Physical Exercise Keeps the Brain Connected: Biking Increases White Matter Integrity in Patients With Schizophrenia and Healthy Controls

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It has been shown that learning a new skill leads to structural changes in the brain. However, it is unclear whether it is the acquisition or continuous practicing of the skill that causes this effect and whether brain connectivity of patients with schizophrenia can benefit from such practice. We examined the effect of 6 months exercise on a stationary bicycle on the brain in patients with schizophrenia and healthy controls. Biking is an endemic skill in the Netherlands and thus offers an ideal situation to disentangle the effects of learning vs practice. The 33 participating patients with schizophrenia and 48 healthy individuals were assigned to either one of two conditions, ie, physical exercise or life-as-usual, balanced for diagnosis. Diffusion tensor imaging brain scans were made prior to and after intervention. We demonstrate that irrespective of diagnosis regular physical exercise of an overlearned skill, such as bicycling, significantly increases the integrity, especially of motor functioning related, white matter fiber tracts whereas life-as-usual leads to a decrease in fiber integrity. Our findings imply that exercise of an overlearned physical skill improves brain connectivity in patients and healthy individuals. This has important implications for understanding the effect of fitness programs on the brain in both healthy subjects and patients with schizophrenia. Moreover, the outcome may even apply to the nonphysical realm.

Key words: physical exercise/schizophrenia/diffusion tensor imaging/connectivity/longitudinal/fractional anisotropy

Introduction

Schizophrenia is associated with loss of brain tissue, in particular in the frontal and temporal cortices as well as in some subcortical structures.1,2 The involvement of distinct brain structures suggests that ineffective communication between brain regions may be involved through changes in white matter.3 This theory is supported by several neuroimaging studies4,5 as well as by postmortem and genetic studies.6,7 Moreover, some of the schizophrenia-related changes in gray8,9 and white matter10 are progressive in nature. The (progressive) brain tissue loss has been associated with genetic factors and with disease-related factors11,12 as well as effects of antipsychotic medication intake.13

Physical exercise has been reported to affect gray matter structure.14-19 Increases in the volume of the cortex14,16,18 and hippocampus17,19 were found after periods of exercise in healthy individuals. However, others did not find significant effect, eg, on cortical architecture.20-22 In patients with schizophrenia, a period of exercise training resulted in hippocampal volume increase in one study19 but other studies did not reveal increases in hippocampal volume20 or cortical density.18

However, it is not known if exercise benefits white matter connectivity in patients with schizophrenia. In healthy students, it has been shown that when a new skill is learned, such as juggling, gray matter volume increases14 and white matter integrity improves.23 But is this really the acquisition of the new skill that induces these changes or is it maintaining the skill? After having acquired proficiency in juggling, the changes in the brain reverted to normal after the students had stopped practicing for 3 months, suggesting it may be practice rather than acquisition that affects the brain. On the other hand, after training a complicated balancing act, white matter changes remained present.23 Interestingly, several cross-sectional studies, mainly conducted in musicians, suggest that it is (early) practice that determines changes in the brain24: proficiency—expressed as practice time—is generally correlated with the degree of brain change, not with the skill of playing the instrument per se.25

To study the effect of practice on brain connectivity in patients with schizophrenia vs healthy individuals, we
examined brain changes after practicing an overlearned skill and measured brain connectivity using diffusion tensor imaging (DTI) at 3 Tesla prior to and after the 6-month intervention in a Dutch cohort. When the skill is endemic in a population, it is evident that learning is not involved. In this study, we chose to examine the effect of exercise on a stationary bicycle on the brain because biking is an endemic skill in the Netherlands. Indeed, 85% of the Dutch owns a bicycle and each year travels 900 km on it. Thus, it offers an ideal situation if one intends to disentangle the effects of acquisition vs practice in patients with schizophrenia as well as healthy population.

### Methods

#### Cohort

A total of 33 patients with schizophrenia and 48 healthy controls from the “The outcome of Psychosis and Fitness therapy” (TOPFIT) cohort were included in the study. Participants were between 18 and 48 years of age (table 1). The majority were males (60 males/21 females). All subjects signed a written informed consent prior to participating in the study and after possible side effects were explained prior to participation. The Medical Ethical Committee at the University Medical Center Utrecht approved the study.

#### Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>demographic and clinical characteristic</th>
<th>exercise patients</th>
<th>exercise controls</th>
<th>nonexercise patients</th>
<th>nonexercise controls</th>
<th>p value</th>
<th>p value</th>
<th>time by randomization (F, P values)</th>
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</thead>
<tbody>
<tr>
<td>number of participants</td>
<td>16</td>
<td>24</td>
<td>17</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>0.95; .33</td>
</tr>
<tr>
<td>sex (males/females)</td>
<td>13/3</td>
<td>17/7</td>
<td>14/3</td>
<td>16/8</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (years)</td>
<td>28.8 (7.4)</td>
<td>28.8 (7.9)</td>
<td>31.3 (8.2)</td>
<td>27.7 (6.4)</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>handedness (right/left/both)</td>
<td>15/1/0</td>
<td>21/0/2</td>
<td>17/0/0</td>
<td>22/1/1</td>
<td>0.58</td>
<td></td>
<td></td>
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<tr>
<td>body length (cm)</td>
<td>180.5 (10.2)</td>
<td>180.4 (10.8)</td>
<td>177.8 (5.4)</td>
<td>176.3 (9.9)</td>
<td>0.09</td>
<td></td>
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<tr>
<td>parental education (y)</td>
<td>13.2 (2.7)</td>
<td>15.2 (1.7)</td>
<td>14.4 (2.0)</td>
<td>14.0 (2.6)</td>
<td>0.70</td>
<td></td>
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<tr>
<td>duration of illness (d)</td>
<td>2358 (2137)</td>
<td>3085 (2180)</td>
<td>3085 (2180)</td>
<td>3085 (2180)</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalization until baseline (d)</td>
<td>114 (113)</td>
<td>279 (375)</td>
<td>—</td>
<td>33.4 (17.6)</td>
<td></td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>intelligence quotient (IQ)</td>
<td>83.8 (11.9)</td>
<td>111.8 (13.5)</td>
<td>95.4 (21.9)</td>
<td>106.2 (14.4)</td>
<td>.81</td>
<td></td>
<td>18.19; &lt;.001*</td>
</tr>
<tr>
<td>body mass (kg/m²)</td>
<td>27.13 (7.78)</td>
<td>23.5 (3.1)</td>
<td>27.5 (6.2)</td>
<td>23.9 (3.2)</td>
<td>.73</td>
<td></td>
<td>2.74; .10</td>
</tr>
<tr>
<td>wpeak (Watt)</td>
<td>222.8 (46.1)</td>
<td>266.4 (55.3)</td>
<td>237.7 (57.3)</td>
<td>245.7 (55.2)</td>
<td>.61</td>
<td></td>
<td>18.19; &lt;.001*</td>
</tr>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>252.0 (41.3)</td>
<td>276.5 (69.5)</td>
<td>232.3 (50.0)</td>
<td>25.7 (58.9)</td>
<td>.03*</td>
<td></td>
<td>9.20; .003*</td>
</tr>
<tr>
<td>heart rate in rest</td>
<td>76.1 (18.0)</td>
<td>70.0 (11.0)</td>
<td>70.6 (14.2)</td>
<td>65.6 (7.9)</td>
<td>.31</td>
<td></td>
<td>0.32; .58</td>
</tr>
<tr>
<td>heart rate maximal</td>
<td>73.3 (15.8)</td>
<td>65.3 (12.5)</td>
<td>72.4 (14.4)</td>
<td>63.7 (12.6)</td>
<td>.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANS score</td>
<td>175.4 (17.3)</td>
<td>190.0 (9.6)</td>
<td>169.9 (22.6)</td>
<td>193.3 (11.1)</td>
<td>.88</td>
<td></td>
<td>0.13; .68</td>
</tr>
<tr>
<td>PANSS positive symptoms</td>
<td>171.6 (22.2)</td>
<td>186.7 (10.6)</td>
<td>167.1 (18.9)</td>
<td>188.4 (13.1)</td>
<td>.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS negative signs</td>
<td>62.3 (13.2)</td>
<td>—</td>
<td>60.3 (10.1)</td>
<td>—</td>
<td>.64</td>
<td></td>
<td>17.47; &lt;.001*</td>
</tr>
<tr>
<td>disorganization</td>
<td>54.7 (12.6)</td>
<td>—</td>
<td>60.6 (9.8)</td>
<td>—</td>
<td>.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS symptom</td>
<td>14.9 (3.9)</td>
<td>—</td>
<td>15.0 (3.9)</td>
<td>—</td>
<td>.93</td>
<td></td>
<td>15.15; .001*</td>
</tr>
<tr>
<td>PANSS disorganization</td>
<td>12.3 (4.5)</td>
<td>—</td>
<td>15.7 (4.6)</td>
<td>—</td>
<td>.04*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS negative signs</td>
<td>19.7 (5.7)</td>
<td>—</td>
<td>15.8 (5.4)</td>
<td>—</td>
<td>.06</td>
<td></td>
<td>3.77; .06</td>
</tr>
<tr>
<td>PANSS</td>
<td>17.6 (4.6)</td>
<td>—</td>
<td>16.5 (5.3)</td>
<td>—</td>
<td>.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS disorganization</td>
<td>18.1 (4.9)</td>
<td>—</td>
<td>19.1 (4.4)</td>
<td>—</td>
<td>.54</td>
<td></td>
<td>4.31; .047*</td>
</tr>
<tr>
<td>PANSS symptom</td>
<td>16.7 (5.4)</td>
<td>—</td>
<td>19.8 (4.2)</td>
<td>—</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS disorganization</td>
<td>12.4 (1.8)</td>
<td>—</td>
<td>12.7 (2.0)</td>
<td>—</td>
<td>.62</td>
<td></td>
<td>9.52; .004*</td>
</tr>
<tr>
<td>PANSS emotional distress</td>
<td>11.3 (1.9)</td>
<td>—</td>
<td>13.6 (1.5)</td>
<td>—</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS disorganization</td>
<td>18.3 (4.5)</td>
<td>—</td>
<td>18.1 (5.1)</td>
<td>—</td>
<td>.94</td>
<td></td>
<td>3.50; .07</td>
</tr>
<tr>
<td>chlorpromazine equivalent dose</td>
<td>362.7 (324.4)</td>
<td>—</td>
<td>458.2 (250.2)</td>
<td>—</td>
<td>.35</td>
<td></td>
<td>0.62; .44</td>
</tr>
<tr>
<td>chlorpromazine equivalent dose</td>
<td>397.7 (343.5)</td>
<td>—</td>
<td>477.7 (227.9)</td>
<td>—</td>
<td>.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: ANOVA, one-way analysis of variance; PANSS, Positive and Negative Symptoms Scale.

*ANOVA for noncategorical variables and chi-square test for categorical variables were used to examine differences between the exercise and nonexercise groups (E/N). Repeated measurement ANOVA was used to calculate the effect of time (measurement at the beginning and after 6 months intervention) by randomization (exercise vs nonexercise group). *P < .05.
approved the study. To be included, individuals had to be physically healthy, meaning that they have no evidence of significant cardiovascular, neuromuscular, endocrine, or another somatic disorders. Individuals did not have a primary alcohol or substance abuse/dependence diagnosis and had an intelligence quotient of at least 70, as measured with Wechsler Adult Intelligence Scale Short Form (WAIS-III-NL). To be included, individuals had to be physically inactive, defined as undertaking less than 1 h of moderate physical activity weekly.

Patients with schizophrenia were recruited via primary health centers. Diagnosis was according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) as confirmed by psychiatrists using the Comprehensive Assessment of Schizophrenia and History (CASH). Healthy participants were recruited via local advertisements. Healthy participants had no diagnosis of psychiatric disorder according DSM-IV lifetime and no first-degree relative with psychotic or depressive disorder.

No significant differences were found between patients and controls in mean age, gender, handedness, and parental level of education. Body mass index (BMI) was significantly higher in patients as compared to healthy subjects. Information about hand preference was obtained using a questionnaire that was part of the CASH test.

Randomization was performed as a computer-generated procedure, incorporating a concealed allocation (ratio 1:1), with stratification for gender, recruitment site and Body Mass Index.

Before and after the intervention DTI brain scans were made, and cardiovascular fitness measurements, clinical, and cognitive assessments were completed.

In patients, the Positive and Negative Symptoms Scale (PANSS) was completed to evaluate severity of symptoms. The antipsychotics dosage was recalculated to Chlorpromazine equivalents (ChE) (table 1) (for details see supplementary data).

### Intervention

All subjects underwent a 6-month intervention. Individuals were assigned to either one of the two conditions, ie, physical exercise or life-as-usual, balanced for diagnosis. Patients were assigned to the physical exercise intervention or occupational therapy for 6 months. Occupational therapy consisted of creative and recreational activities as painting, reading, and computer activities, to provide a similar amount of structure and attention as that for life-as-usual in the healthy participants. Healthy individuals were assigned to the physical exercise intervention or life-as-usual. The level of physical activity was monitored during three 24-hour timeslots by the means of the SenseWear Armband (SWA) (BodyMedia Inc) and using a structured questionnaire to assess the level of daily life physical activities at baseline (repeated monthly).

A research assistant and a sport physician assessed the demographic and clinical baseline and follow-up measurements while being blind to the randomization. All measurements and DTI scans were acquired within a time frame of 14 days.

Cardiorespiratory fitness parameters were defined as a peak work rate at the moment of exhaustion (Wpeak in Watts) and the highest oxygen uptake during the last 30 s of the test (VO2 in ml/kg/min) and were assessed with a cycle ergometer cardiopulmonary exercise test (CPET; Lode excalibur, Lode BV, Groningen, The Netherlands). The maximal efforts at exhaustion were assumed when the respiratory exchange rate (ratio between CO2 produced and O2 consumed in one breath) equaled or exceeded 1.1.

The exercise followed the recommendations of American of Sports Medicine. Exercise duration was 1 h twice weekly, consisting of 40 min of aerobic and 20 min of anaerobic exercise. Aerobic exercise was performed using the upright bicycle ergometer, recumbent bicycle ergometer, rowing machine, cross trainer, and treadmill, as well as muscle strength exercises (6 exercises per week, 3 times, 10–15 repetition maximum for biceps, triceps, abdominal, quadriceps, pectoral, deltoid muscles). Anaerobic exercise consisted of working with weights. Biking took approximately 50% of the duration of physical exercise. Compliance was registered as a percentage of sessions attended and was over 50% in the subjects included in the study (for details see supplementary data).

### Brain Imaging

Brain scans were acquired on a 3 Tesla Philips Achieva Medical Scanner (Philips Medical Systems, Best, The Netherlands) at University Medical Center Utrecht, The Netherlands. Two DTI sets of 30 directions (b = 1000 s/mm2) and 5 unweighted B0 scans (b = 0 s/mm2) were acquired using parallel imaging SENSE p-reduction 3 (for details see supplementary data). Postprocessing was performed using the FSL software version 5.0.6 (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl). After correction for susceptibility (TOPUP) and eddy current (ECC) distortions, preprocessed images were fitted to the tensor model to generate fractional anisotropy (FA) images using DTIFIT. Tractography-based analyses (both deterministic and probabilistic) usually require a selection of white matter fiber bundles to be studied a priori. In this study, we did not want to exclude white matter regions beforehand and therefore we...
performed the analysis using Tract-based spatial statistics (TBSS), part of FSL. TBSS is a full-automated analysis that allows investigating the whole brain. First, all FA images were registered into a common space using nonlinear registration. FMRIB58_FA was used as a registration target image. Next, the transformed images were averaged to create a mean FA image and then a study-specific skeleton was generated. This study-specific FA skeleton consists of voxels that represent the center voxels of the tracts. To exclude gray matter and CSF containing voxels, only skeleton voxels with an FA value larger than 0.2 were considered. Finally, FA skeletons were computed for each individual and aligned with the study-specific FA skeleton. This allowed for a point-by-point comparison between all subjects for each of the individual skeleton voxels.

A second analysis was performed using the JHU-ICBM-tract atlas (The John Hopkins University—The International Consortium of Brain Mapping) included in FSL to define regions of interest (ROI) for the various fiber tracts. Mean FA values for the skeleton voxels within the various tract ROIs were computed to measure FA values for the entire white matter tract. Average FA values for skeleton voxels within tract ROIs were extracted and used for statistical analysis. With this analysis average FA values for 6 tracts in each hemisphere and 2 commissural tracts were computed: ie, the corticospinal tracts (CST), superior and inferior longitudinal fascicles (SLF, ILF), inferior fronto-occipital fascicles (IFOF), uncinate fascicles, cingulum, and both forceps major (FM) and minor.

In addition, a program allowing mathematical manipulation of images (FSLmaths) was used to calculate the actual average FA value for all voxels inside the skeleton (\(FA_{\text{skeleton}}\)) as well as for clusters that showed significant FA increase in threshold-free cluster enhancement (TFCE) analysis longitudinally (\(FA_{\text{picked}}\)) for each subject and each measurement separately.

**Statistical Analyses**

**Baseline Analysis.** For baseline and follow-up measurements, one-way analysis of variance for noncategorical variables and chi-square test for categorical variables were utilized to examine demographic and clinical differences for randomization (exercise/occupational therapy) and group (healthy controls/patients) using SPSS 20.0.0 (SPSS Inc) statistical software package. All statistical tests were performed two-tailed with critical \(P\) value for significance set at < .05. Pearson two-tailed correlation was done between averaged FA skeleton values (\(FA_{\text{skeleton}}\)) and ChE dose at baseline.

**Longitudinal Analysis**

**Cluster-Based TBSS Analysis** To assess longitudinal changes, measurements at baseline were subtracted from measurements at follow up using FSLmaths. A general linear model (GLM) was used (part of FSL) to test for differences in longitudinal changes between the various groups (exercise vs occupational therapy as well as healthy individuals vs patients) with compliance percentage included as a covariate.

For the TBSS results, nonparametric voxel–wise statistical analyses of the skeleton voxels were carried out using the “randomize” program part of FSL (\(P < .05\)) with the number of permutations set to 5000 and corrected for multiple comparison using threshold-free cluster enhancement (TFCE).

**JHU-Atlas-Based ROI Analysis** The average FA values of the skeleton voxels within the ROIs were analyzed using SPSS 20.0.0 (SPSS Inc).

The GLM-repeated measurement in SPSS was designed identically to FSL-design to analyze longitudinal measurements of white matter parameters of selected ROIs, with time (2 levels: measurement at the beginning and measurement after 6 months of intervention) as within-subject factor, randomization (exercise group, nonexercise group), and group (patients, healthy controls) as between-subject factors, and compliance as covariate.

**Correlation Analysis.** Differences between follow-up and baseline measurements in intelligence level (dIQ), cardiorespiratory fitness parameters (d\(W_{\text{peak}}\), d\(V_{\text{O2peak}}\)), body mass index (dBMI), heart rate in rest (dHR\(_{\text{rest}}\)), maximal heart rate (dHR\(_{\text{max}}\)), and FA values from the whole skeleton (d\(FA_{\text{skeleton}}\)) and clusters with significant FA increase longitudinally (d\(FA_{\text{picked}}\)) were calculated. In patients changes between follow-up and baseline overall PANSS score (dPANSS) and subscores as well as Chlorpromazine Equivalent (dChE) dose were computed. Pearson two-tailed correlations were measured between these variables.

**Results**

**Baseline**

No significant baseline difference between the exercise group and nonexercise group was found in heart rate in rest (HR\(_{\text{rest}}\)), peak work rate at the moment of exhaustion (\(W_{\text{peak}}\) in Watt), highest oxygen uptake during the last 30 s of the test (\(VO_{2}\) in ml/kg/min), and IQ (table 1).

At baseline, a significant difference was found between the patients and the controls, irrespective of intervention condition, in heart rate in rest (HR\(_{\text{rest}}\)), maximal heart rate (HR\(_{\text{max}}\)), together with difference in peak work rate at the moment of exhaustion (\(W_{\text{peak}}\) in Watt) as a measure of cardiorespiratory fitness, although no significant difference in the highest oxygen uptake during the last 30 s of the test (\(VO_{2}\) in ml/kg/min) was observed. In addition, a significant difference in IQ was found. There was no significant correlation between antipsychotic medication intake (ChE) and baseline FA in patients. Significant differences in compliance between exercise and nonexercise group and patients vs controls were found. Despite the
differences measured between patients and controls in clinical characteristics, no significant difference in FA was detected using cluster-based and JHU-ICBM-atlas-based approaches, although mean FA value calculated for whole skeleton was lower in patients (mean = 0.420, SD = 0.017) than in controls (mean = 0.422, SD = 0.013).

**Following the Intervention**

Clusters with significant increases in FA between the first and second measurement were found in the exercise group in the left corticospinal tract (LCST), the left superior longitudinal fascicle (LSLF), the left inferior longitudinal fascicle (LILF), the left inferior fronto-occipital fascicle (LIFOF), left anterior thalamic radiation (ATR) and in the body and splenium of the corpus callosum (CC) \( (p_{FWEcorr} < 0.05) \) (figure 1; table 2). Decreases in FA in these same clusters were found in the life-as-usual group. No significant differences in plasticity between patients and controls were found. These results were corrected for Family-wise error (FWEcorr) (for additional information see supplementary data).

Repeating the analysis with the JHU-atlas-based ROI analysis, significant increases in FA were found over time in the exercise group as compared to the nonexercise group (time by randomization) in the LCST \( (F = 4.15, P = .045) \), the LSLF \( (F = 5.092, P = .027) \) and FM \( (F = 5.687, P = 0.02) \) in both patients and controls (figure 2; table 3), but after the correction for the number of ROIs (14) in this analysis, the \( P \) threshold was set at \( .05/14 = .0035 \). Therefore, after the multiple comparison correction the results from the atlas-based analysis did not reach the corrected level of significance.

Significant differences in the exercise and nonexercise group from the first to second measurement (time by randomization) were found in the cardiorespiratory fitness parameters \( (W_{\text{peak}}, V_{\text{O2peak}}) \), and in PANSS scores decreases in overall PANSS score, positive symptoms, excitement score, and disorganization score in exercise group of patients, contrary to increases in the nonexercise group were demonstrated (table 1).

**FA with Cardiovascular Fitness, Oxygen Uptake, BMI, and IQ**

Significant correlations between longitudinal differences in \( W_{\text{peak}} \) (\( dW_{\text{peak}} \)) and both FA_skeleton \( \text{(dFA}_\text{skeleton}) \) \( (r = .246, P = .028, \text{two-tailed}) \) and FA_picked \( \text{(dFA}_\text{picked}) \) \( (r = .374, P = .001) \) were found irrespective of disease. For the maximal oxygen uptake measurement \( (\text{ie, } V_{\text{O2peak}}) \), a significant correlation was demonstrated only for the difference in overall FA values \( \text{(dFA}_\text{skeleton}) \) \( (r = 0.270, P = .016) \), and not for the FA difference in clusters showing longitudinal FA increase \( \text{(dFA}_\text{picked}) \). In patients, a decrease in positive symptoms over time \( \text{(dPANSS}_\text{pos}) \)
significantly correlated with FA improvement over time (dFA_{picked}) \((r = -0.455, \ P = .008)\).

There were no significant associations of FA or change in FA with BMI, HR_{max}, HR_{rest}, IQ in both groups and with overall PANSS, PANSS\_neg, PANSS\_dis, PANSS\_exc, PANSS\_emo, or ChE dose in the patients.

### Discussion

Our findings imply that practicing an overlearned physical skill (ie, biking) improves brain connectivity. Twice weekly physical training during a period of 6 months improved white matter integrity in fiber tracts—in particular those implicated in motor functioning. Importantly, both patients with schizophrenia and healthy controls benefitted equally from the repeated physical activity. These findings suggest that physical training of an overlearned skill can (continue) to improve structural connectivity of the brain, in healthy individuals and in patients with schizophrenia alike. Moreover, our findings also indicate that the capacity of the brain to reshape its structure remains preserved in schizophrenia.

Regular training on a bicycle thus improves the brain network and learning of a new—and often complicated—skill is not required for this training to be beneficial. This finding contributes to a growing literature on benefits of physical training on the brain in health\(^{14,18}\) and in disease, such as schizophrenia\(^{19}\) and early Alzheimer disease.\(^{42}\) It supports a growing literature that exercise therapy in patients with schizophrenia\(^{43,44}\) may be beneficial. In addition, it adds to earlier findings measuring FA following learning of a new skill (juggling).\(^{23}\) Moreover, a higher FA has been related to interhemispheric transition time measured with event-related potentials (ERP)\(^{45}\) and quantitative electroencephalography (EEG).\(^{46}\) Finally, as higher FA has been associated with better functional connectivity between anatomically distant gray matter regions using resting-state fMRI (functional MRI)\(^{35,47,48}\) and better functional connectivity has been associated with higher cognitive functioning,\(^{49,50}\) these findings may also extend to the nonphysical realm.

Specifically, the increase in connectivity was located in fiber tracts that are implicated in motor functioning. The CST represents the major fiber bundle for motor functioning, transferring information from multiple cortical areas to the brain stem and spinal cord.\(^{51}\) Both rodent and human studies suggest that maturation of the CST is driven by neural activity in cortical motor areas and limb experience, thus reflecting the need to adapt to changing motor demands.\(^{52,53}\) The SLF is a major association fiber bundle involved in higher aspects of motor behavior such as coding of body parts in the surrounding space and monitoring (competing) motor actions.\(^{54}\) Interestingly, the continuous exercise predominantly affects white matter in the left hemisphere specifically in right-handed individuals (for details see supplementary data). Finally, increasing FA in the CC suggests more efficient sensory, motor, and cognitive interaction taking place between the two hemispheres.\(^{55-57}\) Positive effects on both CC and CST are in line with previously conducted studies that showed higher number of streamlines count in youths with higher self-reported fitness levels in CST and anterior CC\(^{58}\) and the correlation between cardiorespiratory fitness parameters and FA suggested in healthy seniors,\(^{59}\) females and multiple sclerosis patients,\(^{60}\) but they have not been comprehensively demonstrated in a longitudinal setup. Thus, continuous practice of acquired physical skills improves fiber bundles in the brain implicated in primary and associative motor functioning.

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**Table 2. Increases in Fractional Anisotropy Following Physical Exercise**

<table>
<thead>
<tr>
<th>Index</th>
<th>Most prominent tracts in cluster</th>
<th>Corrected P value</th>
<th>Number of voxels</th>
<th>MNI coordinates of maximum intensity voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>LSLF, LCST, body, and forceps major of CC</td>
<td>.032</td>
<td>1533</td>
<td>X: -30, Y: -22, Z: 38</td>
</tr>
<tr>
<td>7</td>
<td>LILF, LIFO, LCST, LSLF</td>
<td>.032</td>
<td>1279</td>
<td>X: -41, Y: -35, Z: -4</td>
</tr>
<tr>
<td>6</td>
<td>LSLF, LCST</td>
<td>.044</td>
<td>218</td>
<td>X: -32, Y: -32, Z: 39</td>
</tr>
<tr>
<td>5</td>
<td>LCST, LSLF</td>
<td>.048</td>
<td>77</td>
<td>X: -28, Y: -17, Z: 19</td>
</tr>
<tr>
<td>4</td>
<td>ATR</td>
<td>.048</td>
<td>34</td>
<td>X: -20, Y: -32, Z: -3</td>
</tr>
<tr>
<td>3</td>
<td>CST</td>
<td>.048</td>
<td>13</td>
<td>X: -21, Y: -29, Z: 45</td>
</tr>
<tr>
<td>2</td>
<td>CST</td>
<td>.048</td>
<td>7</td>
<td>X: -20, Y: -31, Z: 50</td>
</tr>
<tr>
<td>1</td>
<td>SLF</td>
<td>.048</td>
<td>3</td>
<td>X: -37, Y: -7, Z: 38</td>
</tr>
</tbody>
</table>

*Note: ATR, anterior thalamic radiation; CC, corpus callosum; CST, corticospinal tract; LATR, the left anterior thalamic radiation; LCST, the left corticospinal tract; LIFOF, the left inferior fronto-occipital fascicle; LILF, the left inferior fronto-occipital fascicle; LSLF, the left superior longitudinal fascicle.*

*Based on the Threshold-free Cluster Enhancement (TFCE) method. Local statistical maxima of FA values increases in exercise group comparing to nonexercise group (clusters with \(P_{\text{FWEcorr}} < .05\) MNI coordinates showing the location of the maximum intensity voxel of each cluster.*
Physical Exercise Keeps the Brain Connected

Fig. 2. Whole tract white matter integrity and physical exercise. Increases in fractional anisotropy (FA) occur along the left corticospinal tract (CST), the left superior longitudinal fascicle (SLF), and the forceps major (FM) following the 6-months interval in the exercise as compared to nonexercise group. Color-coding represents change in mean FA over the interval (a). Results from the JHU-ICBM-atlas-based analysis measuring mean FA values from skeleton voxels over the entire tract (b).

Table 3. Effects of Intervention on Fractional Anisotropy*

<table>
<thead>
<tr>
<th>Fiber Tract</th>
<th>Intervention</th>
<th>Patients</th>
<th>Controls</th>
<th>Total</th>
<th>Change T6–T0</th>
<th>F, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left CST</td>
<td>Exercise</td>
<td>0.521 (0.014)</td>
<td>0.527 (0.020)</td>
<td>0.525 (0.019)</td>
<td>0.00271</td>
<td>4.15, .045</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0.526 (0.020)</td>
<td>0.528 (0.013)</td>
<td>0.527 (0.016)</td>
<td>-0.00257</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonexercise</td>
<td>0.529 (0.024)</td>
<td>0.519 (0.013)</td>
<td>0.523 (0.018)</td>
<td>-0.00257</td>
<td></td>
</tr>
<tr>
<td>Left SLF</td>
<td>Exercise</td>
<td>0.414 (0.014)</td>
<td>0.423 (0.014)</td>
<td>0.419 (0.014)</td>
<td>0.00256</td>
<td>5.09, .027</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0.418 (0.017)</td>
<td>0.425 (0.011)</td>
<td>0.422 (0.014)</td>
<td>-0.00145</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonexercise</td>
<td>0.417 (0.025)</td>
<td>0.418 (0.016)</td>
<td>0.417 (0.020)</td>
<td>-0.00145</td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>Exercise</td>
<td>0.513 (0.022)</td>
<td>0.517 (0.017)</td>
<td>0.513 (0.019)</td>
<td>0.00344</td>
<td>5.69, .020</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0.516 (0.021)</td>
<td>0.520 (0.015)</td>
<td>0.518 (0.018)</td>
<td>-0.00381</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonexercise</td>
<td>0.518 (0.024)</td>
<td>0.513 (0.030)</td>
<td>0.515 (0.027)</td>
<td>-0.00381</td>
<td></td>
</tr>
</tbody>
</table>

Note: CST, corticospinal tract; FA, fractional anisotropy; FM, forceps major of corpus callosum; GLM, general linear model; SLF, superior longitudinal fascicle.

*Based on JHU-ICBM-atlas based analysis—FA increases between baseline and follow-up in exercise group comparing to decreases of FA in nonexercise group. The GLM-repeated measurement design shows significant changes over time between two randomization groups (exercise vs nonexercise), irrespective of diagnosis (schizophrenia, healthy) ($P_{uncorr} < .05$).
The effects in the ILF, IFOF, and ATR imply that physical exercise may have consequences beyond motor functioning. All aforementioned tracts are involved in attention, visual processing, verbal processing and language functions, and face recognition as well as executive functioning and memory encoding, even though our study has not shown direct evidence of improvement in cognitive functions based on specific psychological tests. We do find that mental health outcome in patients recuperated after the period of exercise; specifically, alleviation of positive symptoms and increasing white matter integrity seemed to go hand-in-hand. This finding is in agreement with some studies reporting beneficial effects of exercise on schizophrenia symptoms, although others revealed no effect. Our results correspond with increased FA in visual spatial, motor control, and coordination-related connections in former master athletes suggesting the possible long-term benefit from physical activity. Finally, as these tracts are altered in schizophrenia and schizophrenia has recently been associated with altered brain plasticity, the relevance of physical exercise in patients is emphasized even further.

This study has several limitations that have to be taken into consideration. In patients implementation and sustainability of regular exercise commitment remains problematic due to poor motivation, side effects of medications, social barriers, and symptoms. Motivational techniques such as family member or caretakers involvement and customization of the exercise might improve adherence of the patients and highlighted the relationship between motivation, awareness of exercise benefits and self-efficacy. Another potential limitation is that no significant baseline differences between patients and controls in FA were found. Although this is consistent with some earlier studies, in a meta-analysis of DTI studies FA was lower in patients. Therefore we cannot predict how our findings will extend to patients with more severe white matter abnormalities, either through more or less prominent improvements in fiber integrity. Moreover, the influence of antipsychotic medication has to be taken into consideration. A positive influence of antipsychotic medication on glia cells and myelination has been demonstrated. However, we found no significant correlation between antipsychotic medication intake and FA in our study. Finally, ongoing exercise activity in subjects might be necessary to maintain the positive FA brain effects of exercise found in this study. If so, this raises the issue of motivation. As desirable as this might be in theory, one might wonder how easy in practice it is to incentivize schizophrenia subjects, in general, particularly, those with negative symptoms and motivational deficits, to embark on a lifelong commitment to exercising regularly.

The mechanisms underlying these plastic changes in FA following exercise are still difficult to explain. A growing body of evidence suggests possibly direct contributions of activation of fiber bundles to changes in white matter. Alternatively, the effect in white matter may be due to improvements in cardiorespiratory fitness, as suggested by positive associations between FA and cardiorespiratory fitness parameters over time. Moreover, these associations imply that changes are caused by practice of an overlearned aerobic activity rather than anaerobic newly learned exercise.

In conclusion, continuous regular practice of an acquired (physical) skill improves connectivity of the brain. The findings have important implications for understanding the effect of fitness programs on the brain in both healthy individuals and patients with schizophrenia.

Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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Conflict of Interest Statement
The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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