkowski, P., Winkler, J., Kaczmarek, L., et al. (2013). Impaired long-term memory retention: Common denominator for acutely or genetically reduced hippocampal neurogenesis in adult mice. *Behavioural Brain Research, 252,* 275–286.
Burghardt, N. S., Park, E. H., Hen, R., & Fenton, A. A. (2012). Adult-born hippocampal neurons promote cognitive flexibility in mice. *Hippocampus, 22,* 1795–1808.
Carro, E., Nuñez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. *Journal of Neuroscience, 20,* 2926–2933.
Carro, E., Trejo, J. L., Busiguina, S., & Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *Journal of Neuroscience, 21,* 5678–5684.
Cassilhas, R. C., Viana, V. A., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S., et al. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Medicine and Science in Sports and Exercise, 39,* 1401.
Chaddock, L., Erickson, K. I., Prakash, R. S., Kim, J. S., Voss, M. W., Vanpatter, M., et al. (2010). A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Research, 1358,* 172–183.
Chambers, R. A., Potenza, M. N., Hoffman, R. E., & Miranker, W. (2004). Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. *Neuropsychopharmacology, 29,* 747–758.
Clelland, C., Choi, M., Romberg, C., Clemenson, G. D., Jr., Fragniere, A., Tyers, P., et al. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science, 325,* 210–213.
Cleva, R. M., Wischerath, K. C., & Olive, M. F. (2011). Extinction learning and adult neurogenesis. *Neuropsychopharmacology, 36,* 360.
Cotman, C. W., & Berchtold, N. C. (2002). Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences, 25,* 295–301.
Cotman, C. W., Berchtold, N. C., & Christie, L.-A. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neurosciences, 30,* 464–472.
Creer, D. J., Romberg, C., Saksida, L. M., van Praag, H., & Bussey, T. J. (2010). Running enhances spatial pattern separation in mice. *Proceedings of the National Academy of Sciences, U.S.A., 107,* 2367–2372.
Curlik, D., & Shors, T. (2013). Training your brain: Do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus? *Neuropharmacology, 64,* 506–514.
Deisseroth, K., Singla, S., Toda, H., Monje, M., Palmer, T. D., & Malenka, R. C. (2004). Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron, 42,* 535–552.
Deng, W., Aimone, J. B., & Gage, F. H. (2010). New neurons and new memories: How does adult hippocampal neurogenesis affect learning and memory? *Nature Reviews Neuroscience, 11,* 339–350.
Déry, N., Goldstein, A., & Becker, S. (2015). A role for adult hippocampal neurogenesis at multiple time scales: A study of recent and remote memory in humans. *Behavioral Neuroscience, 129,* 435.
Déry, N., Pilgrim, M., Gibala, M., Gillen, J., Wojtowicz, J. M., Macqueen, G., et al. (2013). Adult hippocampal neurogenesis reduces memory interference: Opposing effects of aerobic exercise and depression. *Frontiers in Neuroscience, 7,* 66.
Dinoff, A., Herrmann, N., Swardfager, W., Liu, C. S., Sherman, C., Chan, S., et al. (2016). The effect of exercise training on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF): A meta-analysis. *PLoS One, 11,* e0163037.
Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., et al. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus, 19,* 1030–1039.
Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences, U.S.A., 108,* 3017–3022.
Evans, J. J., Greenfield, E., Wilson, B. A., & Bateman, A. (2009). Walking and talking therapy: Improving cognitive–motor dual-tasking in neurological illness. *Journal of the International Neuropsychological Society, 15,* 112–120.
Fabel, K., Wolf, S. A., Ehninger, D., Babu, H., Leal-Galicia, P., & Kempermann, G. (2009). Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Frontiers in Neuroscience, 3,* 2.
Fabre, C., Chamari, K., Mucci, P., Masse-Biron, J., & Prefaut, C. (2002). Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *International Journal of Sports Medicine, 23,* 415–421.
Fahnestock, M. (2011). Brain-derived neurotrophic factor: The link between amyloid-β and memory loss. *Future Neurology, 6,* 627–639.
Fahnestock, M., Marchese, M., Head, E., Pop, V., Michalski, B., Milgram, W. N., et al. (2012). BDNF increases with behavioral enrichment and an antioxidant diet in the aged dog. *Neurobiology of Aging, 33,* 546–554.
Finnegan, R., & Becker, S. (2015). Neurogenesis paradoxically decreases both pattern separation and memory interference. *Frontiers in Systems Neuroscience, 9,* 136.
Garthe, A., Behr, J., & Kempermann, G. (2009). Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. *PloS One, 4,* e5464.
Gilbert, P. E., & Kesner, R. P. (2003). Localization of function within the dorsal hippocampus: The role of the CA3 subregion in paired-associate learning. *Behavioral Neuroscience, 117,* 1385.
Goldstein, A., Déry, N., Pilgrim, M., Ioan, M., & Becker, S. (2016). Stress and binge drinking: A toxic combination for the teenage brain. *Neuropsychologia, 90,* 251–260.
Gothe, N. P., Keswani, R. K., & McAuley, E. (2016). Yoga practice improves executive function by attenuating stress levels. *Biological Psychology, 121,* 109–116.
Gould, E., Beylin, A., Tanapat, P., Reeves, A., & Shors, T. J. (1999). Learning enhances adult neurogenesis in the hippocampal formation. *Nature Neuroscience, 2,* 260–265.
Gould, E., McEwen, B. S., Tanapat, P., Galea, L. A., & Fuchs, E. (1997). Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *Journal of Neuroscience, 17,* 2492–2498.
Griffin, É. W., Mullally, S., Foley, C., Warmington, S. A., O'Mara, S. M., & Kelly, A. M. (2011). Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & Behavior, 104,* 934–941.
Hackney, A., & Viru, A. (1999). Twenty-four-hour cortisol response to multiple daily exercise sessions of moderate and high intensity. *Clinical Physiology, 19,* 178–182.
Heisz, J. J., Gould, M., & McIntosh, A. R. (2015). Age-related shift in neural complexity related to task performance and physical activity. *Journal of Cognitive Neuroscience, 27,* 605–613.

Heisz, J. J., Tejada, M. G. M., Paolucci, E. M., & Muir, C. (2016). Enjoyment for high-intensity interval exercise increases during the first six weeks of training: Implications for promoting exercise adherence in sedentary adults. *PLoS One, 11,* e0168534.

Heisz, J. J., Vandermorris, S., Wu, J., McIntosh, A. R., & Ryan, J. D. (2015). Age differences in the association of physical activity, sociocognitive engagement, and TV viewing on face memory. *Health Psychology, 34,* 83–88.

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Reviews Neuroscience, 9,* 58–65.

Holzschneider, K., Wolbers, T., Röder, B., & Hötting, K. (2012). Cardiovascular fitness modulates brain activation associated with spatial learning. *Neuroimage, 59,* 3003–3014.

Huang, T., Larsen, K., Ried-Larsen, M., Møller, N., & Andersen, L. B. (2014). The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scandinavian Journal of Medicine & Science in Sports, 24,* 1–10.

Hunsaker, M. R., & Kesner, R. P. (2008). Evaluating the differential roles of the dorsal dentate gyrus, dorsal CA3, and dorsal CA1 during a temporal ordering for spatial locations task. *Hippocampus, 18,* 955–964.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Shah, P. (2011). Short- and long-term benefits of cognitive training. *Proceedings of the National Academy of Sciences, U.S.A., 108,* 10081–10086.

Jaeggi, S. M., Buschkuehl, M., Shah, P., & Jonides, J. (2014). The role of individual differences in cognitive training and transfer. *Memory & Cognition, 42,* 464–480.

Kalm, M., Karlsson, N., Nilsson, M. K., & Blomgren, K. (2013). Loss of hippocampal neurogenesis, increased novelty-induced activity, decreased home cage activity, and impaired reversal learning one year after irradiation of the young mouse brain. *Experimental Neurology, 247,* 402–409.

Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., & Brennan, S. (2014). The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: A systematic review and meta-analysis. *Ageing Research Reviews, 15,* 28–43.

Kheirbek, M. A., Tannenholz, L., & Hen, R. (2012). NR2B-dependent plasticity of adult-born granule cells is necessary for context discrimination. *Journal of Neuroscience, 32,* 8696–8702.

Kirwan, C. B., & Stark, C. E. (2007). Overcoming interference: An fMRI investigation of pattern separation in the medial temporal lobe. *Learning & Memory, 14,* 625–633.

Knaepen, K., Goekint, M., Heyman, E. M., & Meeusen, R. (2010). Neuroplasticity—Exercise-induced response of peripheral brain-derived neurotrophic factor. *Sports Medicine, 40,* 765–801.

Kuhn, H. G., Dickinson-Anson, H., & Gage, F. H. (1996). Neurogenesis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. *Journal of Neuroscience, 16,* 2027–2033.

Law, L. L., Barnett, F., Yau, M. K., & Gray, M. A. (2014). Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A systematic review. *Ageing Research Reviews, 15,* 61–75.

Linde, K., & Alfermann, D. (2014). Single versus combined cognitive and physical activity effects on fluid cognitive abilities of healthy older adults: A 4-month randomized controlled trial with follow-up. *Journal of Aging and Physical Activity, 22,* 302–313.

Liu-Ambrose, T., & Donaldson, M. G. (2009). Exercise and cognition in older adults: Is there a role for resistance training programmes? *British Journal of Sports Medicine, 43,* 25–27.

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C., & Handy, T. C. (2010). Resistance training and executive functions: A 12-month randomized controlled trial. *Archives of Internal Medicine, 170,* 170–178.

Luu, K., & Hall, P. A. (2016). Hatha yoga and executive function: A systematic review. *Journal of Alternative and Complementary Medicine, 22,* 125–133.

Luu, P., Sill, O. C., Gao, L., Becker, S., Wojtowicz, J. M., & Smith, D. M. (2012). The role of adult hippocampal neurogenesis in reducing interference. *Behavioral Neuroscience, 126,* 381.

Maass, A., Düzel, S., Brigadski, T., Goerke, M., Becke, A., Sobieray, U., et al. (2016). Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. *Neuroimage, 131,* 142–154.

Maass, A., Düzel, S., Goerke, M., Becke, A., Sobieray, U., Neumann, K., et al. (2014). Vascular hippocampal plasticity after aerobic exercise in older adults. *Molecular Psychiatry, 20,* 585–593.

Makin, S. (2016). Brain training: Memory games. *Nature, 531,* S10–S11.

Marín-Burgin, A., Mongiat, L. A., Pardi, M. B., & Schinder, A. F. (2012). Unique processing during a period of high excitation/inhibition balance in adult-born neurons. *Science, 335,* 1238–1242.

Marquez, C. M. S., Vanaudenaerde, B., Troosters, T., & Wenderoth, N. (2015). High-intensity interval training evokes larger serum BDNF levels compared with intense continuous exercise. *Journal of Applied Physiology, 119,* 1363–1373.

Marrone, D. F., Adams, A. A., & Satvat, E. (2011). Increased pattern separation in the aged fascia dentata. *Neurobiology of Aging, 32,* 2317. e2323-2317. e2332.

McDaniel, M. A., Binder, E. F., Bugg, J. M., Waldum, E. R., Default, C., Meyer, A., et al. (2014). Effects of cognitive training with and without aerobic exercise on cognitively demanding everyday activities. *Psychology and Aging, 29,* 717.

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews, 87,* 873–904.

Melby-Lervåg, M., & Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Developmental Psychology, 49,* 270.

Monti, J. M., Hillman, C. H., & Cohen, N. J. (2012). Aerobic fitness enhances relational memory in preadolescent children: The FITKids randomized control trial. *Hippocampus, 22,* 1876–1882.

Nakashiba, T., Cushman, J. D., Pelkey, K. A., Renaudineau, S., Buhl, D. L., McHugh, T. J., et al. (2012). Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell, 149,* 188–201.

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., et al. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet, 385,* 2255–2263.

Niibori, Y., Yu, T. S., Epp, J. R., Akers, K. G., Josselyn, S. A., & Frankland, P. W. (2012). Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. *Nature Communications, 3,* 1253.

Nixon, K., & Crews, F. T. (2002). Binge ethanol exposure decreases neurogenesis in adult rat hippocampus. *Journal of Neurochemistry, 83,* 1087–1093.

Noonan, M. A., Bulin, S. E., Fuller, D. C., & Eisch, A. J. (2010). Reduction of adult hippocampal neurogenesis confers

vulnerability in an animal model of cocaine addiction. *Journal of Neuroscience, 30,* 304–315.
O'Dwyer, S. T., Burton, N. W., Pachana, N. A., & Brown, W. J. (2007). Protocol for fit bodies, fine minds: A randomized controlled trial on the affect of exercise and cognitive training on cognitive functioning in older adults. *BMC Geriatrics, 7,* 23.
Olesen, P. J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nature Neuroscience, 7,* 75–79.
Olsen, R. K., Moses, S. N., Riggs, L., & Ryan, J. D. (2012). The hippocampus supports multiple cognitive processes through relational binding and comparison. *Frontiers in Human Neuroscience, 6,* 146.
Olson, A. K., Eadie, B. D., Ernst, C., & Christie, B. R. (2006). Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus, 16,* 250–260.
Owen, A. M., Hampshire, A. M., Grahn, J. A. M., Stenton, R., Dajani, S., Burns, A. S., et al. (2010). Putting brain training to the test. *Nature, 465,* 775–778.
Pan, Y.-W., Chan, G. C., Kuo, C. T., Storm, D. R., & Xia, Z. (2012). Inhibition of adult neurogenesis by inducible and targeted deletion of ERK5 mitogen-activated protein kinase specifically in adult neurogenic regions impairs contextual fear extinction and remote fear memory. *Journal of Neuroscience, 32,* 6444–6455.
Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., et al. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences, U.S.A., 104,* 5638–5643.
Rolls, E. T. (2013). The mechanisms for pattern completion and pattern separation in the hippocampus. *Frontiers in Systems Neuroscience, 7,* 74.
Sahay, A., Scobie, K. N., Hills, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., et al. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature, 472,* 466–470.
Sakalem, M. E., Seidenbecher, T. E., Zhang, M., Saffari, R., Kravchenko, M., Wordemann, S., et al. (2017). Environmental enrichment and physical exercise revert behavioral and electrophysiological impairments caused by reduced adult neurogenesis. *Hippocampus, 27,* 36–51.
Schaaf, M. J., Hoetelmans, R. W., de Kloet, E. R., & Vreugdenhil, E. (1997). Corticosterone regulates expression of BDNF and trkB but not NT-3 and trkC mRNA in the rat hippocampus. *Journal of Neuroscience Research, 48,* 334–341.
Schmidt, H. D., & Duman, R. S. (2010). Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. *Neuropsychopharmacology, 35,* 2378–2391.
Schmidt-Hieber, C., Jonas, P., & Bischofberger, J. (2004). Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature, 429,* 184–187.
Shelton, D. J., & Kirwan, C. B. (2013). A possible negative influence of depression on the ability to overcome memory interference. *Behavioural Brain Research, 256,* 20–26.
Shors, T. J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., & Gould, E. (2001). Neurogenesis in the adult is involved in the formation of trace memories. *Nature, 410,* 372–376.
Siette, J., Westbrook, R. F., Cotman, C., Sidhu, K., Zhu, W., Sachdev, P., et al. (2013). Age-specific effects of voluntary exercise on memory and the older brain. *Biological Psychiatry, 73,* 435–442.
Snyder, J., Hong, N., McDonald, R., & Wojtowicz, J. (2005). A role for adult neurogenesis in spatial long-term memory. *Neuroscience, 130,* 843–852.
Snyder, J., Kee, N., & Wojtowicz, J. (2001). Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. *Journal of Neurophysiology, 85,* 2423–2431.
Stupien, G., Florian, C., & Roullet, P. (2003). Involvement of the hippocampal CA3-region in acquisition and in memory consolidation of spatial but not in object information in mice. *Neurobiology of Learning and Memory, 80,* 32–41.
Toner, C. K., Pirogovsky, E., Kirwan, C. B., & Gilbert, P. E. (2009). Visual object pattern separation deficits in nondemented older adults. *Learning & Memory, 16,* 338–342.
Trejo, J. L., Carro, E., & Torres-Alemán, I. (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *Journal of Neuroscience, 21,* 1628–1634.
Van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience, 2,* 266–270.
Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience, 20,* 2580–2590.
Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences, 17,* 525–544.
Wang, S., Scott, B. W., & Wojtowicz, J. M. (2000). Heterogenous properties of dentate granule neurons in the adult rat. *Journal of Neurobiology, 42,* 248–257.
Webb, H. E., Rosalky, D. S., Tangsilsat, S. E., McLeod, K. A., Acevedo, E. O., & Wax, B.(2013). Aerobic fitness affects cortisol responses to concurrent challenges. *Medicine and Science in Sports and Exercise, 45,* 379–386.
Weisz, V. I., & Argibay, P. F. (2009). A putative role for neurogenesis in neurocomputational terms: Inferences from a hippocampal model. *Cognition, 112,* 229–240.
Weisz, V. I., & Argibay, P. F. (2012). Neurogenesis interferes with the retrieval of remote memories: Forgetting in neurocomputational terms. *Cognition, 125,* 13–25.
Whiteman, A. S., Young, D. E., Budson, A. E., Stern, C. E., & Schon, K. (2016). Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: A voxel-based morphometry study. *Neuroimage, 126,* 229–238.
Whiteman, A. S., Young, D. E., He, X., Chen, T. C., Wagenaar, R. C., Stem, C. E., et al. (2014). Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults. *Behavioural Brain Research, 259,* 302–312.
Winocur, G., Becker, S., Luu, P., Rosenzweig, S., & Wojtowicz, J. M. (2012). Adult hippocampal neurogenesis and memory interference. *Behavioural Brain Research, 227,* 464–469.
Wojtowicz, J. M., Askew, M. L., & Winocur, G. (2008). The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. *European Journal of Neuroscience, 27,* 1494–1502.
Yassa, M. A., & Stark, C. E. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences, 34,* 515–525.