Aerobic Endurance Exercise Improves Executive Functions in Depressed Patients

Sabine Kubesch, M.A.; Volker Bretschneider, M.A.; Roland Freudenmann, M.D.; Niels Weidenhammer, M.A.; Manfred Lehmann, M.D.†; Manfred Spitzer, M.D., Ph.D.; and Georg Grön, Ph.D.

Received Aug. 28, 2002; accepted Dec. 30, 2002. *From the Departments of Psychiatry (Ms. Kubesch, Messrs. Bretschneider and Weidenhammer, and Drs. Freudenmann, Spitzer, and Grön) and Sports and Rehabilitation Medicine (Dr. Lehmann), University of Ulm, Ulm, Germany.*

†Deceased.

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Corresponding author and reprints: Manfred Spitzer, M.D., Ph.D., Department of Psychiatry, University of Ulm, Leimgrubenweg 12-14, D-89075 Ulm, Germany (e-mail: manfred.spitzer@medizin.uni-ulm.de).

Background: Aerobic endurance exercise has been shown to improve higher cognitive functions such as executive control in healthy subjects. We tested the hypothesis that a 30-minute individually customized endurance exercise program has the potential to enhance executive functions in patients with major depressive disorder.

Method: In a randomized within-subject study design, 24 patients with DSM-IV major depressive disorder and 10 healthy control subjects performed 30 minutes of aerobic endurance exercise at 2 different workload levels of 40% and 60% of their predetermined individual 4-mmol/L lactic acid exercise capacity. They were then tested with 4 standardized computerized neuropsychological paradigms measuring executive control functions: the task switch paradigm, flanker task, Stroop task, and GoNogo task. Performance was measured by reaction time. Data were gathered between fall 2000 and spring 2002.

Results: While there were no significant exercise-dependent alterations in reaction time in the control group, for depressive patients we observed a significant decrease in mean reaction time for the congruent Stroop task condition at the 60% energy level ($p = .016$), for the incongruent Stroop task condition at the 40% energy level ($p = .02$), and for the GoNogo task at both energy levels (40%, $p = .025$; 60%, $p = .048$). The exercise procedures had no significant effect on reaction time in the task switch paradigm or the flanker task.

Conclusion: A single 30-minute aerobic endurance exercise program performed by depressed patients has positive effects on executive control processes that appear to be specifically subserved by the anterior cingulate.

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Physical activity exerts effects on well-being in younger and older adults.[1,2] Reports have already been published on the therapeutic benefit of exercise training in depressive patients.[3–6] These studies were performed in older patients and almost exclusively targeted mood effects and clinical symptoms of depression. As one study[7] has demonstrated beneficial effects of endurance training on executive control in healthy human subjects, we implemented a program of individually customized endurance exercise for depressive patients[8] to investigate its effects on executive functions known to be impaired in depression (see, for example, Murphy et al.[9]). Selection of standardized computerized neuropsychological testing procedures was guided by neuroimaging studies that have identified specific blood flow and metabolic alterations in depressive patients.[10,11] We used test procedures on specific executive functions that are known to predominantly rely on prefrontal or anterior cingulate functioning.

METHOD

Control and Patient Groups

Healthy controls. Ten right-handed healthy subjects (6 women) with no history of neurologic or psychiatric disorders served as a control group to test simple test-retest effects that might confound interpretation of the experimental group's results. As no group comparisons were intended, a relatively young group was investigated to rule out that age might act as a moderator variable in control analyses (mean [SD] age = 29.4 [5.7] years; range, 21–41 years).

Depressive patients. Twenty-four right-handed patients (13 men) with major depressive disorder (DSM-IV: 296.xx) from the open ward and the day hospital of the Psychiatric Hospital of the University of Ulm (Ulm, Germany) participated in this study. They were a mean (SD) of 42.2 (12.2) years of age (range, 19–60 years) and had a mean score of 17.6 (10.7) on the Hamilton Rating Scale for Depression.[12] Subjects were accepted for participation in the study after physical examination to exclude the presence of cardiovascular, endocrinologic, and metabolic disorders. All patients were medicated with antidepressive drugs. Several substances in various doses were given, together with add-on medications in some patients. Medication was not changed during the 2-week testing period. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the local ethical committee and was in accordance with the Declaration of Helsinki. Data were gathered between fall 2000 and spring 2002.

Study Design

The study was performed according to a randomized within-subject design. Each participant was investigated on 3 days within 2 weeks. On the first day of the study, subjects performed a graded bicycle lactate test procedure to exhaustion to determine their individual 4-mmol/L lactic acid workload level. On the next day, subjects were administered the rating scales and neuropsychological pretesting. Thereafter, participants were randomly assigned to exercise for 30 minutes at either 40% or 60% of their 4-mmol/L lactic acid workload level. Such workloads can be defined as percentages of the 4-mmol/L lactic acid workload level, in contrast to a workload level defined as a percentage of the maximum workload (or aerobic capacity, VO_{2max} [maximal oxygen uptake]), since exercise to exhaustion is clearly influenced subjectively. Immediately after the participants exercised, neuropsychological testing was performed again and self-administered rating scales were completed. Two days later, the same procedure was carried out with endurance exercise at the alternative workload level.

Endurance exercise. Before exercise, individual performance was measured on a cycle ergometer (EXCALIBUR, Lode, Groningen, the Netherlands). Participants rode at graded workloads (in steps of 50 W) for 3 minutes at each level. At the end of each workload, heart rate was measured and arterialized blood was taken from the earlobe. The lactic acid concentration in the blood was analyzed using YSI 2300 STAT PLUS and YSI 2710 Turntable.[13,14]

To ensure aerobic exercise at 2 different workload levels, for each subject the levels (in watts) that corresponded to 40% and 60% of the 4-mmol/L lactic acid workload level were determined. On days of neuropsychological investigation, participants exercised on the cycle ergometer for 30 minutes at either 40% or 60% of their defined individual workload level. Mean (SD) workload levels were 115.06 (37.25) W, corresponding to the 4-mmol/L lactic acid concentration level; 67.63 (22.37) W, corresponding to 60% of the 4-mmol/L lactic acid workload level; and 47.53 (16.47) W, corresponding to 40% of the 4-mmol/L lactic acid workload level.

Neuropsychological Tests

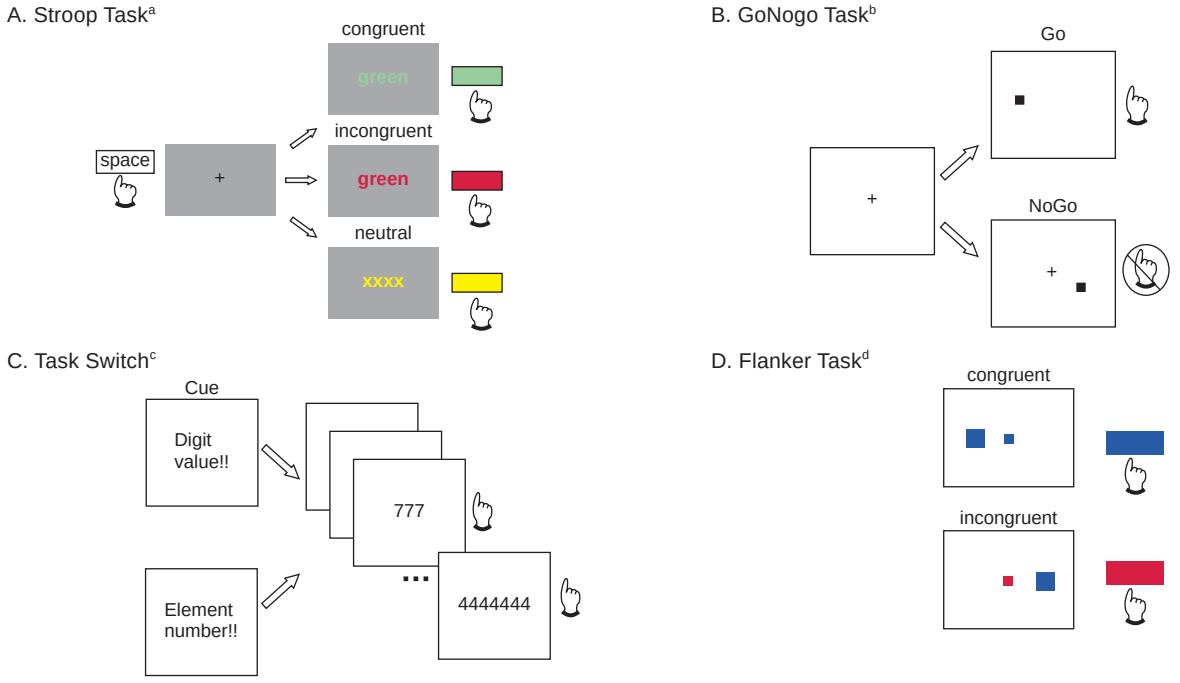
Rationale for test selection. To assess cognitive functions based primarily on the integrity of lateral prefrontal cortices, we implemented a task switch paradigm and a flanker task. The task switch can be seen as tapping into the cognitive domain of planning that is based on working memory resources.[15,16] The flanker task was selected to measure the ability to suppress stimulus-related affinity to interference (a set of processes that guide the selection of environmental objects as triggers of or targets for action).[17] Recent neuroimaging results demonstrated that the neural substrate both of these tasks rely on is predominantly the dorsolateral prefrontal cortex.[15–20]

Computerized versions of the Stroop task and a GoNogo task were used to measure the ability to inhibit inadequate response tendencies in the verbal and nonverbal domains. Recent functional imaging studies demonstrated that successful accomplishment of these tasks involves the anterior cingulate[18–25] or ventral frontal regions[26] to a greater extent than dorsolateral prefrontal cortical structures.[27–31]

Description of tests. The Stroop task (Figure 1A) consisted of 3 conditions where color words were congruent with the presented color (e.g., the word *blue* in blue color) or incongruent with the presented color (e.g., the word *blue* in red color). A neutral condition with colored strings of the letter *x* served as a control condition (e.g., "xxxx" in blue color). Stimuli were presented in the center of the screen on a black background. Five colors were used (blue, red, yellow, green, and brown). The start of each trial was initiated by the participant (by pressing the space bar). A fixation cross then appeared in the middle of the screen for a duration of 700 msec. With the appearance of the test stimulus, patients were to press 1 of 5 response keys marked with the same color as the stimuli. A total of 120 trials were presented with equal probability of all 3 conditions.

During the GoNogo task (Figure 1B), a centered fixation cross was presented for parametrically varied durations between 400 and 800 msec (steps of 10 msec). After the cross was presented, a black dot randomly appeared at 1 of 11 positions that were arranged in a clockwise fashion at a distance of between 4 and 8 cm from the center. For the Go condition, participants were to press a key when the central cross simultaneously disappeared with presentation of the dot. During NoGo, participants were asked not to press any key when the cross remained vis-

Figure 1. Examples of the 4 Neuropsychological Tasks



[a]The Stroop task was administered at subjects' own speed; subjects pressed the space bar to start each trial. Within congruent trials, test stimuli were of the same color. During incongruent trials, the color words were presented in different colors. Neutral trials (no color word) served as a control condition.
[b]During the Go condition of the GoNogo task, subjects pressed a response key when the central fixation cross disappeared while the black dot was still on the screen. They were asked not to respond when the fixation cross remained on the screen while the dot was presented.
[c]Cues informed the subject to decide whether the values of the subsequently presented digits were higher or lower than 5 (digit value) or whether the number of digits was fewer or greater than 5 (element number).
[d]Subjects responded to a small, centered square, indicating whether it was in blue or red. Targets were simultaneously flanked by rectangles that were of the same color (congruent) or a different color (incongruent).

ible on the screen. Responses were given by pressing a predefined key (the space bar) with the index finger of the dominant hand. The mean number of Go trials was 225.

The task switch experiment consisted of 2 alternating conditions with the same stimuli but different instructions.[32] In the center of the screen, a string of between 1 and 9 (except for 5) identical digits appeared, with the value of the digit ranging from 1 to 9 with the exception of the value of 5 (Figure 1C). Digit strings were presented for a duration of 1000 msec. In the digit value condition, participants were asked to judge the value of the digit and to press the left or right key when the value was lower or higher than 5, respectively. In the element number condition, participants were to indicate whether the number of digits was fewer or greater than 5. One block consisted of 5 to 8 trials in the same condition. The intertrial interval was 200 msec. Switches between blocks were indicated by a short cue on the personal computer (PC) monitor ("Digit value!!" and "Element number!!") for a duration of 1000 msec. Reaction times were automatically recorded by the PC. Participants were informed that no within-block switches occurred. Altogether, 40 task switches had to be performed (switches from digit value to element number were of the same frequency as switches from element number to digit value). As the dependent variable, "switch costs" were defined as the increase in reaction times on switch trials compared with nonswitch trials.[33,34]

During the flanker task (Figure 1D), participants focused on the color of a small red or blue rectangle in the center of the screen. The target stimulus was flanked by a rectangle that appeared 4.5 cm to the left or right of the target and was either red or blue. In the interference ("incongruent") condition, the flanker was blue when the target was red, and vice versa. In the congruent condition, both target and flanker matched in color. The width of the flanker was 3 times that of the target, while the height was kept constant between the target and flanker. Participants were to respond depending on the color of the target by pressing 1 of 2 keys using the index and third fingers of their right hand. The target and flanker were displayed simultaneously until the participant responded. Appearance of the 4 combinations of target and flanker color was equiprobable with a probability of 25% (blue-blue,

blue-red, red-blue, red-red). Consequently, the whole task comprised 50% congruent and 50% incongruent trials. The total number of trials was 220 (55 per condition), with the order of trials random. The position of the flanker was balanced across subjects and study condition. (For 50% of subjects before and after the 40% workload level, the flanker was always on the left side of the screen and for the remaining 50%, it was always on the right side. This regimen was reversed before and after the 60% workload level.)

Technical implementation. All experiments were conducted by means of a standard PC (Apple Macintosh clone, 32 MB RAM, 180 MHz CPU) and a 17-in color monitor (screen resolution of 1024 × 768 pixels, 75 Hz) (computer and monitor manufactured by Umax Systems GmbH, Willich, Germany) positioned at eye level and at a distance of 50 cm from the patient. The desktop microcomputer was equipped with PsyScope 1.2.5.[35] The keyboard was placed on a table in front of the participant at a comfortable distance. For ease of use, the response keys were the space bar or keys marked with different stickers. The overall computerized testing procedure, including short breaks, took about 30 minutes. In general, participants were instructed to respond as quickly and accurately as possible. Prior to the study, participants were repeatedly trained to become familiar with the neuropsychological tests in order to avoid simple learning effects.

Psychometric Scales

To assess the effects of endurance exercise on mood and mental state, we used the Befindlichkeitsskala (actual subjective mental state scale)[36] that has 2 parallel forms, which renders it suitable and sensitive for repeated measurements,[37] especially in settings with rather small pre-to-post time intervals. A set of 28 pairs of contradictory adjectives allows the subject to describe his or her actual subjective mental state, ranging from elevated mood to depression.

Statistical Analysis

Reaction time data were considered to be relevant dependent variables, because they were judged to be more informative about the quality of information processing than accuracy data. Accuracy data are usually small in range (especially in the control group) and simply indicate that an information process was deficient. Reaction time data were analyzed by means of 4 separate multivariate analyses of variance (MANOVAs) for repeated measures per study group. For the neuropsychological tasks with only 1 within-task condition (GoNogo, task switch), there was 1 within-subject factor, "exercise," with 4 levels (pre-exercise at 40% workload level, post-exercise at 40% workload level, pre-exercise at 60% workload level, and post-exercise at 60% workload level). For tasks with 2 within-task conditions (Stroop task, flanker task), a second within-subject factor, "condition," with 2 levels (congruent/incongruent), was added. Planned 2-tailed t tests for paired samples comparing pre-exercise and post-exercise mean reaction times (mRTs) for each of the exercise conditions were computed whenever the corresponding MANOVA revealed a significant main effect of the exercise factor. In cases of significant post-to-pre accelerations of mRTs, a coefficient of acceleration for each task and condition was calculated. Mean differences in reaction times were divided by the mRTs during the pretests and multiplied by 100 to reflect changes in mRTs in units of percent.

RESULTS

Stroop Task

Controls. A MANOVA for repeated measures on mRT revealed a significant effect of condition ($F = 12.98$, $df = 1,9$; $p = .006$), while neither exercise ($F = 3.80$, $df = 3,7$; $p = .07$) nor the interaction of both factors ($F = 0.80$, $df = 3,7$; $p = .53$) was significant.

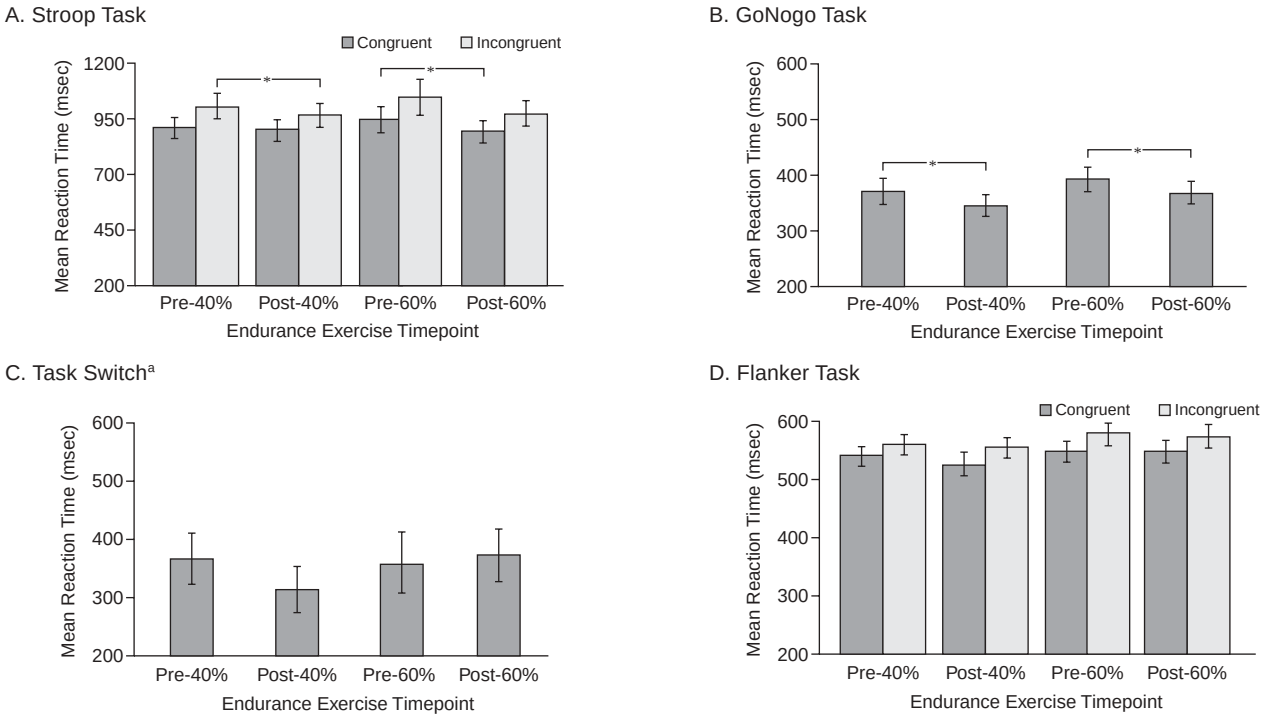
Patients. A MANOVA for repeated measures on mRTs revealed a significant main effect of the condition ($F = 16.19$, $df = 1,22$; $p = .001$) and exercise factors ($F = 3.04$, $df = 3,20$; $p = .05$); however, the interaction between the 2 factors was not significant ($F = 0.99$, $df = 3,20$; $p = .42$). Single, planned comparisons between pre-exercise and post-exercise measurements for both exercise procedures were computed for both conditions separately (Figure 2A). For the congruent Stroop task, we observed a significant decrease in mRT for the exercise procedure at the 60% workload level ($t = 2.61$, $df = 23$, $p = .016$; coefficient of acceleration: 5.8%), while the pre-to-post difference for the exercise procedure at the 40% workload level was not significant ($t = 0.91$, $df = 23$, $p = .37$; coefficient of acceleration: 1.6%). The incongruent Stroop condition revealed a significant decrease between pre-exercise and post-exercise measurements for the exercise procedure at the 40% workload level ($t = 2.49$, $df = 23$, $p = .02$; coefficient of acceleration: 4.0%). After the exercise level procedure at the 60% workload level, the pre-to-post differences approached significance ($t = 1.99$, $df = 23$; $p = .058$; coefficient of acceleration: 7.1%).

GoNogo Task

Controls. A MANOVA for repeated measures revealed no significant effect of exercise ($F = 2.83$, $df = 3,7$; $p = .12$).

Patients. A MANOVA for repeated measures demonstrated a significant effect of the exercise factor ($F = 5.56$, $df = 3,21$; $p = .006$). Planned t tests showed that mRTs were significantly decreased after exercise at the 40% workload level ($t = 2.39$, $df = 23$, $p = .025$; coefficient of acceleration: 7.1%) as well as after exercise at the 60%

Figure 2. Results of 4 Neuropsychological Tasks in 24 Major Depressive Disorder Patients Before and After 30 Minutes of Exercise at 2 Energy Levels (40% and 60% of 4-mmol/L lactic acid workload level)



[a]Although numerically decreased, the pre/post difference for the 40% energy level exercise was not significant.
*p < .05.

workload level (t = 2.09, df = 23, p = .048; coefficient of acceleration: 6.2%). Results for this task are summarized in Figure 2B.

Task Switch

Controls. No significant exercise effect was observed in controls (F = 2.55, df = 3,7; p = .14).

Patients. For this task, a MANOVA for repeated measures did not reveal a significant effect of the exercise factor (F = 1.76, df = 3,20; p = .19). Figure 2C illustrates the pre- and post-exercise results. As shown in Figure 2C, a numerical decrease in mRT was observed for exercise at the 40% workload level, while there was an increase in mRT for exercise at the 60% workload level. Two separate t tests, calculated to control for possible underestimations of pre- to post-exercise differences, revealed no significant results (40% exercise level: t = 1.73, df = 23, p = .10; 60% exercise level: t = –0.42, df = 23, p = .68).

Flanker Task

Controls. A significant effect of condition was observed with MANOVA (F = 58.25, df = 1,9; p < .001), while neither exercise (F = 1.92, df = 3,7; p = .22) nor the interaction of condition by exercise (F = 3.40, df = 3,7; p = .08) was significant.

Patients. While a significant effect of the condition factor was observed (F = 41.68, df = 1,22; p < .001), there were no significant influences of the exercise procedures (F = 0.94, df = 3,20; p = .73). Mean reaction times for both conditions (congruent/incongruent) are presented in Figure 2D. Notably, the mRTs for each of the pre- and post-exercise conditions were approximately the same (range of mRT differences, 1–13 msec; range of standard deviations/condition, 86–96 msec).

Psychopathometric Rating

Analysis of an effect of the exercise procedures on alterations of the general subjective mental state revealed no significant effects in controls or patients.

DISCUSSION

The results are summarized as follows: we observed no significant pre-exercise to post-exercise alterations in mRT for the task switch or flanker task. The GoNogo task revealed significant exercise effects with comparable rates of acceleration of reaction time in both exercise conditions. For the Stroop task, only the exercise procedure at 60% of workload level led to a significant decrease in mRT for the congruent condition. With incongruent

stimuli, the exercise benefit was significant for the procedure at 40% of workload, although decrease in mRT was numerically larger after exercise at 60% of workload (4.0% vs. 7.1%, respectively). Subjective mental states remained stable during exercise in both groups. No significant pre- to post-exercise effects were observed for the control group, indicating no relevant test-retest effects that might confound interpretation of patients' results.

Specificity of Effects

Endurance exercise with depressive patients at 2 workload levels (40% and 60% of the individual's workload at 4-mmol/L lactic acid concentration) was found to increase performance in a subset of cognitive tasks. Comparisons of pre- and post-exercise performance showed significantly decreased mRTs that were exclusively demonstrated in the Stroop task and the GoNogo task. No difference in response time before and after either of the exercise procedures was observed in control subjects in any of the tasks, ruling out the possible confound of simple test-retest effects in the depressive group. Moreover, the consistency of reaction time data for depressive patients during the flanker task indicates that the beneficial effects are not simply due to acceleration in psychomotor speed. As there were no differences on psychopathometric measures, alterations in subjective mental state do not appear to be correlated with the present results as a relevant variable. The differential pattern of cognitive enhancement indicates that only dysregulated brain systems benefit from endurance exercise and that especially those cognitive functions that are mainly mediated by functioning of the anterior cingulate can be modified.

Results From Controls

Previous studies of healthy subjects showed improved mental functioning after endurance training.[7,38] These findings appear to contradict our finding of no improvement due to exercise in the control group. However, besides different sample sizes, there are fundamental differences between those studies and our study with respect to the interventions performed. In particular, the beneficial effects on executive control that were demonstrated in a sample of healthy elderly controls were observed after a longer period of aerobic endurance training,[7] while in our study an exercise program was administered for a short interval to persons without training. The beneficial effects seen in the studies may have resulted from the activation of different brain mechanisms, owing to the differences in treatment. While longer periods of exercise training probably result in an increased rate of oxygen consumption, short intervals may lead to central serotonergic up-regulation (see Assumptions About Possible Mechanisms). Consequently, as healthy controls have no evident serotonergic dysfunction, the beneficial effects are restricted to subjects with dysregulated serotonergic tone (depressive patients).

Other studies reported enhancement in frontal functions after exercise training,[38] but did not report on any specificity of the effects observed.

Role of the Anterior Cingulate

A prominent role in the course of depressive illness is attributed to the anterior cingulate cortex. It is seen as the common denominator of change and therapy effects in depressive states.[11] Differences in the excitability of this structure may indicate therapy response. Mayberg[39] observed that an increased metabolic state at the onset of a depressive episode was correlated with a positive therapeutic outcome, whereas decreased metabolic activity was predictive of poor therapeutic outcome. The prominent role for the anterior cingulate further emerges from combined neuropsychological and imaging studies on cognitive functioning in depressive patients. A positron emission tomography study by Elliot and coworkers[40] of prefrontal dysfunction in depressed patients performing a complex planning task demonstrated evidence for an association of cingulate, prefrontal, and striatal dysfunction with impaired task performance in depression. The authors attributed a central role to cingulate dysfunction in depression, which they saw as being in line with impaired frontostriatal function, which was also proposed by Rogers et al.[34] Reviewing the literature on resting state functional imaging studies and activation imaging studies, Rogers et al.[34] concluded that there is less consistent evidence of dorsolateral prefrontal deficit, while anterior cingulate deficit has been more consistently demonstrated.

As the anterior cingulate plays a key role in the inhibition of inadequate responses,[23,24,41] the Stroop task was recently used to directly address the question of the role of cingulate functions in a sample of depressive patients and healthy controls by means of functional neuroimaging.[42] As expected, healthy control subjects activated the left cingulate during this task. Depressive patients instead activated the right anterior cingulate only slightly and seemed to compensate for this failure by activation of the left dorsolateral prefrontal cortex. Degl'Innocenti et al.[43] concluded from a behavioral neuropsychological study on the effects of depression on executive functions that depressive patients demonstrate differential impairments on the various executive functions. Most importantly, the authors did not observe substantial increases in perseverative responses, while the latencies to alter response tendencies were significantly increased. Results indicate that response conflict monitoring, one of the key functions in Stroop-like tasks,[25] is more impaired in depressive patients than functions relying on working memory resources.

Assumptions About Possible Mechanisms

With respect to the mechanism of action of physical exercise on cognitive function, 2 possibilities come to mind. According to Kramer and coworkers,[7] exercise may increase oxygen saturation in brain areas crucial for task performance. The authors investigated the influence of a 6-month aerobic endurance exercise training (walking) program on executive control processes in persons aged 60 to 75 years. They compared the effects of walking training with those of stretching training. After a 6-month training period, the participants of the walking group showed a significant improvement in the maximum rate of oxygen consumption (5.1%) compared with the stretching group (–2.8%). Furthermore, the walking group, but not the stretching group, showed a significant improvement for task conditions depending on executive control. Kramer et al. explained the improvements in the computer tasks, and therefore in executive control processes, with a higher maximum rate of oxygen consumption in the walking group. However, it is rather unlikely that the positive effects in our study can be explained only by an increase of the maximum rate of oxygen consumption, because this rate could not sufficiently be influenced with a single training session.

Alternatively, we suggest that the increased synthesis of serotonin (5-HT) may directly lead to an increase of the serotonergic tone and thereby facilitate information processing.[44] Neurobiologically, endurance training, when carried out for at least half an hour, increases the concentration of tryptophan in the brain. This increase is caused by an increased muscle uptake of the essential amino acids leucine, isoleucine, and valine during recovery after endurance training, thereby decreasing the competitors for tryptophan at active carrier sites for crossing the blood-brain barrier.[44,45] In previous work,[46] it was shown that physical activity significantly elevates the level of 5-hydroxyindoleacetic acid in the cerebrospinal fluid of depressive patients. Using microdialysis technique, it was concluded that an increase in extracellular 5-HT release is correlated with the increase in motor activity that is associated with a variety of experimental manipulations.[47] The increased concentration of tryptophan will cause increased 5-HT concentrations in the brain, which are known to have an antidepressant effect and may have an effect on executive functions that rely on 5-HT–dependent structures. Further investigations controlling the amine metabolites in affective illness before and after endurance exercise should test this hypothesis directly.

In conclusion, the present study provides support for a role of aerobic endurance exercise in the treatment of depression and suggests a mechanism of action via alteration of the activity of the anterior cingulate cortex. In full recognition of the pilot character of this study, further investigations in drug-free patients, possibly in conjunction with parameters of 5-HT biochemistry and oxygen consumption as well as brain activation, should be performed on a larger scale. In the same vein, follow-up studies appear necessary to test whether the executive benefits observed remain stable over time such that they can act as a therapeutic adjunct.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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