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High impact running improves learning

Bernward Winter [a,*,1], Caterina Breitenstein [a,b,1], Frank C. Mooren [c], Klaus Voelker [d], Manfred Fobker [e], Anja Lechtermann [d], Karsten Krueger [c], Albert Fromme [d], Catharina Korsukewitz [a], Agnes Floel [a], Stefan Knecht [a,b]

[a] *Department of Neurology, University of Muenster, Muenster, Germany*
[b] *IZKF Muenster, University of Muenster, Muenster, Germany*
[c] *Institute of Sports Medicine, Justus-Liebig University of Giessen, Giessen, Germany*
[d] *Institute of Sports Medicine, University Hospital of Muenster, Muenster, Germany*
[e] *Institute of Clinical Chemistry and Laboratory Medicine, University Hospital of Muenster, Muenster, Germany*

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Abstract

Regular physical exercise improves cognitive functions and lowers the risk for age-related cognitive decline. Since little is known about the nature and the timing of the underlying mechanisms, we probed whether exercise also has *immediate* beneficial effects on cognition. Learning performance was assessed directly after high impact anaerobic sprints, low impact aerobic running, or a period of rest in 27 healthy subjects in a randomized cross-over design. Dependent variables comprised learning speed as well as immediate (1 week) and long-term (>8 months) overall success in acquiring a novel vocabulary. Peripheral levels of brain-derived neurotrophic factor (BDNF) and catecholamines (dopamine, epinephrine, norepinephrine) were assessed prior to and after the interventions as well as after learning. We found that vocabulary learning was 20 percent faster after intense physical exercise as compared to the other two conditions. This condition also elicited the strongest increases in BDNF and catecholamine levels. More sustained BDNF levels during learning after intense exercise were related to better short-term learning success, whereas absolute dopamine and epinephrine levels were related to better intermediate (dopamine) and long-term (epinephrine) retentions of the novel vocabulary. Thus, BDNF and two of the catecholamines seem to be mediators by which physical exercise improves learning.

Keywords: Learning; Memory consolidation; Catecholamines; Dopamine; Epinephrine; Brain-derived neurotrophic factor; Physical exercise; Language; Arousal

1. Introduction

Physical exercise seems to be beneficial to cognition. Epidemiological studies show that more frequent (self-reported) regular physical activity is associated with a reduced risk for age-related neurodegenerative diseases, like dementia or Parkinson's disease (Abbott et al., 2004; Colcombe et al., 2004; Larson et al., 2006; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; van Gelder et al., 2004; Weuve et al., 2004). Beneficial effects of exercise on cognition may, however, be due to an overall healthier life style (non-smoking, better nutrition) in already cognitively high functioning subjects (Abbott et al., 2004; Kalmijn et al., 2000). Another confounder is that a preexisting, yet undiagnosed cognitive disorder may have led to a concomitant reduction in physical activity (Weuve et al., 2004). Thus, longitudinal intervention studies are better suited to determine the link between physical exercise and cognition. These studies show that several months of regular physical exercise led to improved mental functions or a slower cognitive decline in elderly subjects (Colcombe & Kramer, 2003 for a meta-analysis), with varying effect sizes for different cognitive functions (Fig. 1).

* Corresponding author. Fax: +49 251 83 48181.
E-mail address: bwinter@uni-muenster.de (B. Winter).
[1] These authors contributed equally.

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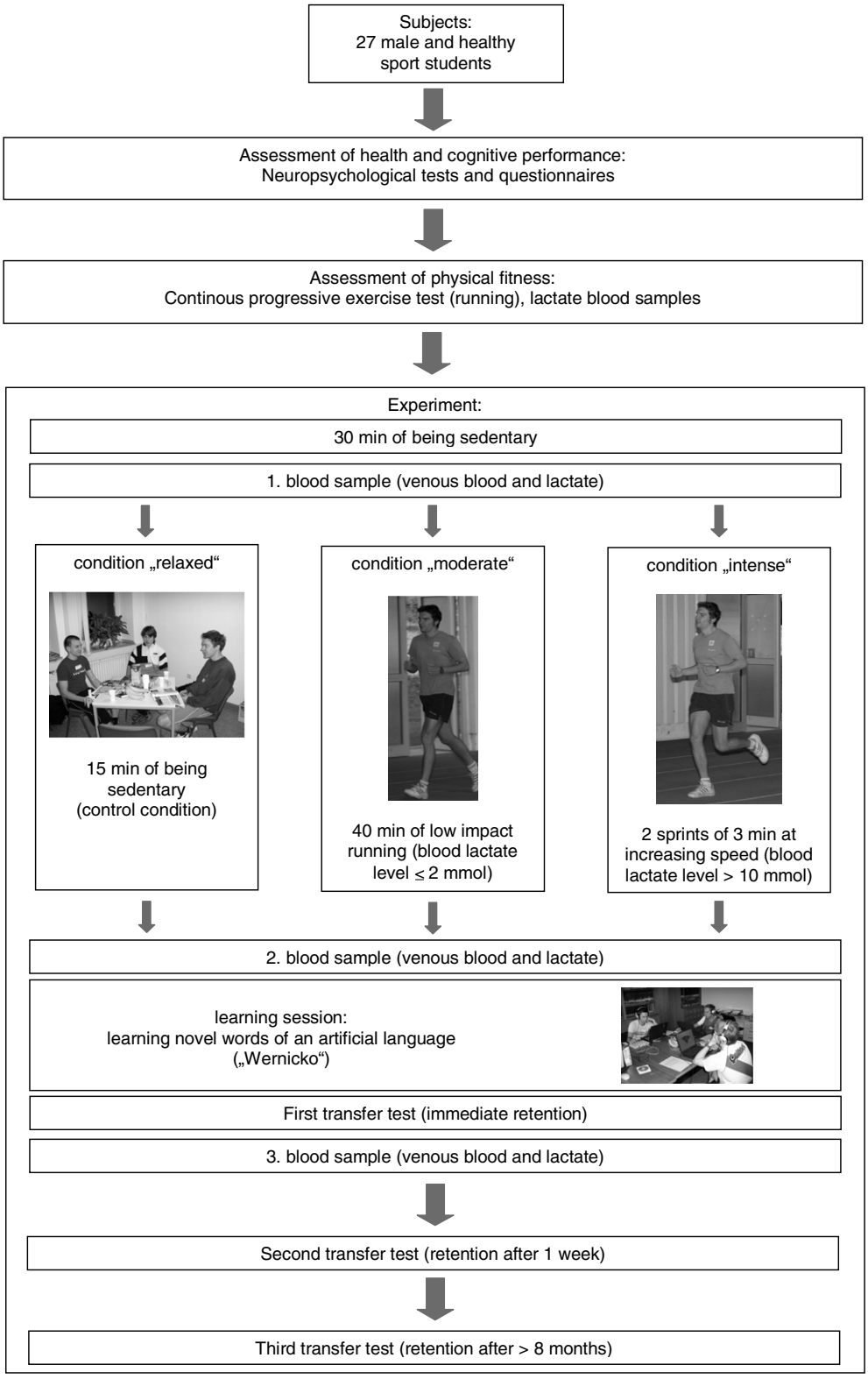

Fig. 1. Design of the present cross-over study showing the different interventions, points of measurement and retention.

Several studies probed the effect of acute bouts of exercise on cognitive functions (Etnier et al., 1997; Tomporowski, 2003; Tomporowski & Ellis, 1986 for a review). Most of these studies, however, did not directly assess effects on learning or memory, but rather investigated the effect of exercise on various neuropsychological measures, like simple reaction time tasks (e.g., Hogervorst, Riedel, Jeukendrup, & Jolles, 1996), or on exercise-related tasks like decision making in soccer (e.g., McMorris & Graydon, 1997). Studies probing the effect of exercise on memory led

to divergent results, depending on the length and intensity of the exercise intervention. After short-duration anaerobic exercise (up to 2 min), short-term memory was facilitated (Davey, 1973). During or immediately after long anaerobic exercise (5–40 min), no effects on memory were found (Sjoberg, 1980; Tomporowski, Ellis, & Stephens, 1987). When the exercise condition led to dehydration, either no effects or even negative effects on memory were noted (Cian, Barraud, Melin, & Raphel, 2001; Cian et al., 2000).

Similar results were obtained for healthy children: Sibley and Etnier reported positive effects of regular physical exercise for various cognitive tasks, but not for "pure" memory performance in their recent meta-analysis (Sibley & Etnier, 2003). Findings in children with attention deficit disorder are less conclusive: positive effects of exercise on disturbing behaviors have been found (Allison, Faith, & Franklin, 1995; Tantillo, Kesick, Hynd, & Dishman, 2002), but effects on cognition have not been reported so far (Craft, 1983).

In contrast to the preliminary evidence regarding the relation of physical exercise and cognition in humans, animals consistently showed improved learning after daily physical exercise for up to 7 months (Anderson et al., 2000; Baruch, Swain, & Helmstetter, 2004; Fordyce & Farrar, 1991; van Praag, Christie, Sejnowski, & Gage, 1999). Negative reports can be explained by an interaction of task complexity and heterogeneous task performance of the animals (Braszko, Kaminski, Hryszko, Jedynak, & Brzosko, 2001) or may be due to the use of a non-voluntary exercise condition (forced treadmill running; Burghardt, Fulk, Hand, & Wilson, 2004).

In animal studies, upregulations of various neurotransmitters in the brain, especially dopamine and norepinephrine, were found (Hattori, Naoi, & Nishino, 1994; Meeusen & De Meirleir, 1995; Sutoo & Akiyama, 2003). In addition to catecholamines, the release of neurotrophic factors, like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), or insulin-like growth factor (IGF-1), is increased in the brain after a regimen of daily physical exercise in animals (Carro, Nunez, Busiguina, & Torres-Aleman, 2000; Gobbo & O'Mara, 2005; Neeper, Gomez-Pinilla, Choi, & Cotman, 1995; Neeper, Gomez-Pinilla, Choi, & Cotman, 1996). The amount of neurotrophic factor release correlated with faster learning and better retention over a period of 1 week (Vaynman, Ying, & Gomez-Pinilla, 2004). Exercise also enhances neurogenesis (van Praag et al., 1999; van Praag, Kempermann, & Gage, 1999), which could also contribute to better learning.

In humans, the association between learning improvement and exercise-induced humoral changes has not yet been investigated. It has only been shown that the P300 component of the event-related brain potential (ERP) has a larger amplitude and a shortened latency in attentional challenging tasks, consistent with an overall arousing effect, after a short bout of anaerobic exercise compared to rest (Hillman, Snook, & Jerome, 2003; Magnie et al., 2000; Nakamura, Nishimoto, Akamatu, Takahashi, & Maruyama, 1999). Furthermore, peripheral catecholamine levels may increase after physical exercise (Hyyppa, Aunola, & Kuusela, 1986; Koch, Johansson, & Arvidsson, 1980; Kraemer et al., 1999; Musso, Gianrossi, Pende, Vergassola, & Lotti, 1990), but several other studies found no changes (Bracken, Linnane, & Brooks, 2005; Hartling, Kelbaek, Gjorup, Nielsen, & Trap-Jensen, 1989; Sothmann, Gustafson, & Chandler, 1987). The only study probing central dopamine level changes after a single bout of exercise by positron emission tomography yielded negative results (Wang et al., 2000).

Outside the realm of exercise research, increased peripheral epinephrine levels were correlated with enhanced memory performance in both animals (Costa-Miserachs, Portell-Cortes, Aldavert-Vera, Torras-Garcia, & Morgado-Bernal, 1994) and humans (Cahill & Alkire, 2003). Together, these findings suggest that an exercise-induced increase of catecholamines and neurotrophic factors might improve learning.

We here examined the effects of single bouts of controlled intense anaerobic or moderate aerobic physical exercises (lactate levels above 10 mmol/l or below 2 mmol/l, respectively; Spurway, 1992) on learning and memory. We chose a language learning model because lexical learning is an important aspect of every day life. In search of the mediating mechanisms, we additionally assessed exercise-induced changes in mood, peripheral catecholamine plasma levels and BDNF serum levels and correlated these parameters with subjects' cognitive performance.

2. Materials and methods

2.1. Subjects

A total of 30 healthy male sport students (mean age: 22.2 ± 1.7 years; range: 19–27) participated as subjects in this prospective randomized controlled trial. Two subjects failed to complete the study due to exercise injuries unrelated to the study. Another subject failed to learn, presumably due to inattentive responding (reactions times on average <300 ms). Therefore, data analysis was conducted with a total of 27 subjects[2]. Participants' written informed consent was obtained according to the declaration of Helsinki. The Ethical Committee of the University of Muenster had approved the physiological intervention of the study. All subjects were native German speakers and right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). They had at least 13 years of formal education.

Exclusion criteria comprised bilingualism, a history of neurological, psychiatric or medical diseases, acute infections, intake of medications affecting the central nervous system, recent consumption of recreational drugs as assessed by urinary drug screening, smoking >10 cigarettes/day or drinking >6 cups of coffee/day or >50 g alcohol (equivalent of two glasses of wine) consumption/day.

2.2. Study design

2.2.1. Preexamination

2.2.1.1. Cognitive screening. Subjects were screened with a comprehensive neuropsychological test battery prior to participation. This battery comprised tests of general intellectual functioning, attention, verbal fluency, digit spans, verbal and visuospatial memory, and personality scales. Additionally, two questionnaires assessed possible exercise dependency (Hausenblas & Downs, 2002) and quantified the average amount of physical

[2] For the retention test 8–10 months after the training, only 25 subjects were available.

Table 1
Means and standard deviations of the neuropsychological background measures and correlation coefficients (Pearson) with training success on the novel vocabulary

Test	Mean	*SD*	Correlation with learning success (*r*), condition		
			"relaxed"	"moderate"	"intense"
Edinburgh Handedness Inventory (laterality index)	85.9	16.0	−0.17	−0.15	−0.32
Number of languages spoken fluently	1.6	0.6	−0.20	−0.14	−0.06
VLMT: list A leaning success (block 5 minus 1)	5.4	1.4	−0.13	−0.29	−0.19
VLMT: immediate free recall (PR)	77.0	13.8	0.17	0.18	0.10
VLMT: interference list B (PR)	58.5	34.9	0.06	0.33	0.32
VLMT: delayed free recall (PR)	62.2	30.5	0.28	0.21	0.19
WMS verbal paired associates: sum of blocks 1–3	22.3	1.7	0.36	0.39[a]	0.23
WMS verbal paired associates: delayed recall	7.6	0.6	0.31	0.37	0.42[a]
WMS visual paired associates: sum of blocks 1–3	15.7	2.5	0.36	0.37	0.18
WMS visual paired associates: delayed recall	5.9	0.3	0.12	0.09	0.26
Rey-Figure, Copy	34.9	1.0	0.10	0.10	−0.04
Rey-Figure, delayed recall	24.7	4.1	0.05	0.32	0.32
RWT: Word fluency (mean PR)	32.9	14.7	0.33	0.32	0.15
Trail Making A (PR)	54.8	25.6	0.21	0.32	0.15
Trail Making B (PR)	57.0	28.0	0.05	0.03	−0.25
WAIS-R: Vocabulary (WP)	9.8	1.9	0.22	0.23	0.23
WAIS-R: Similarities (WP)	11.7	2.2	−0.30	−0.03	−0.33
WAIS-R: Picture Completion (WP)	11.8	1.7	0.07	0.09	−0.15
WAIS-R: Block design (WP)	11.2	2.9	0.22	0.44[a]	0.06
digit span forward (PR)	66.3	23.8	0.37	0.04	0.27
digit span backward (PR)	59.2	30.7	0.07	0.06	−0.20
Corsi block tapping forward (PR)	70.2	26.9	0.10	−0.08	−0.24
Corsi block tapping backward (PR)	72.7	20.1	0.25	0.13	−0.01
Sensation Seeking Scale (total score)	21.6	3.4	−0.16	−0.31	−0.28
BDI scores	3.0	3.0	0.20	0.00	0.27
Neo-FFI: neuroticism	1.3	0.5	0.14	−0.08	0.09
Neo-FFI: extroversion	2.5	0.4	0.23	0.10	0.17
Neo-FFI: openness to experience	2.2	0.5	0.18	0.39[a]	0.50[b]
Neo-FFI: agreeableness	2.6	0.4	−0.44[a]	−0.24	−0.06
Neo-FFI: conscientiousness	2.6	0.5	0.23	0.49[a]	0.31
STAI Trait (PR)	52.3	19.8	0.41[a]	0.18	0.34
FfkA (total activity)	17.3	11.0	0.19	0.21	0.26
EDS (total score)	2.9	0.6	0.19	0.32	−0.08

VLMT = Verbaler Lern- und Merkfaehigkeitstest (German version of the Rey Auditory Verbal Learning Test); RWT = Regensburger Wortfluessigkeitstest (German version of the Controlled Oral Word Association Test); WMS = Wechsler Memory Scale (German version); WAIS = Wechsler Adult Intelligence Scale (German version); Neo-FFI = German version of the Neo Five Factor Inventory; FFkA = "Freiburger Fragebogen zur koerperlichen Aktivitaet" (German questionnaire of the average amount of physical activity per week; Frey et al., 1999); EDS = Exercise Dependence Scale (Hausenblas & Downs, 2002); *SD* = standard deviation; PR = percent rank; WP = Wechsler points.

[a] Significant correlation on a 0.05-level (without correction for multiple testing).

[b] Significant correlation on a 0.01-level (without correction for multiple testing).

activity per week (Frey, Berg, Grathwohl, & Keul, 1999). Cognitive measures were all within the normal range. The results of the neuropsychological tests are shown in Table 1.

2.2.1.2. Fitness test. Physical fitness levels were determined by a field test on a 200 m track. The exercise test started at a speed of 8 km/h. Every 3 min, running speed was enhanced by 2 km/h until exhaustion (generally at 18 km/h). On each speed level, participants received continuous acoustic signals in a given frequency as pacing signals. For the determination of lactate concentrations, capillary blood samples were taken from the ear lobe immediately after each speed level as well as after 3 and 6 min during the recovery phase afterwards. At the same time samples, subjective ratings of the perceived exertion were obtained using the Borg-Scale (Borg 1975 in Nybo, Nielsen, Blomstrand, Moller, & Secher, 2003), ranging from 6 (no exhaustion at all) to 20 (complete exhaustion).

2.2.2. Exercise interventions

Using a cross-over design, every subject took part in three conditions on different days, spaced at least 1 week apart (see Fig. 1). The conditions differed with regard to the intensity of physical activity. The condition "relaxed" served as a control and consisted of 15 min being sedentary. The condition "moderate" consisted of 40 min of low impact running at a fixed individual heart rate. The individual target heart rate was based on the results of the initial physical fitness test and ensured that lactate levels remained below 2 mmol/l (aerobic condition). In the condition "intense", subjects performed two sprints of 3 min each, separated by a 2 min break. Each sprint started at 8 km/h, increased every 10 s by 2 km/h, until exhaustion. This was an anaerobic condition with lactate levels greater than 10 mmol/l.

The sequence of the three conditions was randomized across subjects. For the moderate and intense conditions, subjects also rated their perceived exertion on the Borg-Scale immediately after the intervention. Heart rates were assessed prior to and after each of the interventions (2 time samples per condition). Vocabulary learning started 15 min after the respective intervention.

Peripheral levels of BDNF and catecholamines (dopamine, epinephrine, and norepinephrine), lactate levels, and mood ratings were assessed prior to as well as following each of the interventions and immediately after vocabulary learning. For mood ratings, the Positive and Negative Affective Schedule (PANAS) was used (Watson, Clark, & Tellegen, 1988; German version: Krohne, Egloff, Kohlmann, & Tausch, 1996), comprising

ten positive and ten negative adjectives, which measure the dimensions positive affect (high score: a state of high energy, low score: sadness and lethargy) and negative affect (high score: state of distress; low score: state of calmness).

2.2.3. Language learning paradigm

The detailed structure of the vocabulary learning task has been described elsewhere (Breitenstein et al., 2005; Breitenstein, Kamping, Jansen, Schomacher, & Knecht, 2004; Breitenstein & Knecht, 2002; Knecht et al., 2004). The learning principle was associative learning: the "correct" pairings of an visually presented daily object and a novel word (e.g., car and /glump/) co-occur over the course of the five training blocks ten times more often as "incorrect" pairings (e.g., bike and /glump/), which are shown only once (Breitenstein & Knecht, 2002). For each subject and each condition, there were a total of 600 training trials (5 blocks × 120 trials). Each trial consisted of a visually presented object picture, presented 200 ms after the onset of the auditory presentation of a novel word (pseudoword, all normalized to a duration of 600 ms). During picture presentation, which lasted for 1 s, subjects had to press one of two keys with their right hand on a response pad to indicate whether the pairing was correct or not. To prevent subjects from reflecting on their responses, the intertrial interval was limited to 1 s. The instruction was to "intuitively decide if objects and novel words match or not".

Subjects were told that only responses occurring in the 1 s interval of picture presentation were accepted for data analysis. They were not informed about the underlying frequency principle.

Subjects' ability to translate the novel words into German was tested in a transfer test immediately after the training session. During this transfer test (1 block with 120 trials), German object names were acoustically presented in pairs with one of the spoken pseudowords. Subjects had to decide whether the pairing was correct or not. The transfer test was administered again 1 week and >8 months after the last training day to assess retention of the vocabulary. On the 1 week retention session, subjects had to also name each picture in the novel vocabulary by writing down the correct novel word (free recall test).

A different version of the novel vocabulary was used for every condition. The three sets were matched for frequency, number of syllables, and familiarity of the German objects names and for number of syllables, associations with existing words, and acoustic valence of the pseudowords.

Dependent variable were learning speed (increase of correct responses from block 1 to block 5) and the overall learning success (performance on the transfer and the free recall tasks) immediately after the training, at the retention sessions 1 week and 6–8 months post, respectively. In addition to accuracy, response times during the vocabulary training were analyzed.

2.2.4. Biochemical blood analyses

Lactate concentration in capillary blood was measured by a photometric method using a commercially available kit (EKF Diagnostic, Magdeburg, Germany).

The HPLC assay kit for plasma catecholamines was provided by Chromsystems (Munich, Germany). Reversed-phase chromatography was performed on an isocratic Kontron 422 liquid chromatograph (Neufahrn, Germany), interfaced with a model 41,000 electrochemical detector (Chromsystems, Munich, Germany). Complete blood cell count, including an automated differential, was performed by a SE9500 automated full blood count analyzer (Sysmex Deutschland GmbH, Norderstedt, Germany). BDNF level in serum was measured using an ELISA kit (Quantikine human BDNF, R&D Systems, Wiesbaden, Germany).

Dopamine and epinephrine blood plasma levels below the biochemical detection threshold (30 ng/l for dopamine, 15 ng/l for epinephrine) were set to a mean value between zero and the respective detection threshold (15 ng/l for dopamine, 7.5 ng/l for epinephrine).

All BDNF and catecholamine blood plasma levels were corrected for changes in overall blood volume (Dill & Costill, 1974).

2.3. Data analysis

Behavioral (accuracy and reaction times on the vocabulary learning task) and biochemical blood data and mood ratings were analyzed using repeated measures ANOVAs, with polynomial contrasts on the factor training block (blocks 1–5) or time sample (3: prior to exercise, after exercise, after vocabulary training). Greenhouse–Geisser adjustments were applied in analyses with two or more degrees of freedom. Significant interactions or main effects were followed up by paired t-tests in case of significance. For clarity of presentation, only effects involving the factor exercise condition (relaxed, moderate, intense) are presented.

Immediate and delayed (1 week and >8 months post) retention data of the vocabulary were analyzed separately using univariate ANOVAs with the repeated factor exercise condition.

Correlations were analyzed using Pearson's correlations coefficients. Because of the explorative nature of the present study, it was considered appropriate to omit Bonferroni-corrections of significance levels.

3. Results

3.1. Learning performance

Using a cross-over study design, learning performance was assessed directly after high impact anaerobic sprints (intense condition), low impact aerobic running (moderate condition), or a period of rest (relaxed condition).

3.1.1. Accuracy

There was a difference in learning speed between these three conditions (condition × block: quadratic trend, $F(1,26) = 9.39$, $p = .005$). Post hoc tests showed that learning speed across the five training blocks was significantly faster after intense running compared to being sedentary (condition × block: quadratic trend, $F(1,26) = 9.39$, $p = .005$) and moderate running (condition × block: quadratic trend, $F(1,26) = 5.27$, $p = .03$) conditions (see Fig. 2). Please note that performance in the intense condition was already at ceiling in block 4. For the other two conditions, subjects needed one more training block (block 5) to reach a comparable level of performance. This indicates that learning was accelerated by 20 percent in the intense condition.

The transfer sessions immediately after training, 1 week and >8 months post training, respectively, were not significantly different for the three conditions (main effects of condition: all $p > .18$). However, exploratory comparisons showed that subjects presented with a better 1-week retention for the intense as compared to the moderate condition ($t(26) = 2.24$, $p = .03$; see Fig. 2). The free recall naming task at the 1-week post assessment did not yield significant differences between the three conditions (main effect of condition: $p = .57$).

3.1.2. Analysis of training reaction times

Only the main effect of condition yielded significance ($F(2,52) = 5.11$, $p = .01$). Post hoc tests revealed significantly faster responding in the condition "intense" compared to both "relaxed" and "moderate" (both $F(1,26) > 4.35$, $p < .05$; see Fig. 3). However, overall learning success (accuracy on block 5 minus block 1) was neither correlated with the mean reaction time on block 1 nor with the mean

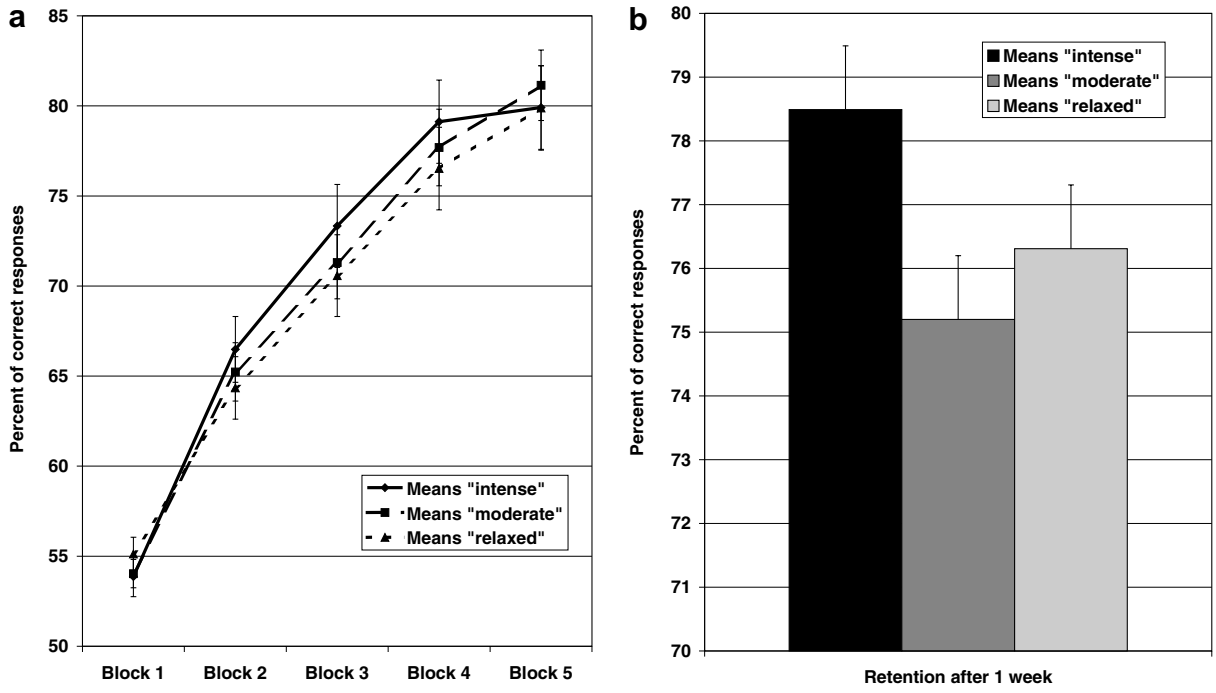

Fig. 2. (a) Vocabulary learning success (means ± SEM) across the five training blocks was faster after intense physical exercise (solid line) compared to after moderate exercise (dashed line) or the relaxed condition (dotted line). (b) Retention (means ± SEM) of the vocabulary after 1 week was better in the "intense" condition (black) as compared to the "moderate" condition (dark gray).

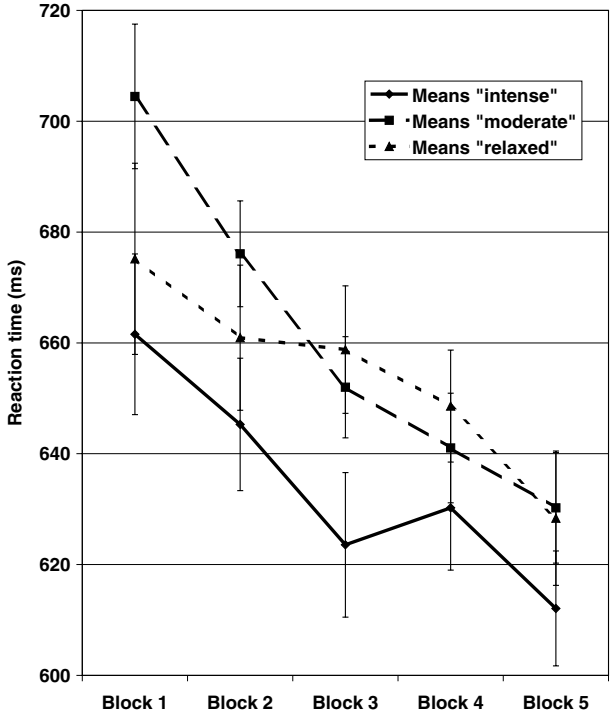

Fig. 3. Mean reaction times (±SEM) in ms across the five training blocks. Responses were faster after intense exercise (solid line) compared to both moderate exercise (dashed line) and being sedentary (dotted line).

reaction time across all blocks, indicating that unspecific motor arousal after intense physical exercise cannot explain the superior learning rates.

3.2. Measures of unspecific arousal

Measures of unspecific arousal were assessed to control for unspecific effects mediating the exercise-induced learning improvement.

3.2.1. Heart rate

In the moderate condition, subjects' heart rates were in the range of 110 and 160 beats/min (median: 140 beats/min). After intense exercise the heart rates were in the range of 163 and 202 beats/min (median: 184 beats/min).

There was a significant interaction of time sample (baseline, post intervention) and condition (linear trend: $F(1,26) = 1680.63$, $p < .001$). Post hoc analyses showed that heart rates increased post intervention only for the moderate (mean increase of 67.3, *SD*: 14.3 beats/min) and intense (mean increase of 111.1, *SD*: 10.8 beats/min) conditions (both $t(26) > |24.52|$, $p < .001$), but not for the relaxed condition. Baseline heart rates did not differ between the conditions. There were no correlations between exercise-induced heart rate changes and learning outcome, although baseline heart rates prior to intense exercise were correlated with immediate and delayed (1 week/>8 months) retention outcomes (all $r > .41$, $p < .03$).

3.2.2. Blood lactate concentrations

The analyses of the peripheral lactate levels revealed a significant interaction of condition and time of measurement (quadratic trend: $F(1,26) = 1002.42$, $p < .001$). As

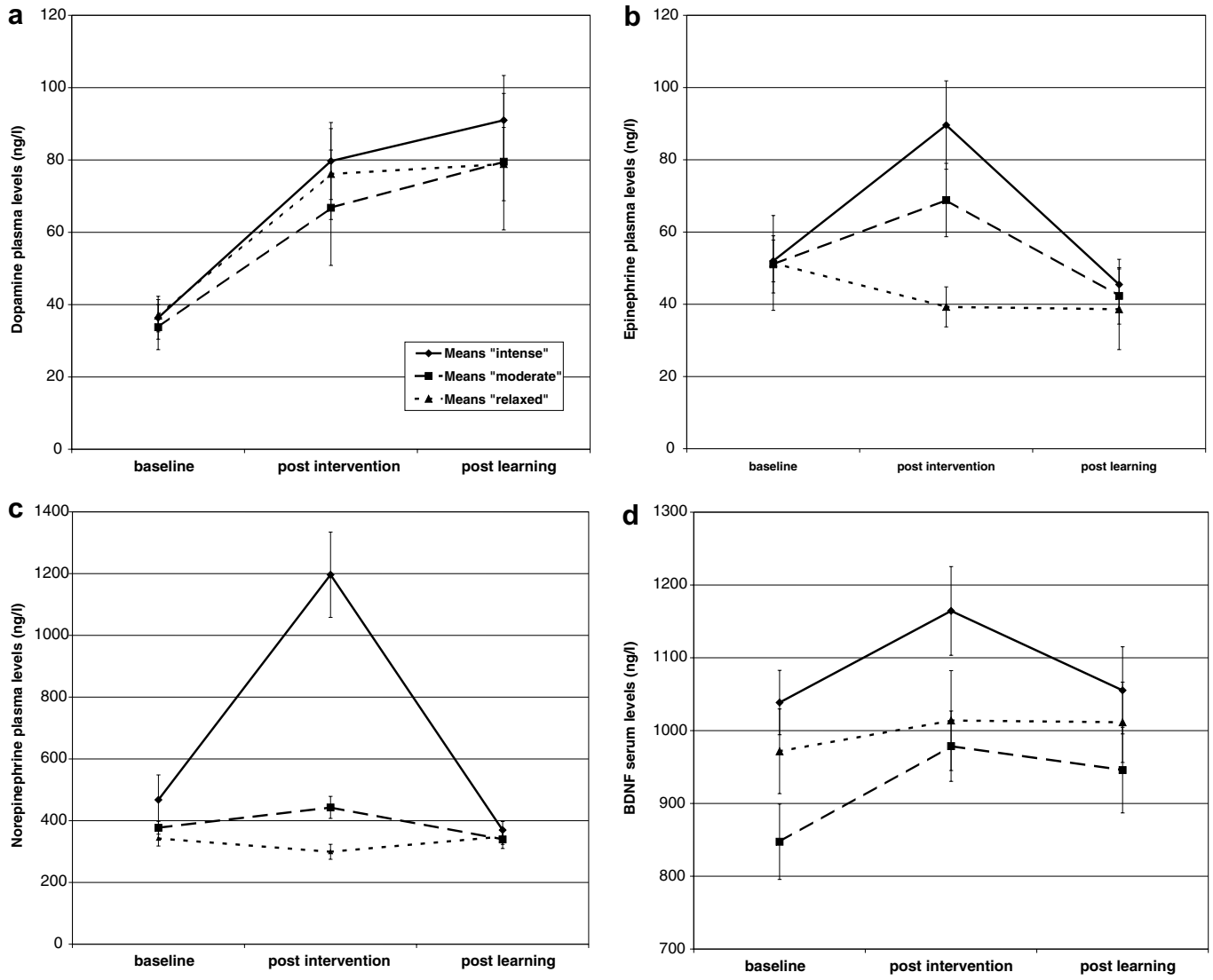

Fig. 4. Exercise-induced changes in blood plasma levels (±SEM, corrected for differences in overall blood volume) of dopamine (a), epinephrine (b), norepinephrine (c) and blood serum levels of BDNF (d) for the conditions "relaxed" (dotted line), "moderate" (dashed line) and "intense" (solid line) across the three time samples (baseline, post intervention, post learning).

expected, lactate levels showed a greater exercise-induced increase during the intense as compared to each of the other two conditions (interaction of condition × time sample: quadratic trend, both $F(1,26) > 1002{,}42$, $p < .001$). There were also differences at baseline ($F(2,52) = 4.62$, $p = .02$; "moderate" > "relaxed, $t(26) = 2.84$, $p = .009$). There were no correlations between exercise-induced lactate level changes and learning outcome.

3.3. Exercise-induced neurotransmitter changes: Catecholamine blood plasma levels

Peripheral catecholamine plasma levels (dopamine, epinephrine, norepinephrine) were assessed at baseline, immediately after the respective intervention, and after vocabulary learning to determine possible contributions to the boost in learning.

3.3.1. Dopamine

There were significant linear increases in dopamine plasma levels across the three time samples for all three conditions (main effect of time sample: linear trend, $F(1,26) = 30.66$, $p < .001$). Visual inspection of the data suggested that plasma dopamine levels showed a steeper increase in the intense as compared to the other two condition, but the interaction of condition and time sample did not yield significance (see Fig. 4a). Baseline dopamine plasma levels were not different for the three conditions.[3]

[3] Two subjects were excluded because their dopamine levels were greater than two times the *SD* of the group mean ($n = 25$). Values below the detection threshold were substituted (see Section 2). Separate analyses for the subsample of subjects with values above the biochemical detection threshold ($n = 11$) also yielded a main effect of time sample (linear trend, $F(1,10) = 15.77$, $p = .003$) and no interaction of condition and time sample.

3.3.2. Epinephrine

The ANOVA yielded a significant interaction of condition and time sample (quadratic trend, $F(1,24) = 7.03$, $p = .01$). Post hoc tests showed stronger exercise-induced changes for the intense as compared to the relaxed condition (condition × time sample: quadratic trend, $F(1,24) = 7.03$, $p = .01$). Additional post hoc analyses for each level of time sample separately yielded a main effect of condition only for the time sample after the intervention ($F(2,48) = 6.67$, $p = .006$; "moderate", "intense" > "relaxed", both $t(24) > |3.01|$, $p < .006$). There were no baseline differences between conditions (see Fig. 4b).[4]

3.3.3. Norepinephrine

There was a significant interaction between condition and time sample (quadratic trend: $F(1,26) = 31.32$, $p < .001$). Post hoc analyses showed that the intense condition yielded significantly steeper norepinephrine changes after exercise as compared to the other two conditions (interaction of condition × time sample: quadratic trend, both $F(1,26) > 27.79$, $p < .001$). Furthermore, moderate exercise led to steeper increases as compared to being sedentary (interaction of condition × time sample: quadratic trend, $F(1,26) = 12.81$, $p = .001$). Separate analyses for each time sample separately showed that the conditions differed only at the time sample immediately post intervention ($F(2,52) = 39.46$, $p < .001$; "intense" > "moderate" > "relaxed", all $t(26) > |3.51|$, $p \leqslant .002$). There were no significant differences at baseline (see Fig. 4c).

3.4. Exercise-induced changes in BDNF blood serum levels

To also determine the possible contribution of neurotrophic factors in exercise-induced learning enhancement, peripheral BDNF serum levels were determined at baseline, immediately after the respective exercise, and after vocabulary training. BDNF baseline values differed for the three conditions ($F(2,52) = 5.88$, $p = .006$; intense > moderate: $t(26) = -3.33$, $p = .003$). We will therefore only interpret significant slope differences across the three time samples between conditions. The ANOVA yielded a significant interaction of condition and time sample (quadratic trend, $F(1,26) = 4.38$, $p = .05$). Post hoc tests revealed significantly stronger changes across times samples for the intense as compared to the relaxed condition (interaction of condition × time sample: quadratic trend, $F(1,26) = 4.38$, $p = .05$; see Fig. 4d).

3.5. Correlations between behavioral and physiological parameters

To examine the association of learning success with exercise-induced changes in physiological parameters, we calculated the correlations of learning indicators (overall learning success and retention outcome after 1 week and after 8–10 months) with the respective changes in physiological parameters. There were no significant correlations with norepinephrine blood plasma level changes. For the other physiological parameters, the following significant correlations emerged:

A decrease in dopamine blood plasma levels during learning (post intervention minus post learning) was related to a better retention outcome immediately after learning and after 1 week in the intense condition (both $r > .46$, $p < .02$, see Figs. 6a and b)[5]. The absolute dopamine concentration after intense exercise also predicted the immediate and 1 week delayed retention outcomes (both $r > .33$, $p < .10$)[5]. Because subjects with higher absolute dopamine concentrations prior to learning (post exercise) also showed the strongest dopamine level decreases during learning ($r = .85$, $p < .001$), absolute dopamine concentrations during learning may be the crucial factor for the enhanced immediate/intermediate learning outcome.

For epinephrine exercise-induced blood plasma changes, there were no significant correlations with learning outcome. Because absolute concentrations of epinephrine could be more important for memory consolidation than relative increases from baseline, we correlated the absolute epinephrine blood plasma concentrations after exercise with immediate and delayed learning success. Only the epinephrine concentrations after the intense intervention (prior to learning) correlated with long-term retention of the vocabulary (retention after >8 months $r = .41$, $p < .05$, see Fig. 6c)[6]. A trend was also seen for the correlation between epinephrine concentrations post intense exercise and vocabulary retention after 1 week ($r = .38$, $p = .06$)[6].

To additionally support the link between epinephrine changes and learning success, we contrasted subjects with low versus high exercise-induced epinephrine changes in the intense condition (median split using the peripheral epinephrine blood plasma levels after intense exercise). These analyses yielded a significantly better outcome for the "high" as compared to the "low" epinephrine changes group for the retention results after 1 week and after >8 months ($t(23) = -2.60$, $p = .02$ and $t(22) = -2.27$, $p = .03$, respectively, see Fig. 5)[6].

For BDNF serum levels, the more sustained the BDNF levels during learning (BDNF levels after learning minus

[4] Two subjects were excluded because their epinephrine levels were greater than two times the *SD* of the group mean ($n = 25$). Values below the detection threshold were substituted (see Section 2). Separate analyses for the subsample of subjects with values above the biochemical detection level ($n = 11$) yielded a significant interaction of condition and time sample (quadratic trend, $F(1,10) = 7.75$, $p = .02$). Post hoc tests only showed a difference between the conditions "relaxed" and "intense" (condition × time sample: quadratic trend, $F(1,10) = 7.75$, $p = .02$), but not between the other pairwise comparisons. Additional post hoc analyses for each level of time sample separately yielded a main effect of condition only for the time sample after the intervention ($F(2,20) = 4.70$, $p = .05$; "moderate", "intense" > "relaxed", both $t(10) > |3.03|$, $p < .01$).

[5] Two subjects were excluded because their dopamine levels were greater than two times the *SD* of the group mean ($n = 25$).

[6] Two subjects were excluded because their epinephrine levels were greater than two times the *SD* of the group mean ($n = 25$ or 24 for the retention after >8 months, see Section 2).

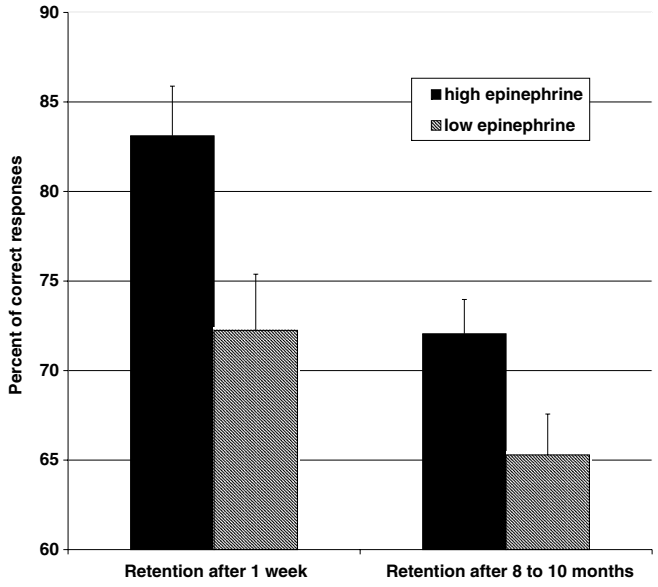

Fig. 5. Differences in retention outcome (means ± SEM) after 1 week and after 8–10 months for subjects with high and low epinephrine blood plasma levels after intense exercise (split-half method).

BDNF levels after exercise), the greater the immediate learning success (accuracy on block 5 minus block 1) for the "intense" condition ($r = .38$, $p = .05$; see Fig. 6d).

3.6. Analyses of positive and negative mood ratings

There were no significant interactions or main effects involving the factor condition for negative mood ratings.

The analysis of the positive mood ratings yielded a significant interaction of condition and time sample (quadratic trend, $F(1,25) = 11{,}26$, $p = .003$[7]). Ratings at baseline and after learning did not differ significantly between the conditions. Ratings differed only for the time sample after the respective interventions ($F(2,50) = 6.52$, $p = .004$), with significantly higher positive mood ratings for the condition "intense" versus "relaxed" as well as for "moderate" versus "relaxed" (both $t(25) > |2.94|$, $p \leqslant .007$[8]).

Furthermore, in the intense conditions, a more sustained exercise-induced increase in positive mood (mood rating post intervention minus mood rating immediate after learning) was marginally associated with an overall better learning success (accuracy on block 5 minus block 1; $r = -.37$, $p = .06$), a better outcome at the immediate transfer session ($r = -.33$, $p = .10$) and with a better retention after 1 week ($r = -.37$, $p = .06$). Changes in mood ratings were not correlated with the changes in peripheral epinephrine plasma levels, indicating that both factors contributed independently to better learning.

[7] $n = 26$ because one subject did not entirely complete one of the PANAS questionnaires.

[8] Two subjects were excluded because their epinephrine levels were greater than two times the *SD* of the group mean ($n = 25$ or 24 for the retention after >8 months, see Section 2).

4. Discussion

The main finding of the present study was that intense exercise directly improves learning: After two sprints of less than 3 min each, subjects learned 20 percent faster compared to moderate exercise or being sedentary. To our knowledge, this is the first study of immediate exercise-induced effects on a complex learning task with a parallel analysis of neurophysiological correlates (changes in peripheral catecholamine or BDNF levels) in humans. Our results suggests that short bouts of exercise could be used in situations which require an immediate boost of learning, e.g., immediately prior to study phases in children with and without learning deficits.

We were further able to elucidate at least some of the underlying neurophysiological mechanisms of improved learning through exercise. Intense running led to elevated levels of peripheral catecholamines (dopamine, epinephrine, norepinephrine) and BDNF. More sustained BDNF levels during learning (levels after intense exercise minus levels after learning) were related to better short-term learning success, and absolute dopamine and epinephrine levels after intense exercise were related to better intermediate (dopamine) and long-term (epinephrine) retentions of the novel vocabulary. The latter finding was endorsed by the observation, that subjects with relatively higher (as compared to the group mean) epinephrine blood plasma levels after intense exercise had a better long-term retention of the trained vocabulary up to >8 months. We will discuss these findings in more detail below.

4.1. Short-term learning improvement and BDNF

We found that more sustained BDNF blood serum levels during learning predicted immediate learning success after intense exercise. This finding is consistent with prior work showing that BDNF secretion is increased after exercise in animals (Neeper et al., 1995; Vaynman et al., 2004) and in humans (Gold et al., 2003). BDNF plays an import role in learning due to its involvement in long-term potentiation in the hippocampus (Pang et al., 2004). BDNF also contributes to synaptic efficacy, neuronal connectivity, and brain plasticity (McAllister, Katz, & Lo, 1999; Schinder & Poo, 2000; Vaynman et al., 2004). The release of other neurotrophic factors like IGF-1 is increased after physical exercise in humans as well (Carro et al., 2000). We chose BDNF because it has been shown to be elevated after physical exercise in humans (Gold et al., 2003), and most of the genes up-regulated after exercise and relevant to plasticity are associated with BDNF (Molteni, Ying, & Gomez-Pinilla, 2002). We could only assess peripheral BDNF levels, but there seems to be an influx of natural BDNF from the blood into the brain (Pan, Banks, Fasold, Bluth, & Kastin, 1998); although, this is challenged by other authors (Sakane & Pardridge, 1997; Wu, 2005). Our findings show that BDNF could be one mediator between physical

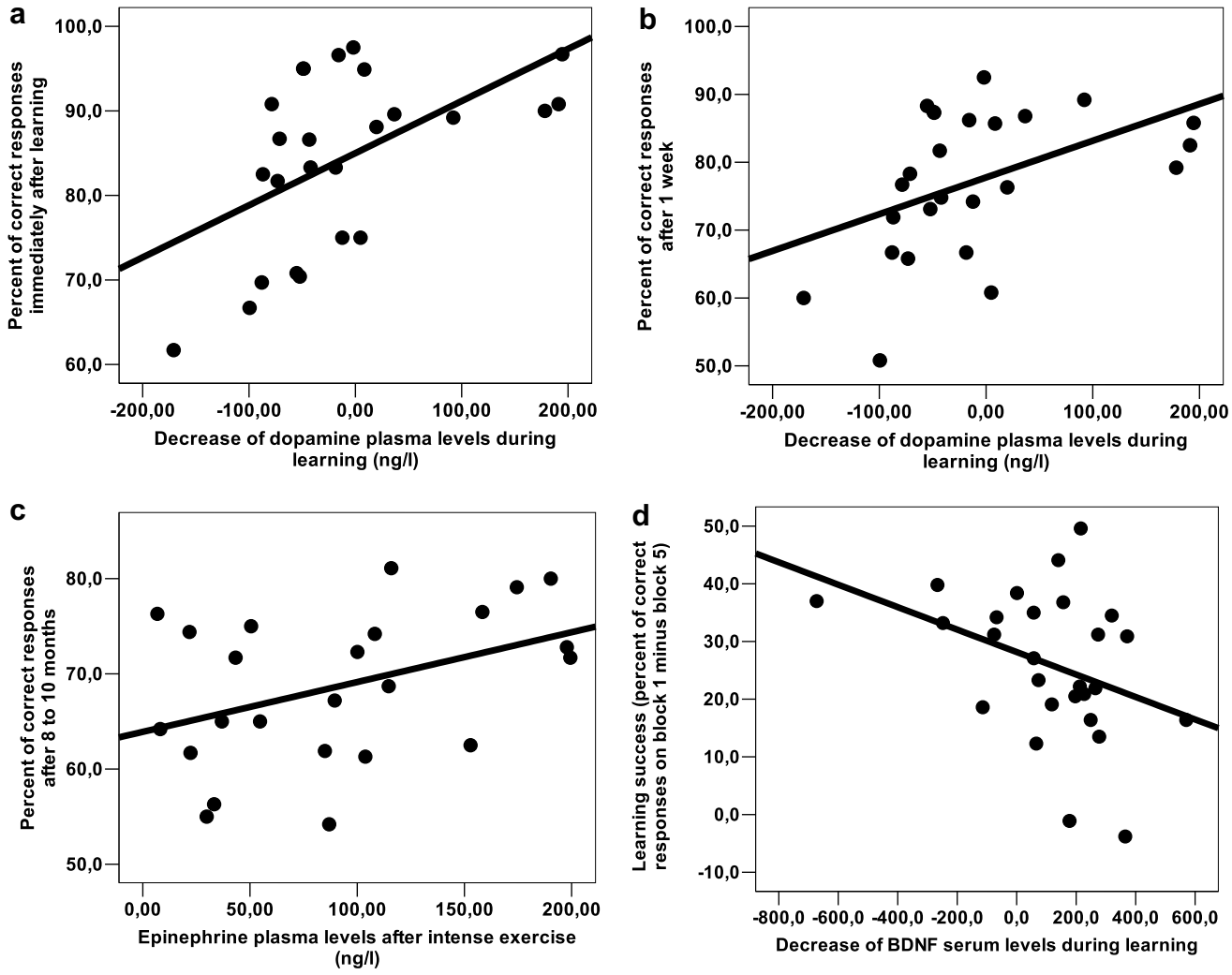

Fig. 6. (a,b) Peripheral dopamine plasma levels during learning (after intense intervention minus after learning) predicted immediate retention outcome (a) and retention outcome after 1 week (b). (c) Peripheral epinephrine plasma levels post intense exercise correlated with the retention outcome after >eight months; (d) BDNF serum levels during learning (levels after intense intervention minus levels after learning) were related to immediate learning success (accuracy on block 5 minus block 1).

exercise and learning improvement (Cotman & Berchtold, 2002; Vaynman et al., 2004).

4.2. Intermediate learning improvement and dopamine

We observed a correlation between greater decreases of dopamine blood plasma levels during learning and better intermediate retention after intense exercise. This may seem counterintuitive at first sight, but further analyses showed that higher *absolute* dopamine levels in the initial stages of learning drove the correlation of an enhanced retention outcome.

The role of dopamine for learning has been variously demonstrated (Fiorillo, Tobler, & Schultz, 2003; Floel et al., 2005; Jay, 2003; Knecht et al., 2004; Wise, 2004). Dopamine is part of the internal reward system (Schultz, 2002), regulates the prefrontal cortical circuitry underlying working memory (Castner & Goldman-Rakic, 2004; Marie & Defer, 2003) and modulates arousal and attention (Nutt & Fellman, 1984). It even seems to be critical for neurogenesis (Baker, Baker, & Hagg, 2004).

Animal studies suggest an increase in dopamine release in the brain during exercise (Hattori et al., 1994; Meeusen & De Meirleir, 1995; Sutoo & Akiyama, 2003). Our controlled intense exercise condition also led to elevated levels of peripheral dopamine levels, contrary to the results of other studies in humans with less objective criteria for physical exertion levels (Bracken et al., 2005; Kraemer et al., 1999). Peripheral dopamine levels are less than perfect correlates of dopamine release in the brain, because dopamine cannot cross the blood-brain barrier. We had to operate on the assumption that brain and systemic dopamine levels responded similarly to physical exercise. Thus, an enhanced presynaptic availability of endogenous dopamine could have led to stronger phasic dopamine signals coding for stimulus salience (Breitenstein, Korsukewitz K, Floel A, Kretzschmar T, & Diederich K, 2006; Schultz, 2002), contributing to better memory consolidation.

4.3. Long-term learning improvement and epinephrine

We found a correlation between absolute blood plasma concentrations of epinephrine after intense exercise and long-term retention outcome. There are several explanations for the beneficial influence of exercise on cognitive functions mediated by epinephrine. One is that the increased memory consolidation after intense exercise was driven by increased arousal during learning (Hollmann & Struder, 2000; Sharot & Phelps, 2004) and improved attention (Hillman et al., 2003; Magnie et al., 2000; Nakamura et al., 1999). Heart rates and lactate levels were higher and the reaction times during learning were shorter after the intense exercise as compared to the other two conditions, but neither of these parameters was correlated with learning success. These findings speak against increased arousal as the exclusive mediator of improved learning. Nevertheless, arousal may have mediated part of the effect, because prior studies already demonstrated that absolute peripheral epinephrine during learning contributes to memory consolidation in animals (Costa-Miserachs et al., 1994; Liang, Chen, & Huang, 1995) and in humans (Cahill & Alkire, 2003), with the crucial factor being the grade of arousal during encoding (Cahill & Alkire, 2003).

Peripheral epinephrine does not cross the blood-brain barrier (Bradbury, 1993), but there might be an indirect pathway to influence the central nervous system: One possible route is the activation of vagal afferent fibers via β-adrenergic receptors. This vagal stimulation by peripheral epinephrine leads to an increased neural firing in the noradrenergic connections between the nucleus solitarius and the amygdala (Clayton & Williams, 2000; Miyashita & Williams, 2006) or the hippocampus (Miyashita & Williams, 2004). Enhanced noradrenergic release in this area might then lead to increased general brain excitability with improved learning capability (Boyeson & Feeney, 1990; Feeney & Hovda, 1985; Goldstein, 1999). This indirect pathway could be the neurophysiological link for the observed correlation between peripheral epinephrine plasma levels and enhanced vocabulary retention in the present study.

4.4. Aerobic versus anaerobic physical exercise

We did not observe an effect of a single bout of moderate (aerobic) physical exercise on learning and memory. The two exercise interventions differed not only in terms of intensity, but also in duration. However, the intense condition led to a facilitation of learning, despite a *shorter* duration compared to the moderate condition. It also seems unlikely that the lack of learning improvement in the moderate condition was due to the greater fatigue or the longer duration (40 min), because the moderate intervention did not differ from the resting condition in terms of learning success. But we cannot rule out that this was due to an interaction of facilitation and debilitation (Tomporowski & Ellis, 1986). However, after prolonged moderate exercise, there may be effects on mental functioning (e.g., Colcombe et al., 2004). It remains to be determined in future studies whether short high impact and prolonged low impact exercise have comparable effects and are mediated by similar mechanisms. Please note that the three conditions of our study yielded comparable immediate learning outcomes (block 5 of the training), presumably due to ceiling effects of ten subjects in the intense learning condition at block 4. Seven of these subjects subsequently showed a small dip in performance in block 5, probably due to a lack of continuous motivation. It is feasible that a different learning paradigm, which allows for greater differentiation of learning success, would also yield qualitative differences between the conditions.

Our study was designed as a "proof of principle" experiment, probing the effects of a single bout of physical exercise on learning and memory. Because of its pilot character, the sample size was relatively small, and the moderate statistical power may explain why some of the reported effects were only marginally significant. Nevertheless, we could show that exercise accelerates learning and improves long-term retention of the learned material (at least in subjects with high exercise-induced epinephrine levels). This is pertinent to the organization of learning-supportive environments, e.g., in schools (intense exercise during the breaks) and as a possible treatment for cognitive impairments in cardiovascularly stable people. Our results may also be of significance for the development of treatment options for learning-impaired neurological patients (stroke, dementia) because we could determine BDNF, dopamine, and epinephrine as important mediators of the exercise-induced learning improvement. Further investigations are necessary to determine if the observed effects generalize to other learning modalities, like visual-spatial learning.

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References

Abbott, R. D., White, L. R., Ross, G. W., Masaki, K. H., Curb, J. D., & Petrovitch, H. (2004). Walking and dementia in physically capable elderly men. *JAMA: The Journal of the American Medical Association, 292*, 1447–1453.

Allison, D. B., Faith, M. S., & Franklin, R. D. (1995). Antecedent exercise in the treatment of disruptive behavior: a meta-analytic review. *Clinical Psychology: Science & Practice, 2*, 279–304.

Anderson, B. J., Rapp, D. N., Baek, D. H., McCloskey, D. P., Coburn-Litvak, P. S., & Robinson, J. K. (2000). Exercise influences spatial learning in the radial arm maze. *Physiology & Behavior, 70*, 425–429.

Baker, S. A., Baker, K. A., & Hagg, T. (2004). Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone. *European Journal of Neuroscience, 20*, 575–579.

Baruch, D. E., Swain, R. A., & Helmstetter, F. J. (2004). Effects of exercise on Pavlovian fear conditioning. *Behavioral Neuroscience, 118*, 1123–1127.

Boyeson, M. G., & Feeney, D. M. (1990). Intraventricular norepinephrine facilitates motor recovery following sensorimotor cortex injury. *Pharmacology Biochemistry and Behavior, 35*, 497–501.

Bracken, R. M., Linnane, D. M., & Brooks, S. (2005). Alkalosis and the plasma catecholamine response to high-intensity exercise in man. *Medicine and Science in Sports and Exercise, 37*, 227–233.

Bradbury, M. W. (1993). The blood–brain barrier. *Experimental Physiology, 78*, 453–472.

Braszko, J. J., Kaminski, K. A., Hryszko, T., Jedynak, W., & Brzosko, S. (2001). Diverse effects of prolonged physical training on learning of the delayed non-matching to sample by rats. *Neuroscience Research, 39*, 79–84.

Breitenstein, C., Korsukewitz, C., Floel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology, 31*, 2552–2564.

Breitenstein, C., Jansen, A., Deppe, M., Foerster, A. F., Sommer, J., Wolbers, T., et al. (2005). Hippocampus activity differentiates good from poor learners of a novel lexicon. *Neuroimage, 25*, 958–968.

Breitenstein, C., Kamping, S., Jansen, A., Schomacher, M., & Knecht, S. (2004). Word learning can be achieved without feedback: implications for aphasia therapy. *Restorative Neurology and Neuroscience, 22*, 445–458.

Breitenstein, C., & Knecht, S. (2002). Development and validation of a language learning model for behavioral and functional-imaging studies. *Journal of Neuroscience Methods, 114*, 173–179.

Burghardt, P. R., Fulk, L. J., Hand, G. A., & Wilson, M. A. (2004). The effects of chronic treadmill and wheel running on behavior in rats. *Brain Research, 1019*, 84–96.

Cahill, L., & Alkire, M. T. (2003). Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. *Neurobiology of Learning and Memory, 79*, 194–198.

Carro, E., Nunez, 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.

Castner, S. A., & Goldman-Rakic, P. S. (2004). Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D1 receptor stimulation. *Journal of Neuroscience, 24*, 1446–1450.

Cian, C., Barraud, P. A., Melin, B., & Raphel, C. (2001). Effects of fluid ingestion on cognitive function after heat stress or exercise-induced dehydration. *International Journal of Psychophysiology, 42*, 243–251.

Cian, C., Koulmann, N., Barraud, P. A., Raphel, C., Jimenez, C., & Melin, B. (2000). Influences of variations in body hydration on cognitive function: effect of hyperhydration, heat stress, and exercise-induced dehydration. *Journal of Psychophysiology, 14*, 29–36.

Clayton, E. C., & Williams, C. L. (2000). Noradrenergic receptor blockade of the NTS attenuates the mnemonic effects of epinephrine in an appetitive light–dark discrimination learning task. *Neurobiology of Learning and Memory, 74*, 135–145.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science, 14*, 125–130.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 3316–3321.

Costa-Miserachs, D., Portell-Cortes, I., Aldavert-Vera, L., Torras-Garcia, M., & Morgado-Bernal, I. (1994). Long-term memory facilitation in rats by posttraining epinephrine. *Behavioral Neuroscience, 108*, 469–474.

Cotman, C. W., & Berchtold, N. C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends in Neuroscience, 25*, 295–301.

Craft, D. H. (1983). Effect of prior exercise on cognitive performance tasks by hyperactive and normal young boys. *Perceptual and Motor Skills, 56*, 979–982.

Davey, C. P. (1973). Physical exertion and mental performance. *Ergonomics, 16*, 595–599.

Dill, D. B., & Costill, D. L. (1974). Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *Journal of Applied Physiology, 37*, 247–248.

Etnier, J. L., Salazar, W., Landers, D. M., Petruzzello, S. J., Han, M., & Nowell, P. M. (1997). The influence of physical fitness and exercise upon cognitive functioning: a meta-analysis. *Journal of Sport & Exercise Psychology, 19*, 249–277.

Feeney, D. M., & Hovda, D. A. (1985). Reinstatement of binocular depth perception by amphetamine and visual experience after visual cortex ablation. *Brain Research, 342*, 352–356.

Fiorillo, C. D., Tobler, P. N., & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science, 299*, 1898–1902.

Floel, A., Breitenstein, C., Hummel, F., Celnik, P., Gingert, C., Sawaki, L., et al. (2005). Dopaminergic influences on formation of a motor memory. *Annals of Neurology, 58*, 121–130.

Fordyce, D. E., & Farrar, R. P. (1991). Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. *Behavioural Brain Research, 46*, 123–133.

Frey, I., Berg, A., Grathwohl, D., & Keul, J. (1999). Freiburger Fragebogen zur körperlichen Aktivität - Entwicklung, Prüfung und Anwendung. *Sozial- und Präventivemedizin, 44*, 55–64.

Gobbo, O. L., & O'Mara, S. M. (2005). Exercise, but not environmental enrichment, improves learning after kainic acid-induced hippocampal neurodegeneration in association with an increase in brain-derived neurotrophic factor. *Behavioural Brain Research, 159*, 21–26.

Gold, S. M., Schulz, K. H., Hartmann, S., Mladek, M., Lang, U. E., Hellweg, R., et al. (2003). Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *Journal of Neuroimmunology, 138*, 99–105.

Goldstein, L. B. (1999). Amphetamine-facilitated poststroke recovery [letter; comment]. *Stroke, 30*, 696–698.

Hartling, O. J., Kelbaek, H., Gjorup, T., Nielsen, M. D., & Trap-Jensen, J. (1989). Plasma concentrations of adrenaline, noradrenaline and dopamine during forearm dynamic exercise. *Clinical Physiology, 9*, 399–404.

Hattori, S., Naoi, M., & Nishino, H. (1994). Striatal dopamine turnover during treadmill running in the rat: relation to the speed of running. *Brain Research Bulletin, 35*, 41–49.

Hausenblas, H. A., & Downs, D. S. (2002). How much is too much? The development and validation of the exercise dependence scale. *Psychology & Health, 17*, 387–404.

Hillman, C. H., Snook, E. M., & Jerome, G. J. (2003). Acute cardiovascular exercise and executive control function. *International Journal of Psychophysiology, 48*, 307–314.

Hogervorst, E., Riedel, W., Jeukendrup, A., & Jolles, J. (1996). Cognitive performance after strenuous physical exercise. *Perceptual and Motor Skills, 83*, 479–488.

Hollmann, W., & Struder, H. K. (2000). Brain function, mind, mood, nutrition, and physical exercise. *Nutrition, 16*, 516–519.

Hyyppa, M. T., Aunola, S., & Kuusela, V. (1986). Psychoendocrine responses to bicycle exercise in healthy men in good physical condition. *International Journal of Sports Medicine, 7*, 89–93.

Jay, T. M. (2003). Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. *Progress in Neurobiology, 69*, 375–390.

Kalmijn, S., Foley, D., White, L., Burchfiel, C. M., Curb, J. D., Petrovitch, H., et al. (2000). Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arteriosclerosis Thrombosis, and Vascular Biology, 20*, 2255–2260.

Knecht, S., Breitenstein, C., Bushuven, S., Wailke, S., Kamping, S., Floel, A., et al. (2004). Levodopa: faster and better word learning in normal humans. *Annals of Neurology, 56*, 20–26.

Koch, G., Johansson, U., & Arvidsson, E. (1980). Radioenzymatic determination of epinephrine, norepinephrine and dopamine in 0.1 ml plasma samples: plasma catecholamine response to submaximal and near maximal exercise. *Journal of Clinical Chemistry and Clinical Biochemistry, 18*, 367–372.

Kraemer, W. J., Hakkinen, K., Newton, R. U., Nindl, B. C., Volek, J. S., McCormick, M., et al. (1999). Effects of heavy-resistance training on hormonal response patterns in younger vs. older men. *Journal of Applied Physiology, 87*, 982–992.

Krohne, H. W., Egloff, B., Kohlmann, C. W., & Tausch, A. (1996). Untersuchungen mit einer deutschen Version der "Positive and Negative Affect Schedule" (PANAS) [Investigations with a German version of the Positive and Negative Affect Schedule (PANAS)]. *Diagnostica, 42*, 139–156.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., et al. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine, 144*, 73–81.

Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology, 58*, 498–504.

Liang, K. C., Chen, L. L., & Huang, T. E. (1995). The role of amygdala norepinephrine in memory formation: involvement in the memory enhancing effect of peripheral epinephrine. *Chinease Journal of Physiology, 38*, 81–91.

Magnie, M. N., Bermon, S., Martin, F., Madany-Lounis, M., Suisse, G., Muhammad, W., et al. (2000). P300, N400, aerobic fitness, and maximal aerobic exercise. *Psychophysiology, 37*, 369–377.

Marie, R. M., & Defer, G. L. (2003). Working memory and dopamine: clinical and experimental clues. *Current Opinion in Neurology, 16*(Suppl 2), S29–S35.

McAllister, A. K., Katz, L. C., & Lo, D. C. (1999). Neurotrophins and synaptic plasticity. *Annual Review of Neuroscience, 22*, 295–318.

McMorris, T., & Graydon, J. (1997). The effect of exercise on cognitive performance in soccer-specific tests. *Journal of Sports Science, 15*, 459–468.

Meeusen, R., & De Meirleir, K. (1995). Exercise and brain neurotransmission. *Sports Medicine, 20*, 160–188.

Miyashita, T., & Williams, C. L. (2004). Peripheral arousal-related hormones modulate norepinephrine release in the hippocampus via influences on brainstem nuclei. *Behavioural Brain Research, 153*, 87–95.

Miyashita, T., & Williams, C. L. (2006). Epinephrine administration increases neural impulses propagated along the vagus nerve: role of peripheral beta-adrenergic receptors. *Neurobiology of Learning and Memory, 85*, 116–124.

Molteni, R., Ying, Z., & Gomez-Pinilla, F. (2002). Differential effects of acute and chronic exercise on plasticity-related genes in the rat hippocampus revealed by microarray. *European Journal of Neuroscience, 16*, 1107–1116.

Musso, N. R., Gianrossi, R., Pende, A., Vergassola, C., & Lotti, G. (1990). Plasma dopamine response to sympathetic activation in man: a biphasic pattern. *Life Science, 47*, 619–626.

Nakamura, Y., Nishimoto, K., Akamatu, M., Takahashi, M., & Maruyama, A. (1999). The effect of jogging on P300 event related potentials. *Electromyography and Clinical Neurophysiology, 39*, 71–74.

Neeper, S. A., Gomez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature, 373*, 109.

Neeper, S. A., Gomez-Pinilla, F., Choi, J., & Cotman, C. W. (1996). Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Research, 726*, 49–56.

Nutt, J. G., & Fellman, J. H. (1984). Pharmacokinetics of levodopa. *Clinical Neuropharmacology, 7*, 35–49.

Nybo, L., Nielsen, B., Blomstrand, E., Moller, K., & Secher, N. (2003). Neurohumoral responses during prolonged exercise in humans. *Journal of Applied Physiology, 95*, 1125–1131.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97–113.

Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., & Kastin, A. J. (1998). Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology, 37*, 1553–1561.

Pang, P. T., Teng, H. K., Zaitsev, E., Woo, N. T., Sakata, K., Zhen, S., et al. (2004). Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science, 306*, 487–491.

Sakane, T., & Pardridge, W. M. (1997). Carboxyl-directed pegylation of brain-derived neurotrophic factor markedly reduces systemic clearance with minimal loss of biologic activity. *Pharmacal Research, 14*, 1085–1091.

Schinder, A. F., & Poo, M. (2000). The neurotrophin hypothesis for synaptic plasticity. *Trends in Neuroscience, 23*, 639–645.

Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron, 36*, 241–263.

Sharot, T., & Phelps, E. A. (2004). How arousal modulates memory: disentangling the effects of attention and retention. *Cognitive Affective & Behavioral Neuroscience*, 294–306.

Sibley, B. A., & Etnier, J. L. (2003). The relationship between physical activity and cognition in children: a meta-analysis. *Pediatric Exercise Science, 15*, 243–256.

Sjoberg, H. (1980). Physical fitness and mental performance during and after work. *Ergonomics, 23*, 977–985.

Sothmann, M. S., Gustafson, A. B., & Chandler, M. (1987). Plasma free and sulfoconjugated catecholamine responses to varying exercise intensity. *Journal of Applied Physiology, 63*, 654–658.

Spurway, N. C. (1992). Aerobic exercise, anaerobic exercise and the lactate threshold. *British Medical Bulletin, 48*, 569–591.

Sutoo, D., & Akiyama, K. (2003). Regulation of brain function by exercise. *Neurobiology of Disease, 13*, 1–14.

Tantillo, M., Kesick, C. M., Hynd, G. W., & Dishman, R. K. (2002). The effects of exercise on children with attention-deficit hyperactivity disorder. *Medicine and Science in Sports and Exercise, 34*, 203–212.

Tomporowski, P. D. (2003). Effects of acute bouts of exercise on cognition. *Acta Psychologica, 112*, 297–324.

Tomporowski, P. D., & Ellis, N. R. (1986). Effects of exercise on cognitive processes: a review. *Psychological Bulletin, 99*, 338–346.

Tomporowski, P. D., Ellis, N. R., & Stephens, R. (1987). The immediate effects of strenuous exercise on free-recall memory. *Ergonomics, 30*, 121–129.

van Gelder, B. M., Tijhuis, M. A., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2004). Physical activity in relation to cognitive decline in elderly men: the FINE study. *Neurology, 63*, 2316–2321.

van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 13427–13431.

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.

Wang, G. J., Volkow, N. D., Fowler, J. S., Franceschi, D., Logan, J., Pappas, N. R., et al. (2000). PET studies of the effects of aerobic exercise on human striatal dopamine release. *Journal of Nuclear Medicine, 41*, 1352–1356.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology, 54*, 1063–1070.

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA: The Journal of the American Medical Association, 292*, 1454–1461.

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews. Neuroscience, 5*, 483–494.

Wu, D. (2005). Neuroprotection in experimental stroke with targeted neurotrophins. *NeuroRx, 2*, 120–128.