ORIGINAL ARTICLE

Hippocampal Plasticity in Response to Exercise in Schizophrenia

Frank-Gerald Pajonk, MD; Thomas Wobrock, MD; Oliver Gruber, MD; Harald Scherk, MD; Dorothea Berner, MD; Inge Kaizl, MD; Astrid Kierer, cand.med; Stephanie Müller, cand.med; Martin Oest, MD; Tim Meyer, MD; Martin Backens, MD; Thomas Schneider-Axmann, PhD; Allen E. Thornton, PhD; William G. Honer, MD; Peter Falkai, MD

Context: Hippocampal volume is lower than expected in patients with schizophrenia; however, whether this represents a fixed deficit is uncertain. Exercise is a stimulus to hippocampal plasticity.

Objective: To determine whether hippocampal volume would increase with exercise in humans and whether this effect would be related to improved aerobic fitness.

Design: Randomized controlled study.

Setting: Patients attending a day hospital program or an outpatient clinic.

Patients or Other Participants: Male patients with chronic schizophrenia and matched healthy subjects.

Interventions: Aerobic exercise training (cycling) and playing table football (control group) for a period of 3 months.

Main Outcome Measures: Magnetic resonance imaging of the hippocampus. Secondary outcome measures were magnetic resonance spectroscopy, neuropsychological (Rey Auditory Verbal Learning Test, Corsi block-tapping test), and clinical (Positive and Negative Syndrome Scale) features.

Results: Following exercise training, relative hippocampal volume increased significantly in patients (12%) and healthy subjects (16%), with no change in the nonexercise group of patients (−1%). Changes in hippocampal volume in the exercise group were correlated with improvements in aerobic fitness measured by change in maximum oxygen consumption ($r=0.71$; $P=.003$). In the schizophrenia exercise group (but not the controls), change in hippocampal volume was associated with a 35% increase in the *N*-acetylaspartate to creatine ratio in the hippocampus. Finally, improvement in test scores for short-term memory in the combined exercise and nonexercise schizophrenia group was correlated with change in hippocampal volume ($r=0.51$; $P<.05$).

Conclusion: These results indicate that in both healthy subjects and patients with schizophrenia hippocampal volume is plastic in response to aerobic exercise.

Arch Gen Psychiatry. 2010;67(2):133-143

SCHIZOPHRENIA CAN BE CONSIDERED as an illness beginning in young adults, but related to a predisposition in brain development. In contrast to other illnesses that may display psychotic features, such as bipolar disorder, schizophrenia is often characterized by incomplete recovery of psychotic symptoms and persistent disability.[1] These clinical features of illness may relate to an impairment of neural plasticity or mechanisms of reorganizing brain function in response to a challenge.[2] Adult neurogenesis is one component of plasticity. Abnormalities of olfactory neurons and of hippocampal granule cell neurons in schizophrenia indicate that impairment in adult neurogenesis could contribute to dysfunction of neural plasticity in schizophrenia.[3,4] Stimuli to modify olfactory neurogenesis in humans are unclear. However, adult neurogenesis in the hippocampus in healthy humans can be stimulated by exercise.[5]

In healthy humans, aerobic exercise resulted in increased hippocampal blood volume, which correlated with improvement in capacity for aerobic exercise.[5] In a parallel study of healthy mice, exercise also resulted in increased hippocampal blood volume, which was correlated with increased neurogenesis. Other studies also indicate increased cardiovascular fitness in humans to be associated with greater activation of cortical networks during cognitive challenges.[6] Although the effects of exercise on hippocampal volume in humans are unknown, several studies indicate plasticity of gray matter volume in humans to be associated with learning and other types of training.[7-9]

Aerobic exercise may be an informative probe into the capacity of the hippocampus for plasticity in schizophrenia.

Author Affiliations are listed at the end of this article.

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

Table 1. Demographic Values for Subjects Participating in the Study

	Mean (SD)		
	Control Group (n=8)	Schizophrenia Exercise Group (n=8)	Schizophrenia Nonexercise Group (n=8)
Age, y	34.8 (10.2)	32.9 (10.6)	37.4 (8.1)
Education, y	11.0 (1.7)	9.8 (1.4)	10.3 (2.4)
Vocabulary test IQ	103.6 (6.4)	102.4 (12.3)	106.8 (20.6)
Duration of illness, y		8.4 (8.4)	12.5 (4.5)
Antipsychotic medication dose, defined daily doses, CPZ		733 (321)	769 (503)
Antipsychotic medication, No.			
Clozapine		5	5
Olanzapine		1	
Amisulpride			2
Risperidone		3	3
Haloperidol		1	1
Quetiapine fumarate			1
Fluphenazine		1	
Sulpiride			1
Promethazine		1	
Flupenthixol			1
Zotepine			1
Antidepressant medication, No.			
Trimipramine for sleep		1	
Mirtazapine			1
Venlafaxine hydrochloride		2	
Paroxetine hydrochloride		1	
Amitriptyline hydrochloride		1	
PANSS score			
Total		68.1 (17.6)	65.9 (13.9)
Positive		13.6 (3.4)	13.5 (3.5)
Negative		22.1 (5.7)	22.0 (7.8)
CGI score		5.1 (1.0)	4.9 (1.0)

Abbreviations: CGI, Clinical Global Impression scale; CPZ, chlorpromazine equivalent dose; PANSS, Positive and Negative Syndrome Scale.

Smaller volume of the hippocampus is a well-replicated feature of schizophrenia and appears related to neuronal atrophy and loss of neuropil.[10,11] However, whether hippocampal volume in schizophrenia is static or becomes progressively smaller during the course of illness remains uncertain.[10,12,13] Antipsychotic drug treatment does not appear to correct the low hippocampal volume in schizophrenia, although there are few longitudinal studies.[13-15] There is some indication that changes in medication associated with increases of hippocampal volume over time in schizophrenia are linked with some improvement in symptoms.[16] While the mechanism remains unclear, these findings suggest a degree of preserved plasticity in the hippocampus in schizophrenia.

The present study was designed to test a primary hypothesis that hippocampal volume would increase with exercise in healthy control subjects as well as in patients with schizophrenia. We sought to determine if the hypothesized increase in hippocampal volume in schizophrenia was related to exercise rather than nonspecific effects of participating in research. As secondary objectives, we hypothesized that exercise-induced change in hippocampal volume in schizophrenia might be associated with clinical or cognitive improvement and with an increase of *N*-acetylaspartate (NAA), a neuronal marker in magnetic resonance spectroscopy (MRS).

METHODS

SUBJECTS

Approximately two-thirds of patients with schizophrenia approached to participate in the study agreed and provided written informed consent. The randomization strategy was designed by an independent statistician. Subjects with schizophrenia were recruited and randomized in blocks of 2 to 4 to an exercise group or a nonexercise group. This strategy was adopted to increase the motivation for adherence to the exercise intervention through participation as a small group, and pairs of subjects were required for the nonexercise (table football) intervention. The person doing the recruitment (T.W.) was unaware of the sequence of assignments, and the person doing the assignments (F.P.) was unaware of the clinical status of the participants. Recruitment and randomization continued until 8 subjects in each group completed the 3-month period of study. We then screened healthy control subjects, with the goal of recruiting a comparison exercise group that would have similar demographics (**Table 1**) (**Figure 1**) as well as verbal intelligence, body mass index, and weight-adjusted peak oxygen uptake ($\dot{V}O_2$) as the schizophrenia exercise group. Sample size was estimated from previous studies of small groups of subjects with schizophrenia where changes in subcortical structure volumes were demonstrated after switching from typical to atypical antipsychotic drug therapy.[17,18] The study was carried out from June 2005 to September 2006.

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

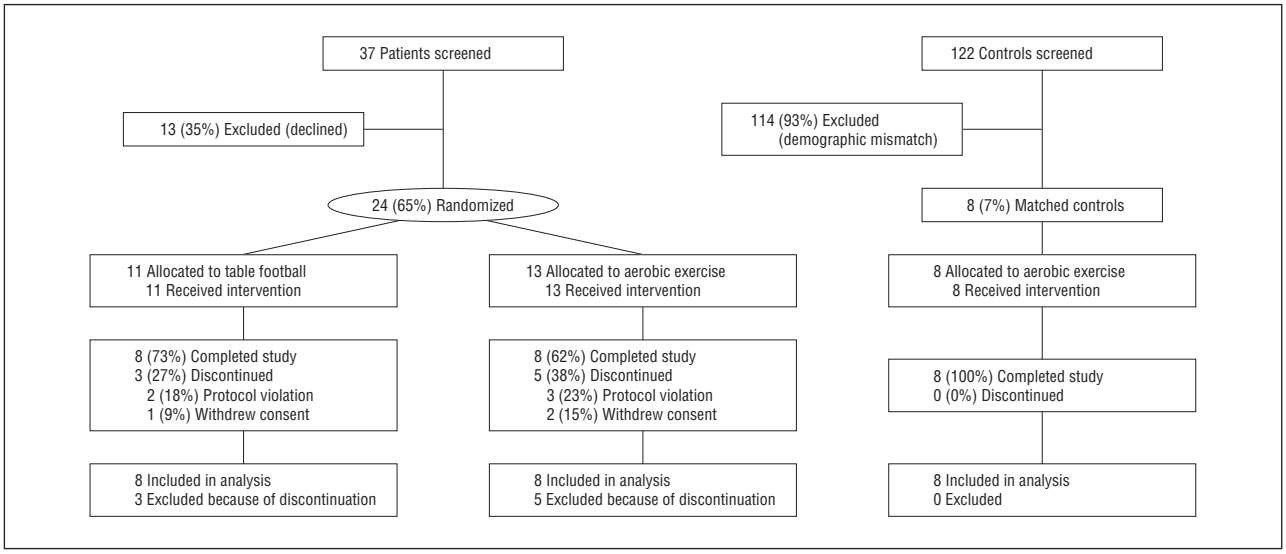

Figure 1. Flow diagram for the study.

Subjects ranged from 20 to 51 years of age (mean [SD], 35.0 [9.5] years), and there was no difference in mean age between groups. Subjects with schizophrenia were diagnosed according to *International Statistical Classification of Diseases, 10th Revision (ICD-10)* and *DSM-IV* criteria and had clinically stable disease. The disease duration (mean [SD], 10.4 [6.8] years) was not significantly different between the schizophrenia exercise and nonexercise groups. Symptom severity in patients was measured with the Positive and Negative Syndrome Scale, and raters were blinded to the intervention (exercise or nonexercise). Patients had chronic illness and attended a day hospital program or an outpatient clinic. All patients were taking stable doses of medications for at least 6 weeks. Antipsychotic medications were administered as monotherapy (n=4) or polypharmacy (n=12). Clozapine was taken by 10 patients; 5 patients were also taking antidepressant medications. In the aerobic exercise group, 1 subject was taking a low dose of trimipramine at the start of the study, but this was discontinued by the end. One subject was taking amitriptyline hydrochloride at the start of the study, and this was switched to venlafaxine hydrochloride by the end. Two subjects were taking stable doses of venlafaxine and paroxetine hydrochloride throughout the study. In the nonexercise group, 1 subject was taking a stable dose of mirtazapine throughout the study. Antidepressants were given to improve sleep disturbances, inner restlessness, and anxiety, not for depression. Five subjects in the exercise group and 1 subject in the nonexercise group were taking lorazepam during the study, and 1 subject in the nonexercise group was taking diazepam.

The protocol was approved by the ethics review board of the Medical Chamber of Saarland. All subjects provided written informed consent.

EXERCISE TESTING

Aerobic fitness was tested before and after the full exercise or comparison training interventions. Patients took their morning medication prior to reporting to the laboratory. Testing was executed in a fixed temporal sequence and started at the same time of day in each individual. After recording a 12-lead resting electrocardiogram, incremental cycle ergometry was carried out in 3-minute stages until volitional exhaustion was reached. On the basis of sex, age, body weight, and training history, the initial stage (25 or 50 W) and the stage increment (25 or 50 W) were chosen with the expectation to reach a total exercise duration of at least 10 minutes. This protocol was held constant on an intraindividual basis during all tests of the study. A 6-lead electrocardiogram was recorded every minute during exercise for calculation of heart rate. Blood pressure was measured at each stage after 2 minutes of elapsed time. Gas exchange measurements (MetaMax I; Cortex Biophysik, Leipzig, Germany; mixing chamber system) were carried out throughout the test. Measurements of $\dot{V}O_2$, carbon dioxide output, and minute ventilation took place every 10 seconds. Additionally, arterialized blood samples were taken from the hyperemized earlobe at rest, at the end of each stage, and immediately after cessation of exercise to determine blood lactate concentrations (enzymatic-amperometric method; Greiner, Flacht, Germany). The power output corresponding to a blood lactate concentration of 3 mmol/L (27 mg/dL) was determined by means of linear interpolation. Additional indicators of endurance capacity were the peak $\dot{V}O_2$, the peak power output, and the power output corresponding to a heart rate of 130 beats/min. Maximal heart rate and maximal lactate concentration served as control parameters for the degree of effort being spent to improve assessment of the validity of maximal ergometric measurements.

EXERCISE AND COMPARISON INTERVENTIONS

Training was conducted in a local gym, 3 times per week, over a period of 12 weeks, supervised by one of the investigators. Each session lasted 30 minutes. Patients were required to participate in a minimum of 75% of the sessions. Heart rate was monitored throughout training. The program consisted of cycling at a heart rate (±10 beats/min) corresponding to a blood lactate concentration of about 1.5 to 2 mmol/L (14-18 mg/dL) derived from the results of the pretest. The patients were allowed to stop exercising whenever they felt uncomfortable.

The comparison group of patients played tabletop football for 30 minutes, 3 times per week, in a setting with comparable levels of stimulation to that provided for aerobic exercise. Tabletop football enhances coordination and concentration but does not improve aerobic fitness.

COGNITIVE TESTING

To assess the level of premorbid intelligence, the multiple-choice vocabulary test was used. The multiple-choice vocabulary test consists of 37 rows, each including 4 meaningless com-

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

binations of letters and 1 real word. The subject must find the meaningful combination of letters. The test is widely used and is considered to produce reliable and valid information on premorbid intelligence, largely independent of illness or age.[19]

Cognitive performance was measured using the German version of the Rey Auditory Verbal Learning Test.[20] Composite measures of short-term memory (STM) and long-term memory (LTM) were based on previous factor analyses of this test.[20] Briefly, a list of 15 words is read to the subject 5 times. After each time, the number of words the subject can recall is recorded. An intrusion list of 15 different items is then presented and must be recalled. The number of words recalled after the first presentation of the original word list and the number of words recalled from the intrusion list were summed as an index of verbal STM. Following recall of the intrusion list, the subject is asked to recall the original list, immediately and after 30 minutes. These 2 measures were summed as an index of verbal LTM. The Corsi block-tapping test[21] is an instrument testing visuospatial STM. The variable of interest is the direct block span, the longest sequence of block positions visualized on a monitor that the subject could repeat in correct order immediately after the presentation. Cognitive performance was tested blinded to intervention type (exercise or nonexercise) for the schizophrenic subjects.

MAGNETIC RESONANCE IMAGING ACQUISITION

Structural magnetic resonance imaging was carried out using a 1.5-T scanner (Sonata; Siemens, Erlangen, Germany). A T1-weighted MPRAGE sequence (echo time = 4.42 milliseconds, repetition time = 1900 milliseconds, inversion time = 700 milliseconds, flip angle = 15°, field of view, 256 × 256 mm) of 176 consecutive slices was acquired with a voxel size of 1 × 1 × 1 mm.

STRUCTURAL IMAGE ANALYSIS

Image processing and analysis used the software packages Analyze (1999; Mayo Foundation, Rochester, Minnesota) and SPM99 (Wellcome Department of Cognitive Neurology, London, England) as well as in-house IDL applications. First, the magnetic resonance images were realigned in parallel to the anterior commissure–posterior commissure plane. A single operator drew outlines of the hippocampus on all sagittal slices in which the structure was visible. These outlines were evaluated for accuracy in the coronal and horizontal views. Intrarater reliability for the hippocampal volumes was $r = 0.95$, and comparison with measurements by another rater indicated reliability of $r = 0.97$. In addition, magnetic resonance images were segmented into gray and white matter and cerebrospinal fluid using SPM99. Subsequently, both the hippocampal volumes as marked by the 2-dimensional drawings and the total brain volumes (overall as well as separately for gray and white matter) were determined using an automatic algorithm programmed in MATLAB (The MathWorks, Natick, Massachusetts) and SPM99. Relative hippocampal volume was computed from absolute hippocampal volume as a percentage of the total brain volume. Structural image analysis was carried out blinded to diagnosis, intervention (exercise or nonexercise), and time (before the training program [t0] or after 3 months when the training program was complete [t3]).

MRS ACQUISITION

Single-volume proton MRS was performed using a spin-echo sequence with water suppression and 128 scan averages (echo time = 30 milliseconds, repetition time = 1500 milliseconds). A left hippocampus region of interest was defined according to a standardized algorithm with multiple rechecking procedures in a T2-gradient echo image (TrueFISP). The voxel size was $10 \times 35 \times 10$ mm^3 and the positions of the voxel were visually inspected and adjusted based on identifiable anatomical landmarks in reference to standard brain atlases. Magnetic resonance spectroscopy data from 3 subjects was excluded because of motion artifacts.

MRS ANALYSIS

The MRS data were analyzed using the manufacturer's standard spectroscopic software. The echo signal was digitized with 1024 data points and a spectral width of 1000 Hz. Postprocessing included zero filling of the time domain data to 2048 data points and apodization with a Hanning function (half-width 700 milliseconds). After Fourier transformation, spectral phasing and a polynomial baseline correction were also performed. The area of metabolite peaks was measured from the frequency-domain spectrum by means of curve fitting to a gaussian line shape. Relative metabolite concentrations for NAA groups, choline-containing compounds, and creatine (Cr)-containing compounds were determined by peak integration. For comparison between subjects, the NAA:Cr peak-area ratio was calculated.

STATISTICAL ANALYSIS

For statistical analysis, SPSS (version 14; SPSS Inc, Chicago, Illinois) was used. All tests were 2-tailed, and the significance level was $\alpha = .05$. Since a small sample size was used, with a repeated-measures approach, the analysis was limited to those subjects who completed the study. The primary dependent variable was relative hippocampal volume as a percentage of the total brain volume. Secondary tests to explore the possible mechanism and effects of the volume change used the dependent measures of the hippocampal MRS NAA:Cr ratio, STM, LTM, and Corsi direct block span. In this context, we did not correct *P* values for multiple comparisons, and the statistical significance of the results must be interpreted as such. All dependent variables were measured at t0 and t3. Kolmogorov-Smirnov tests were applied to test whether the data were normally distributed. As for all dependent variables, no significant deviations from normality at the 1% significance level were found; parametric tests were used. Two analyses were performed. In the first analysis, measurements for the dependent variables at t0 and t3 of the schizophrenia exercise group and the control group were compared using multivariate analyses of variance with a repeated-measures design (within-subject factor, time and between-subject factor, group). Second, the same analysis was done comparing both schizophrenia groups (aerobic exercise vs table football) at t0 and t3. For the relative hippocampal volume, this analysis was repeated for the patients who were not treated with antidepressant medication. Bivariate product moment correlations were used to analyze whether the change in relative hippocampal volume was associated with the changes in maximum power in watts per kilogram, maximum $\dot{V}O_2$ per kilogram ($\dot{V}O_2$ max/kg), MRS NAA:Cr ratio, STM, and Corsi direct block span. Correlations were computed for the combined exercise group and separately for the subgroups.

RESULTS

SUBJECTS

A total of 24 subjects with schizophrenia were enrolled; 13 were randomized to the exercise group and 11, to the nonexercise group. Two subjects in the exercise group and 1 in the nonexercise group withdrew consent be-

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

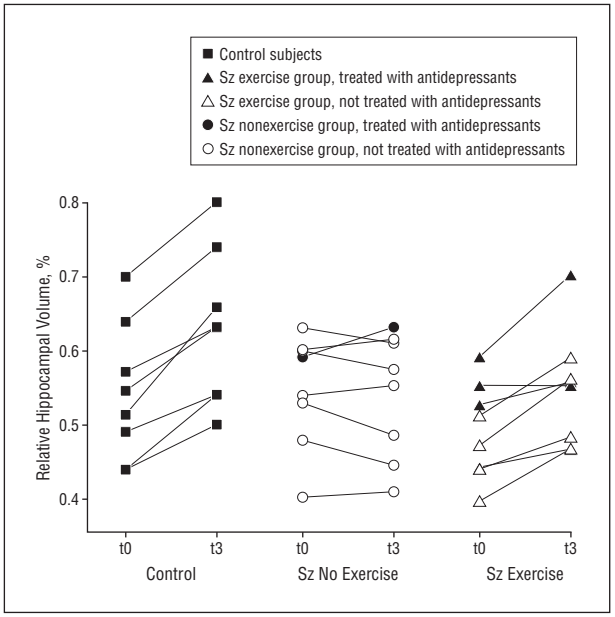

Figure 2. The changes in hippocampal volume in control subjects, schizophrenic (Sz) patients participating in aerobic exercise, and Sz patients with no aerobic exercise intervention. The data points present the relative hippocampal volume of each subject as a percentage of the total brain volume at baseline (t0) and 3 months later at end point (t3).

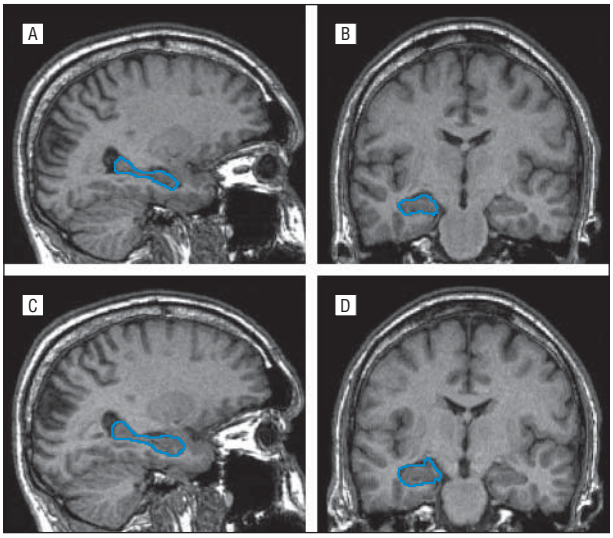

Figure 3. T1-weighted magnetic resonance images in the sagittal and coronal plane, with the right hippocampus marked in blue, comparing baseline (A and B) and end point (C and D) of the patient in the schizophrenia exercise group with the largest increase in hippocampal volume (from 3.898 cm^3 to 4.667 cm^3; +19.7%).

fore starting the intervention. Three subjects in the exercise group and 2 subjects in the nonexercise group could not adhere to the minimal standard of completing 75% of sessions, and data from these subjects were excluded. There were no statistically significant differences in age, marital status, housing, education, occupational status, height, weight, or body mass index between those subjects who completed the study and those who did not. Noncompleters had higher total Positive and Negative Syndrome Scale scores at screening ($F_{1,22}$=9.0; P=.007), largely related to higher scores on the general subscale ($F_{1,22}$=14.4; P=.001). In the total completers group, the subjects participated in 86% of the intervention sessions. Rates were similar in the schizophrenia exercise group (85%), the schizophrenia nonexercise group (81%), and the control (exercise) group (92%). Training during each session was observed by research staff and was carried out at the subject-specific level of activity as described in the "Methods" section. There were no adverse events during the study.

CHANGE IN HIPPOCAMPAL VOLUME AND EXERCISE

The overall relative hippocampal volume before exercise in subjects with schizophrenia was approximately 4% smaller than the controls, which was not statistically significant in this small sample. In the combined group of subjects who completed the exercise training, relative hippocampal volume increased by approximately 14% (effect of time: $F_{1,14}$=70.4; P<.001). **Figure 2** illustrates the quantitative increase of the relative hippocampal volume, and **Figure 3** provides a qualitative example of the maximal change. The mean amount of enlargement in the schizophrenia exercise group (12%) was not statistically different from the enlargement in the control group (16%; group × time interaction, $F_{1,14}$=3.4; P=.09). We also analyzed data for absolute rather than relative hippocampal volumes, and the findings and statistical significance were similar. Total brain volume and total gray matter volume did not change after exercise (**Table 2** and **Table 3**).

The change in relative hippocampal volume over time in the schizophrenia group was compared between subjects who participated in aerobic exercise and those who participated in the control, nonexercise intervention. The enlargement in the aerobic exercise group (12%) was greater than the difference observed in the nonexercise group (–1%; group × time interaction, $F_{1,14}$=13.8; P=.002). This supports the hypothesis that exercise in the schizophrenia group was responsible for the hippocampal enlargement rather than a nonspecific effect of participation in research. The change in aerobic fitness over time was compared between all subjects who participated in aerobic exercise and those who participated in the nonexercise intervention. The increase in power (watts per kilogram) was higher in the aerobic exercise group (11%) as compared with the nonexercise group (1%). However, there was considerable variability within the total exercise group, and the group × time interaction was not statistically significant ($F_{1,21}$=1.9; P=.18). Similar findings were observed for change in $\dot{V}O_2$ max/kg. This measure was higher in the exercise (+5%) compared with the nonexercise (–3%) group, but again the group × time interaction was not statistically significant ($F_{1,19}$=0.9; P=.35).

To examine possible associations between hippocampal volume change and improvement in aerobic fitness more closely, we examined correlations within the total group of subjects participating in aerobic exercise. There was a positive correlation between the change (t3 vs t0) in relative hippocampal volume and the change in fitness parameters (maximum power per kilogram [total: r=0.71; P=.003; schizophrenia exercise group: r=0.83;

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

Table 2. Measures of Brain Structure, Magnetic Resonance Spectroscopy, and Cognition at Baseline and After 3 Months of Aerobic Exercise or a Comparison Nonexercise Intervention

	Control Group		Schizophrenia Exercise Group		Schizophrenia Nonexercise Group	
	Baseline	Outcome	Baseline	Outcome	Baseline	Outcome
Total brain volume, mm^3						
Sample size	8	8	8	8	8	8
Mean (SD)	1 276 576 (131 497)	1 278 257 (135 758)	1 275 835 (181 858)	1 282 388 (181 440)	1 243 268 (104 226)	1 245 625 (105 652)
Gray matter volume, mm^3						
Sample size	8	8	8	8	8	8
Mean (SD)	796 261 (76 247)	798 853 (71 564)	789 057 (111 537)	790 067 (110 981)	761 078 (65 373)	764 207 (67 741)
Absolute hippocampus volume, mm^3						
Sample size	8	8	8	8	8	8
Mean (SD)	6860 (913)	7992 (1042)	6238 (1080)	6991 (1252)	6770 (955)	6704 (1011)
Relative hippocampus volume, % of total brain volume						
Sample size	8	8	8	8	8	8
Mean (SD)	0.542 (0.09)	0.631 (0.10)	0.491 (0.07)	0.548 (0.08)	0.547 (0.08)	0.541 (0.08)
NAA:Cr ratio						
Sample size	7	7	8	8	6	6
Mean (SD)	2.62 (0.76)	2.21 (0.31)	1.66 (0.43)	2.23 (0.70)	1.61 (0.39)	1.83 (0.61)
Short-term memory index						
Sample size	8	8	8	8	8	8
Mean (SD) score	15.6 (2.1)	13.0 (2.7)	7.0 (2.2)	9.4 (3.2)	10.5 (4.4)	9.9 (5.4)
Long-term memory index						
Sample size	8	8	8	8	8	8
Mean (SD) score	25.4 (4.1)	21.1 (6.0)	15.0 (5.9)	13.4 (3.0)	15.6 (6.3)	11.6 (8.4)
Corsi direct block span						
Sample size	8	8	8	8	8	8
Mean (SD) score	6.5 (0.9)	7.1 (0.6)	4.9 (0.6)	5.4 (0.7)	4.6 (1.1)	4.6 (1.1)

Abbreviations: Cr, creatine; NAA, *N*-acetylaspartate.

Table 3. Statistical Significance and Associated Effect Sizes of Comparisons Within the Groups of Exercising Subjects or Within the Groups of Sz Subjects Over Time[a]

	Control and Sz Exercise Groups						Sz Exercise and Nonexercise Groups					
	Time (Exercise)			Group × Time			Time			Group × Time		
	F	*P* Value	η^2	*F*	*P* Value	η^2	*F*	*P* Value	η^2	*F*	*P* Value	η^2
Total brain volume	0.5	.48	0.04	0.18	.67	0.01	2.0	.18	0.12	0.4	.52	0.03
Gray matter volume	0.2	.70	0.01	0.03	.87	0.00	0.2	.63	0.02	0.1	.81	0.00
Absolute hippocampus volume	81.1	<.001	0.85	3.28	.09	0.19	9.9	.007	0.41	14.0	.002	0.50
Relative hippocampus volume	70.4	<.001	0.83	3.39	.09	0.19	9.2	.009	0.40	13.8	.002	0.50
NAA:Cr ratio	0.2	.64	0.02	8.13	.01	0.38	6.5	.02	0.35	1.3	.27	0.10
STM index	0.0	.88	0.00	9.88	.007	0.41	1.7	.22	0.11	5.0	.04	0.26
LTM index	5.6	.03	0.29	1.1	.31	0.07	6.7	.02	0.32	1.2	.29	0.08
Corsi direct block span score	9.0	.01	0.39	0.11	.74	0.01	1.4	.26	0.09	1.4	.26	0.09

Abbreviations: Cr, creatine; LTM, long-term memory; NAA, *N*-acetylaspartate; STM, short-term memory; Sz, schizophrenia.

[a] *P* values represent the statistical significance of the effect of time and of the group × time interaction in a repeated-measures analysis of variance. An estimate of the effect size is the partial $\eta^2=[SS_{effect}/(SS_{effect}+SS_{error})]$, where *SS* is the sum of squares from the analyses of variance. Partial η^2 lies between 0 (no effect) and 1 (very strong effect).

$P=.01$; healthy controls: $r=0.39$; $P=.39$]) and $\dot{V}O_2$ max/kg (total: $r=0.57$; $P=.03$; schizophrenia exercise group: $r=0.72$; $P=.07$; healthy controls: $r=0.09$; $P=.85$), supporting the hypothesis of a relationship between changes in relative hippocampal volume and changes in aerobic fitness (**Figure 4**).

Because antidepressants can increase the rate of hippocampal neurogenesis in animal models, we performed an additional analysis restricted to patients not treated with antidepressants. There was still a significant increase (t3 vs t0) in relative hippocampal volume ($F_{1,9}=16.6$; $P=.003$). Furthermore, the time × group interaction was still significant ($F_{1,9}=33.4$; $P<.005$). For the schizophrenic subjects not taking antidepressants, the change in the relative hippocampal volume in the schizophrenia exercise subgroup was +16%, compared with the change in the schizophrenia nonexercise subgroup of –2%. Figure 2 and Figure 4 illustrate the

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

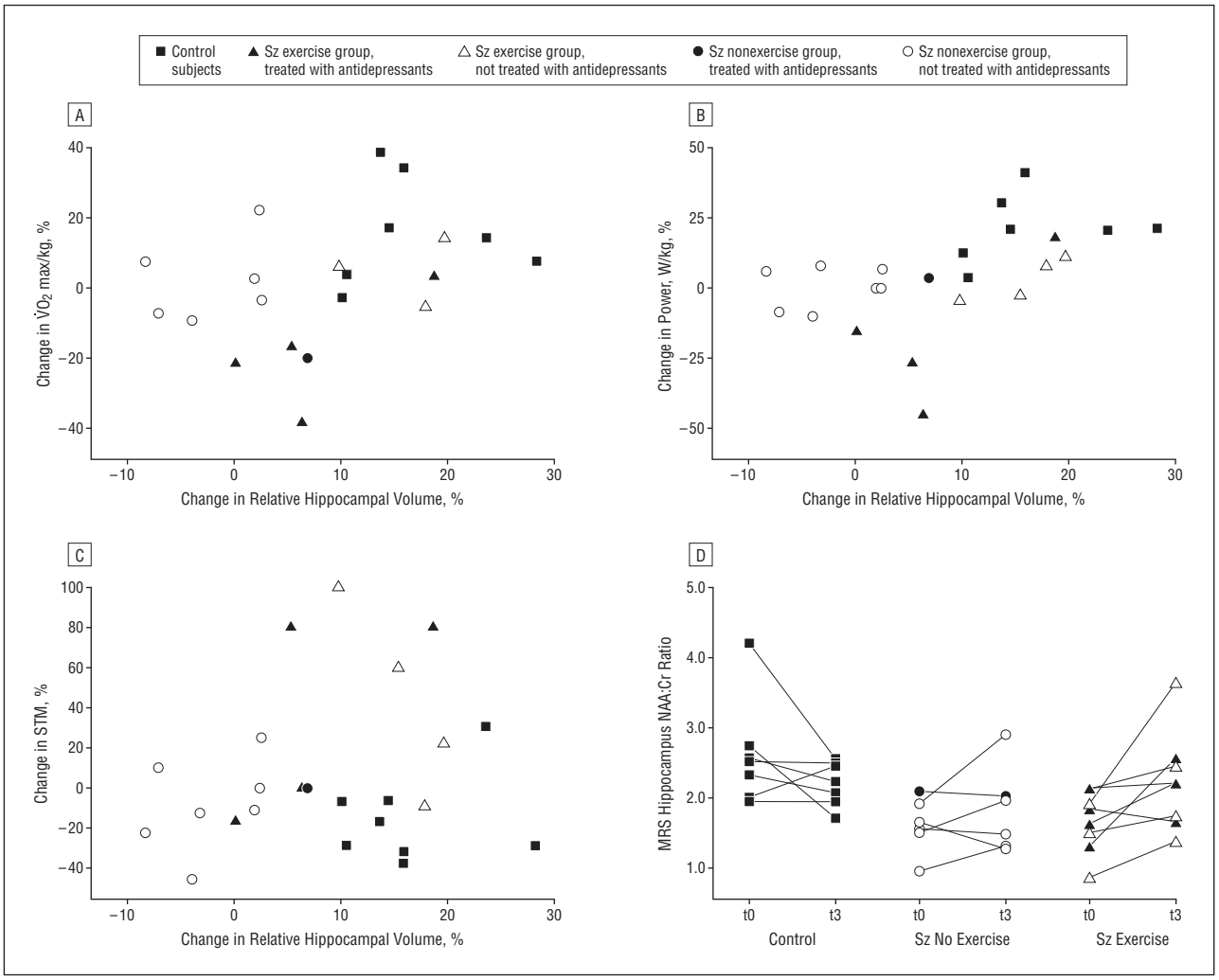

Figure 4. Changes between end point (t3) and baseline measures (t0) in relative hippocampal volume as a percentage of the total brain volume correlated with changes (t3 vs t0) in aerobic fitness as measured by maximum oxygen uptake per kilogram ($\dot{V}O_2$ max/kg) (A) and by the maximum power per kilogram (B). Hippocampal changes correlated with changes (t3 vs t0) in short-term memory (STM) as measured by the number of words recalled in the German version of the Rey Auditory Verbal Learning Test (C). Change (t3 vs t0) in the *N*-acetylaspartate to creatine (NAA:Cr) ratio measured with magnetic resonance spectroscopy in the left hippocampus (D). Sz indicates schizophrenia.

results in individual subjects in relation to antidepressant status.

CHANGE IN HIPPOCAMPAL METABOLITES

Magnetic resonance spectroscopy was used to investigate change in hippocampal metabolites in the exercise group. For the NAA:Cr ratio, a statistically significant time × diagnosis interaction was observed ($F_{1,13}$=8.13; P=.01), indicating that the schizophrenia and control groups differed in response to the exercise intervention. Schizophrenic subjects (n=8) had a 35% increase in the NAA:Cr ratio, while control subjects (n=7) had a 16% lower ratio after exercise. A post hoc analysis indicated the change in the schizophrenia exercise group was statistically significant (P=.04). When only patients not treated with antidepressants were included in the analysis, there was still a statistically significant time × diagnosis interaction ($F_{1,9}$=6.38; P=.03). The increase in NAA:Cr ratio in this subset of the schizophrenia exercise group was 44%, but this was not statistically significant in a post hoc analysis.

The time × diagnosis interactions suggest the mechanism of the exercise-related change in hippocampal volume in patients with schizophrenia and controls could be different. Correlations between the NAA:Cr ratio change and relative hippocampal volume change were not significant (controls: r=0.42; P=.35; schizophrenia exercise: r=0.23; P=.59), and correlations between baseline values of the NAA:Cr ratio and relative hippocampal volume were not significant (controls: r=–0.30; P=.52; schizophrenia exercise: r=–0.11; P=.80).

CHANGE IN MEMORY AND SYMPTOMS

The verbal measure of premorbid intelligence did not differ between the schizophrenia and control groups. Composite measures of memory differed; STM scores were lower in the schizophrenia group ($F_{1,14}$=35.35; P<.001). For STM, a statistically significant time × diagnosis interaction was observed ($F_{1,14}$=9.88; P=.007), indicating that the schizophrenia and control groups differed in response to the exercise intervention.

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

Schizophrenic subjects had a 34% increase in STM score after the exercise program, while control subjects had a 17% lower score after exercise. To investigate the possibility that the improvement in STM in the schizophrenia exercise group was related to nonspecific factors, performance was compared with the schizophrenia nonexercise group. The improvement in the aerobic exercise group (34%) was greater than the change observed in the nonexercise group (6% lower; group × time interaction, $F_{1,14}=4.95$; $P=.04$).

Mechanisms of memory may differ between schizophrenic and control subjects. We therefore studied the association between change in STM and change in relative hippocampal volume (controlled for total brain volume) within the combined schizophrenia group. For the total schizophrenia group, the change in hippocampal volume correlated with the change in STM (total: $r_{14}=0.51$; $P<.05$). However, this observation must be interpreted with caution as within the individual groups the correlations were not significant (schizophrenia exercise group: $r=0.19$; $P=.65$; nonexercise group: $r=0.33$; $P=.42$; control group: $r=-0.01$; $P=.97$).

The LTM and Corsi direct block span measures were lower in both schizophrenia groups compared with controls. In the combined exercise group, LTM declined somewhat after the intervention, and Corsi direct block span improved (Table 2 and Table 3). However, in the absence of a group × time interaction for either measure in the comparison between the schizophrenia exercise and the schizophrenia nonexercise groups, the interpretation of these findings is unclear. No further analysis of these data was carried out.

The severity of total symptoms of schizophrenia improved somewhat in the exercise group (9% lower) and worsened in the nonexercise group (13% higher). The time × group interaction was significant ($F_{1,14}=6.76$; $P=.02$). However, there was no relationship between changes in the Positive and Negative Syndrome Scale total score and hippocampal volumes.

COMMENT

The most robust finding was the exercise-related increase in hippocampal volume in healthy subjects and in patients with schizophrenia. To provide a context, the magnitude of these changes in volume was similar to that observed for other subcortical structures when patients were switched from typical to atypical antipsychotic drug therapy.[16] Exercise-related increases in hippocampal blood volume were reported in healthy subjects,[5] and a similar mechanism may have contributed to the increased tissue volume seen herein. Increased blood volume in animal studies was associated with increased neurogenesis. However, in schizophrenia, the hippocampus differs from healthy subjects, with neuronal atrophy and apparent loss of subsets of neurons and presynaptic proteins.[22,23] These differences could be a consequence of reduced neurogenesis, stress, obstetric complications, or altered mechanisms of aging.[24,25] The present finding of an increased hippocampal NAA:Cr ratio only in the schizophrenic subjects suggests that the mechanisms of volume increase related to exercise may differ from healthy subjects, possibly related to differences in the underlying substrate on which exercise is acting. Exercise is believed to act through a series of growth factors to alter neural plasticity, neurogenesis, and angiogenesis.[25,26] Since NAA is a marker of neuronal integrity, the volume changes after exercise in schizophrenia may be more likely to be associated with the neural compartment. However, we were not able to measure the gray and white matter volumes within the MRS voxels, and our MRS findings in this small sample of 8 patients have to be interpreted with caution.

Pathological studies of the hippocampus in schizophrenia indicate lower neuronal size, possibly fewer neurons of specific types, and lower levels of a range of presynaptic proteins, particularly in the terminal fields of projections from the entorhinal cortex.[11,27] In adult rodents, newborn neurons become integrated in granule cell layer circuitry and form connections with entorhinal afferents.[28] Recently described evidence suggests adult neurogenesis may be reduced in schizophrenia, and this could contribute to impaired cortical-to-hippocampal connectivity.[3] Reduced neurogenesis could be a consequence of a deficient trophic environment, as genes contributing to schizophrenia such as *DISC-1* and *BDNF* are also associated with effects on neurogenesis.[29] Exercise results in increased levels of neurotrophic factors in rodent hippocampus.[30] A similar mechanism occurring in humans might help to ameliorate a relatively atrophic hippocampus in schizophrenia.

In healthy subjects (both young and old), there is considerable variation in the volume of the hippocampus. Differences in volume between the upper and lower quartiles of groups studied at a single point range from 12% to 21%.[31] Physiological processes associated with changes in hippocampal volume over time in individual subjects could contribute to the large variation seen in groups of healthy subjects. Hippocampal volume loss can be a consequence of exposure to stress, aging, and a host of insults.[25] Enlargement of the hippocampus appears to be associated with specific experiences demanding a high degree of spatial learning,[32,33] antidepressant treatment in depressed patients,[34,35] atypical antipsychotic medications in individual patients,[15,16,36] and exercise, as seen herein. The change in volume related to exercise in schizophrenia indicates this type of plasticity remains relatively intact. The patients in the present study had chronic illness, many with refractory forms of illness, and the most commonly used medication was clozapine. The effects of clozapine on neurogenesis in animals are somewhat inconsistent, with the possibility that short-term administration of clozapine in low doses may promote neurogenesis.[37,38] The use of antidepressants in some patients did not appear to have an impact on the results. In rodents, the beneficial effects of antidepressants on electrophysiological measures of neural plasticity related to experience are attenuated by benzodiazepines.[39] The implications of combined clozapine or other medications and exercise are unclear. However, other studies indicate different stimuli to neurogenesis and plasticity, such as exer-

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

cise, environmental enrichment, and antidepressants, appear to work through independent pathways in rodents and may not be synergistic.[40,41] Patients with schizophrenia may be responsive to individualized interventions capable of increasing plasticity, depending on the nature of the underlying impairments.

The present study has several limitations. Since there is relatively little information concerning the effects of exercise on the hippocampus in even healthy subjects, we chose to investigate a relatively small sample with intensive measures as a test of the concept that exercise could alter hippocampal volume in schizophrenia. We selected a sample of subjects willing to engage in 3 months of relatively demanding physical training and restricted the sample to those with chronic illness taking stable doses of medication. Relating change in the volume of the hippocampus to the cumulative effects of aerobic exercise relies on the accuracy of cross-sectional exercise testing at baseline and at outcome. Exercise testing depends on effort as well as actual fitness. Effort may be variable and could result in apparent reductions in $\dot{V}O_2$ max/kg or power watts per kilogram following training if motivation was less at the second testing session. These challenges in using $\dot{V}O_2$ max/kg are not unique to the present study; although the measure is widely accepted as a reference value, similar issues occur with cardiac patients.[42] The interpretation of the relationship between change in the volume of the hippocampus and changes in measures of aerobic fitness could also be complicated by antipsychotic drug treatment in the schizophrenia group. Antipsychotic medications with cardiac and peripheral vascular effects (such as chlorpromazine) blunt the acute effects of exercise on cardiac stroke volume and on cardiac output.[43] As well, the effects of exercise on measures of aerobic fitness may also be less in patients treated with drugs having considerable peripheral effects.[44,45] We observed a relationship between change in hippocampal volume and change in aerobic fitness in the overall group of exercising subjects. Further investigation of this relationship in patients with schizophrenia will need to consider the effects of antipsychotic drugs with different effects on the heart and peripheral vascular system. This also applies to the possible effects of antipsychotic drugs on the interaction between exercise and central metabolism, because both typical and atypical antipsychotic drugs may impair the function of the mitochondrial electron transport chain.[46]

Over the time course studied herein, there were only very modest clinical changes that might indicate functional implications of the volume expansion. Previous studies of healthy subjects demonstrated increased brain activation during cognitive tasks following a period of exercise training[6] and better immediate recall during memory testing.[5] The latter observation was not replicated in the small sample of healthy subjects tested herein. Somewhat surprisingly, the changes in cognition expected in healthy subjects were seen in the patients with schizophrenia and correlated with the changes in hippocampal volume. Previous work indicated lower amounts of the presynaptic proteins SNAP-25 and complexin I and II were associated with increased cognitive impairment in schizophrenia.[27,47] Exercise-induced increases in metabolic and synaptic plasticity-related proteins in the hippocampus could contribute to improved cognitive function.[48] However, the changes in cognition observed herein were very modest, and the schizophrenia group remained considerably impaired relative to the healthy subjects. Finally, the observed change in hippocampal volume after aerobic exercise was associated with a relatively large effect size and *P* value on statistical testing. However, the other secondary measures, including relationships with metabolites and cognitive variables, were associated with *P* values that would have failed to pass statistical significance if a multiple testing correction was applied, although in some cases the effect sizes were moderate (partial η^2=0.26-0.41).

In summary, the present study indicates that the hippocampus in schizophrenia retains a degree of plasticity, at least in response to a specific challenge such as exercise. Further clinical studies are needed to determine if an incremental improvement in the disability related to schizophrenia could be obtained by incorporating exercise into treatment planning and lifestyle choice for individuals with the illness.

Submitted for Publication: September 21, 2008; final revision received June 16, 2009; accepted June 19, 2009.
Author Affiliations: Departments of Psychiatry and Psychotherapy (Prof Pajonk, Drs Berner, Kaizl, and Oest, and Mss Kierer and Müller) and Diagnostic and Interventional Radiology (Dr Backens), The Saarland University Hospital, Homburg, Center for Psychiatric Care and Rehabilitation, Dr K. Fontheim's Hospital for Mental Health, Liebenburg (Prof Pajonk), Department of Psychiatry, University of Göttingen (Drs Wobrock, Scherk, and Schneider-Axmann and Profs Gruber and Falkai) and DFG Research Center Molecular Physiology of the Brain (Prof Falkai), Göttingen, and Institute of Sports Medicine, University of Paderborn, Paderborn (Prof Meyer), Germany; and Department of Psychology, Simon Fraser University, Burnaby (Dr Thornton), and Department of Psychiatry, University of British Columbia, Vancouver (Prof Honer), Canada.
Correspondence: Frank-Gerald Pajonk, MD, Center for Psychiatric and Psychotherapeutic Care and Rehabilitation, Dr K. Fontheim's Hospital for Mental Health, Lindenstrasse 15, D-38704 Liebenburg, Germany (pajonk@klinik-dr-fontheim.de).
Author Contributions: Prof Pajonk and Dr Wobrock contributed equally to this article.
Financial Disclosure: Prof Pajonk has acted as a consultant for AstraZeneca, Eli Lilly, Janssen, Novartis, and Wyeth and an expert witness for AstraZeneca, Eli Lilly, and Janssen; has received research funding from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi-Synthélabo, and Wyeth; is a member of a speakers' bureau for Merz; and has accepted paid speaking engagements in industry-sponsored symposia from AstraZeneca, Eli Lilly, Janssen, and Pfizer and travel or hospitality not related to a speaking engagement from As-

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

traZeneca, Eli Lilly, and Janssen. Dr Wobrock has participated in speaker bureaus for Alpine Biomed, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Essex, Organon, Janssen-Cilag, Pfizer, and Sanofi-Synthélabo/Aventis and received travel or hospitality not related to a speaking engagement from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, and Sanofi-Synthélabo and grant/research support from AstraZeneca. Prof Gruber was an honorary speaker for AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, and Otsuka and has been invited to scientific congresses by AstraZeneca, Janssen-Cilag, and Pfizer. Dr Scherk has accepted paid speaking engagements in industry-sponsored symposia from AstraZeneca, BMS, Eli Lilly, Janssen-Cilag, Pfizer, and Servier and travel or hospitality not related to a speaking engagement from AstraZeneca, Eli Lilly, and Janssen-Cilag. Dr Meyer has received funding from the German Football Association, the German Football League, the Federal Institute of Sports Science, and the Joao Havelange Foundation. Prof Honer has received consulting fees or participated in paid advisory boards for In Silico Biosciences, Pfizer, Wyeth/Solvay, Janssen-Cilag, Novartis, and AstraZeneca; lecture fees from Janssen and AstraZeneca; and educational grant support from Janssen, Eli Lilly, and AstraZeneca. Prof Falkai has been a member of advisory boards for Janssen-Cilag, BMS, Lundbeck, Pfizer, Lilly, and AstraZeneca and received an educational grant for an ITT by AstraZeneca and honoraria and travel support as a lecturer from Janssen-Cilag, BMS, Lundbeck, Pfizer, Lilly, and AstraZeneca.

Funding/Support: Prof Honer was supported by the Michael Smith Foundation for Health Research and BC Mental Health and Addictions Services.

Previous Presentations: Preliminary results described in this article were presented at the Winter Workshop on Schizophrenia Research; February 5, 2008; Montreux, Switzerland, and the First International Schizophrenia Research Society Conference; June 22, 2008; Venice, Italy. The abstracts were published in 2 supplements of *Schizophrenia Research*.

REFERENCES

1. Freedman R. Schizophrenia. *N Engl J Med*. 2003;349(18):1738-1749.
2. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. *Annu Rev Neurosci*. 2005;28:377-401.
3. Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch KP. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. *Mol Psychiatry*. 2006;11(5):514-522.
4. Arnold SE, Han L-Y, Moberg PJ, Turetsky BI, Gur RE, Trojanowski JQ, Hahn CG. Dysregulation of olfactory receptor neuron lineage in schizophrenia. *Arch Gen Psychiatry*. 2001;58(9):829-835.
5. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A*. 2007;104(13):5638-5643.
6. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A*. 2004;101(9):3316-3321.
7. Gaser C, Schlaug G. Brain structures differ between musicians and non-musicians. *J Neurosci*. 2003;23(27):9240-9245.
8. May A, Hajak G, Ganssbauer S, Steffens T, Langguth B, Kleinjung T, Eichhammer P. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. *Cereb Cortex*. 2007;17(1):205-210.
9. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Changes in grey matter induced by training. *Nature*. 2004;427(6972):311-312.
10. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry*. 2006;188:510-518.
11. Harrison PJ. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. *Psychopharmacology (Berl)*. 2004;174(1):151-162.
12. Velakoulis D, Pantelis C, McGorry PD, Dudgeon P, Brewer W, Cook M, Desmond P, Bridle N, Tierney P, Murrie V, Singh B, Copolov D. Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry*. 1999;56(2):133-141.
13. Wood SJ, Velakoulis D, Smith DJ, Bond D, Stuart GW, McGorry PD, Brewer WJ, Bridle N, Eritaia J, Desmond P, Singh B, Copolov D, Pantelis C. A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophr Res*. 2001;52(1-2):37-46.
14. Velakoulis D, Wood SJ, Wong MTH, McGorry PD, Yung A, Phillips L, Smith D, Brewer W, Proffitt T, Desmond P, Pantelis C. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry*. 2006;63(2):139-149.
15. Chakos MH, Schobel SA, Gu H, Gerig G, Bradford D, Charles C, Lieberman JA. Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia. *Br J Psychiatry*. 2005;186:26-31.
16. Panenka WJ, Khorram B, Barr AM, Smith GN, Lang DJ, Kopala LC, Vandorpe RA, Honer WG. A longitudinal study on the effects of typical versus atypical antipsychotic drugs on hippocampal volume in schizophrenia. *Schizophr Res*. 2007;94(1-3):288-292.
17. Khorram B, Lang DJ, Kopala LC, Vandorpe RA, Rui Q, Goghari VM, Smith GN, Honer WG. Reduced thalamic volume in patients with chronic schizophrenia after switching from typical antipsychotic medications to olanzapine. *Am J Psychiatry*. 2006;163(11):2005-2007.
18. Lang DJ, Kopala LC, Vandorpe RA, Rui Q, Smith GN, Goghari VM, Lapointe JS, Honer WG. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. *Am J Psychiatry*. 2004;161(10):1829-1836.
19. Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short estimate of premorbid intelligence. *Acta Neurol Scand*. 1995;91(5):335-345.
20. Müller H, Hasse-Sander I, Horn R, Helmstaedter C, Elger CE. Rey auditory-verbal learning test: structure of a modified German version. *J Clin Psychol*. 1997;53(7):663-671.
21. Milner B. Interhemispheric differences in the localization of psychological processes in man. *Br Med Bull*. 1971;27(3):272-277.
22. Young CE, Arima K, Xie J, Hu L, Beach TG, Falkai P, Honer WG. SNAP-25 deficit and hippocampal connectivity in schizophrenia. *Cereb Cortex*. 1998;8(3):261-268.
23. Heckers S, Konradi C. Hippocampal neurons in schizophrenia. *J Neural Transm*. 2002;109(5-6):891-905.
24. Ebner F, Tepest R, Dani I, Pfeiffer U, Schulze TG, Rietschel M, Maier W, Träber F, Block W, Schild HH, Wagner M, Steinmetz H, Gaebel W, Honer WG, Schneider-Axmann T, Falkai P. The hippocampus in families with schizophrenia in relation to obstetric complications. *Schizophr Res*. 2008;104(1-3):71-78.
25. McEwen BS. Possible mechanisms for atrophy of the human hippocampus. *Mol Psychiatry*. 1997;2(3):255-262.
26. Hu S, Ying Z, Gomez-Pinilla F, Frautschy SA. Exercise can increase small heat shock proteins (sHSP) and pre- and post-synaptic proteins in the hippocampus. *Brain Res*. 2009;1249:191-201.
27. Sawada K, Barr AM, Nakamura M, Arima K, Young CE, Dwork AJ, Falkai P, Phillips AG, Honer WG. Hippocampal complexin proteins and cognitive dysfunction in schizophrenia. *Arch Gen Psychiatry*. 2005;62(3):263-272.
28. Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH. Synapse formation on neurons born in the adult hippocampus. *Nat Neurosci*. 2007;10(6):727-734.
29. Reif A, Schmitt A, Fritzen S, Lesch K-P. Neurogenesis and schizophrenia: dividing neurons in a divided mind? *Eur Arch Psychiatry Clin Neurosci*. 2007;257(5):290-299.
30. Cotman CW, Berchtold NC, Christie L-A. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci*. 2007;30(9):464-472.
31. Lupien SJ, Evans A, Lord C, Miles J, Pruessner M, Pike B, Pruessner JC. Hippocampal volume is as variable in young as in older adults: implications for the notion of hippocampal atrophy in humans. *Neuroimage*. 2007;34(2):479-485.
32. Maguire EA, Woollett K, Spiers HJ. London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus*. 2006;16(12):1091-1101.

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013

33. Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD. Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci U S A*. 2000;97(8):4398-4403.
34. Yucel K, McKinnon MC, Taylor VH, Macdonald K, Alda M, Young LT, MacQueen GM. Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. *Psychopharmacology (Berl)*. 2007;195(3):357-367.
35. Yucel K, Taylor VH, McKinnon MC, Macdonald K, Alda M, Young LT, MacQueen GM. Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology*. 2008;33(2):361-367.
36. McClure RK, Phillips I, Jazayerli R, Barnett A, Coppola R, Weinberger DR. Regional change in brain morphometry in schizophrenia associated with antipsychotic treatment. *Psychiatry Res*. 2006;148(2-3):121-132.
37. Halim ND, Weickert CS, McClintock BW, Weinberger DR, Lipska BK. Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. *Neuropsychopharmacology*. 2004;29(6):1063-1069.
38. Schmitt A, Weber S, Jatzko A, Braus DF, Henn FA. Hippocampal volume and cell proliferation after acute and chronic clozapine or haloperidol treatment. *J Neural Transm*. 2004;111(1):91-100.
39. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, Castrén E, Maffei L. The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science*. 2008;320(5874):385-388.
40. Engesser-Cesar C, Anderson AJ, Cotman CW. Wheel running and fluoxetine antidepressant treatment have differential effects in the hippocampus and the spinal cord. *Neuroscience*. 2007;144(3):1033-1044.
41. Olson AK, Eadie BD, Ernst C, Christie BR. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus*. 2006;16(3):250-260.
42. Meyer T, Scharhag J, Kindermann W. Peak oxygen uptake: myth and truth about an internationally accepted reference value. *Z Kardiol*. 2005;94(4):255-264.
43. Carlsson C, Dencker SJ, Grimby G, Häggendal J. Circulatory studies during physical exercise in mentally disordered patients, I: effects of large doses of chlorpromazine. *Acta Med Scand*. 1968;184(6):499-509.
44. Carlsson C, Dencker SJ, Grimby G, Häggendal J, Johnsson G. Hemodynamic effects of thiothixene and chlorpromazine in schizophrenic patients at rest and during exercise. *Int J Clin Pharmacol Biopharm*. 1976;13(4):262-268.
45. Carlsson C, Dencker SJ, Grimby G, Häggendal J. Circulatory studies during physical exercise in mentally disordered patients, II: effects of physical training in patients with and without administration of chlorpromazine. *Acta Med Scand*. 1968; 184(6):511-516.
46. Casademont J, Garrabou G, Miró O, López S, Pons A, Bernardo M, Cardellach F. Neuroleptic treatment effect on mitochondrial electron transport chain: peripheral blood mononuclear cells analysis in psychotic patients. *J Clin Psychopharmacol*. 2007;27(3):284-288.
47. Barr AM, Young CE, Sawada K, Honer WG. Relevance of presynaptic proteins to neuropsychiatric disorders. In: Dityatev A, El-Husseini A, eds. *Molecular Mechanisms of Synaptogenesis*. New York, NY: Springer; 2006:391-408.
48. Ding Q, Vaynman S, Souda P, Whitelegge JP, Gomez-Pinilla F. Exercise affects energy metabolism and neural plasticity-related proteins in the hippocampus as revealed by proteomic analysis. *Eur J Neurosci*. 2006;24(5):1265-1276.

Announcement

Readers Reply

Archives of General Psychiatry is introducing a new feature, Readers Reply, which will publish online readers' discussions of articles published in the *Archives*. We hope that this opportunity will stimulate interactions not only between readers and the authors but also among the readers. Letters can be submitted electronically via the Readers Reply link that appears on the right side of the article's full-text page. Letters that are submitted directly to the *Archives* for consideration for print and online (archival) publication but are not accepted (as space constraints limit our ability to publish most letter submissions) will be returned to the authors for their submission to Readers Reply.

We are pleased to announce the appointment of Peter Siekmeier, MD, MS, who will serve as the editor of Readers Reply. Dr Siekmeier received his BSE from Princeton University, an MS from Massachusetts Institute of Technology, and an MD from Yale University and completed his residency training in psychiatry at the Massachusetts General Hospital–McLean Program.

We hope that this new feature further increases the scientific impact of the *Archives*.

©2010 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/22/2013