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Effects of Three Months of Aerobic Endurance Training on Motor Cortical Excitability in Schizophrenia Patients and Healthy Subjects

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Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that is widely used in the examination of excitability and inhibitory networks of the primary motor cortex (M1). A broad consensus has emerged that TMS is a valid method to quantify motor cortex plasticity in awake subjects [1–3]. TMS can be used to evaluate motor thresholds and the excitability of different inhibitory and excitatory intracortical networks. By evaluating changes in motor cortical excitability before and after a given intervention, different concepts of plasticity can be studied [4].

In schizophrenia, reduced motor cortical inhibition compared to healthy subjects has been shown, linking these system level effects to findings from postmortem studies displaying a GABAergic dysfunction in various cortical areas [3, 5]. However, not all studies have confirmed this finding of impaired cortical inhibition in schizophrenia [3]. Moreover, deficits in motor cortical plasticity have been established using TMS before and after various plasticity-inducing noninvasive brain stimulation techniques in schizophrenia patients [6]. For example, schizophrenia patients failed to show changes in motor cortical excitability following plasticity-inducing anodal transcranial direct stimulation [7], paired associated stimulation [8], or repetitive transcranial magnetic stimulation [9]. These single-session studies have been interpreted as model studies to discuss the theory of impaired plasticity and impaired inhibitory interneuron functions in schizophrenia.

Beyond these single-session studies using noninvasive brain stimulation, other studies applying different plasticity-inducing techniques have been able to show a plastic response in schizophrenia patients [10]. In this context, one should note that physical exercise is one of the possible modulators of plasticity as established in animal and, to a lesser extent, human research [11]. Aerobic exercise induces structural plasticity of the hippocampus [12] and the temporal lobe in schizophrenia patients [13] and has been associated with improvements in different clinical domains [14]. Remarkably, a recent meta-analysis established a beneficial effect of exercise on left hippocampal volumes in adults, whereas the effect was nonsignificant for total hippocampal volumes [15]. With regard to cognition, a recent meta-analysis revealed that exercise interventions can improve global cognition, working memory, social cognition, and attention in schizophrenia patients [16]. In a systematic review, positive effects of physical exercise in severe psychiatric illnesses were found predominantly on depressive symptoms and quality of life and only to a much lesser extent on psychotic symptoms [17].

However, despite the rich clinical data and the reported effects on hippocampal volumes, little is known about the biological and physiological effects of regular aerobic exercise in schizophrenia patients. As detailed above, TMS provides an entry point for an in vivo assessment of cortical physiology in awake subjects at the millisecond level and allows discussion of possibly involved neurotransmitter systems. Prior studies examining the effects of physical exercise in healthy adults using TMS measurements found evidence for exercise-induced plasticity. One study compared 14 active and 14 sedentary subjects using motor cortex TMS and showed a steeper recruitment curve, indicating increased cortical excitability in active subjects, but no differences in $GABA_A$-related short-interval intracortical inhibition (SICI) and in the $GABA_B$-related cortical silent period (CSP). Moreover, motor cortical plasticity using paired associated stimulation could only be induced in physically active subjects, pointing towards an association of exercise and spike time-dependent plasticity [18]. A one-time comparison between 15 elite badminton athletes and 15 novices revealed an increase in SICI and long-interval intracortical inhibition and a steeper recruitment curve in the physically more active group, showing the importance of the excitation/inhibition balance to promote plasticity [19]. As a final example, 13 karate athletes showed reduced resting motor thresholds (RMT) and higher motor-evoked potential (MEP) amplitudes compared to 13 control subjects [20], highlighting the effects of exercise on stabilization of the excitation/inhibition balance. Even though the exercise-induced effects in schizophrenia patients remain to be further understood, exercise therapy (e.g., endurance training and strength training) is becoming more and more established in the multimodal treatment of schizophrenia [16, 21, 22].

In this context, we conducted a monocentric clinical trial comparing the efficacy of 3 months (weeks 1–12) of endurance training (30 min, 3 times a week) combined with add-on computer-assisted cognitive remediation (CACR) training (30 min, 2 times a week) added after 6 weeks in 22 schizophrenia patients and 22 matched healthy controls [14]. 21 schizophrenia patients playing table soccer instead of endurance training served as a second control group. We were able to show that endurance training combined with CACR exclusively improved overall and everyday functioning as well as cognition [14]. Moreover, we could observe an increase in left supe-

rior, middle, and inferior anterior temporal gyrus volumes after endurance training in our schizophrenia patients [13] and the endurance capacity improved in this group [23]. These findings highlight that endurance training combined with CACR has the potential to induce plasticity responses in the cardiovascular system and structural brain adaptations in schizophrenia. To test whether endurance training can also induce functional plasticity related to inhibitory networks that have been shown to be impaired in schizophrenia, we also investigated motor cortical excitability before and after the intervention in a subgroup of our trial participants. To the best of our knowledge, the here presented study is the first to evaluate long-term exercise-induced plasticity using TMS measurements in healthy subjects and schizophrenia patients. We hypothesized that schizophrenia patients would display an inhibitory deficit at baseline compared to healthy controls and that both groups would show adaptive changes as a result of the intervention.

Methods

Participants and Intervention

Schizophrenia patients were recruited in the Department of Psychiatry and Psychotherapy of the University Medical Center Göttingen based on the following inclusion criteria: diagnosis of schizophrenia according to the MINI-Plus interview [24], age between 18 and 60 years, and a history of at least 2 confirmed psychotic episodes [14]. Exclusion criteria were: clinically relevant psychiatric comorbidities, verbal IQ <85 as tested by a multiple-choice vocabulary test, clinically relevant unstable medical conditions, involuntary hospitalization, pregnancy, and participation in systematic endurance training during the last 2 years (assessed via a questionnaire). The antipsychotic medication had to be stable for at least 2 weeks prior to the study. A total of 25 in- and out-patients and 27 healthy controls from the same geographical area matched for age, gender, and handedness were recruited between 2010 and 2013 for the clinical study [14]. We investigated a subgroup of 17 patients and 16 healthy controls receiving endurance training with the TMS protocol described below. The local ethics committee of the University Medical Center Göttingen approved the study protocol. All of the participants gave written informed consent prior to inclusion into the study. The trial is registered at www.clinicaltrials.gov (NCT01776112).

Patients and healthy controls participated in 3 months of aerobic endurance training, with three 30-min sessions per week. For both groups, bicycle ergometers (Ergobike Premium 8; Daum Electronic GmbH, Fürth, Germany) were used for the endurance training and a sport scientist monitored the training. The intensity was defined individually according to the baseline endurance capacity (equivalent to blood lactate concentrations of 2 mmol/L) following the continuous training method [25].

In order to determine the endurance capacity, we performed the incremental maximal exercise test before and after the training [23]. From the results, the physical working capacity (PWC in W/kg of bodyweight) was calculated at heart rates of 130 (PWC130) and 150 beats/min (PWC150) [23]. The mean training attendance was 88% in the schizophrenia group and 91% in the healthy group. After 6 weeks, both groups received additionally CACR training (30 min, 2 times a week). The detailed intervention protocol was previously published [14].

Evaluation of Cortical Excitability by TMS

For the here presented secondary analysis of the original study [14], we performed motor cortex TMS at baseline and after 3 months. All of the participants were seated in a comfortable chair with both arms supported passively. We recorded the electromyographic activity of the right and left first dorsal interosseous muscles. Using a Keypoint system (Medtronic, Denmark), raw signals were amplified and filtered with a band-pass filter of 2–10 kHz and digitized and recorded on a computer for off-line analysis. We used a standard figure-eight coil connected to a MagPro X100 magnetic stimulator (Medtronic) to perform TMS over the left and right primary motor cortices. The coil was placed over the respective stimulation area with the handle pointing backwards in a 45° angle. A suprathreshold intensity was used to determine the optimal stimulation point defined by a position that resulted in sufficiently large and stable MEP over the left or right hemisphere. These positions were marked on the scull to guarantee the same placement position throughout the experiments. RMT was defined as the lowest intensity that produced a reliable MEP ≥50 μV in relaxed first dorsal interosseous muscles in at least 5 out of 10 trials. S1mV was defined as the intensity to evoke an MEP of ~1 mV in peak-to-peak amplitude. Paired-pulse measures [26] were performed with interstimulus intervals of 3, 7, and 15 ms at an intensity of 80% RMT as conditioning and at S1mV as a test stimulus. Ratios of conditioned/unconditioned MEP were calculated (relative 3 ms [Rel 3 ms], 7 ms [Rel 7 ms], and 15 ms [Rel 15 ms]). We obtained at least 20 recordings for each interstimulus interval. CSP was measured at intensities of 120 and 150% RMT (CSP120 and CSP150, respectively) in tonically and voluntarily contracted first dorsal interosseous muscles in at least 10 recordings. CSP duration was defined as the time from MEP onset to return voluntary electromyographic activity [27].

Statistical Analyses

All analyses were carried out in SPSS23 (IBM, Armonk, NY, USA), with a significance level of $\alpha = 0.05$. Due to missing data and the resulting differences in sample sizes, we used the Kolmogorov-Smirnov test for each variable separately and we detected no significant deviations from normality assumption. Thus, we decided to perform parametric testing for this study. Demographic differences between groups were assessed using independent *t* tests and likelilood ratio χ^2 tests. Repeated-measures analyses of variance with the between-subject factor "group" and the within-subject factor "time" (before and after the exercise intervention) were performed to detect effects of the intervention within and between groups for the dependent variables RMT, S1mV, MEP amplitudes at S1mV, relative paired pulses at 3, 7, and 15 ms, and CSP120 and CSP150. Analyses were conducted separately for the left and right hemispheres. Only complete data sets for a given dependent variable were analyzed (please see Table 1 for the sample sizes for each variable). In the case of significant interactions or main effects, the post hoc observed power was calculated and partial η^2 (abbreviated: η^2) was specified as the effect size. Finally, correlations be-

Table 1. TMS results after 3 months of endurance training

Outcome measure	*N* (SZ/HC ratio)	SZ				HC				Group × time interaction		
		T0		T1		T0		T1				
		mean	SD	mean	SD	mean	SD	mean	SD	*F*	df	*p*
Left hemisphere												
S1mV, %	19 (7/12)	63.86	9.04	69.14	10.45	61.92	12.89	64.92	11.02	0.406	1, 17	0.533
RMT, %	19 (7/12)	54.00	9.13	57.29	8.28	52.58	11.00	54.67	9.60	0.123	1, 17	0.730
1-mV MEP, mV	27 (15/12)	0.92	0.51	1.17	0.51	1.06	0.67	0.90	0.39	3.001	1, 25	0.096
Rel 3 ms	27 (15/12)	0.46	0.31	0.52	0.43	0.40	0.51	0.40	0.27	0.193	1, 25	0.664
Rel 7 ms	27 (15/12)	1.25	0.65	1.27	0.38	1.15	0.70	1.32	0.85	0.185	1, 25	0.671
Rel 15 ms	27 (15/12)	1.70	0.88	1.69	0.87	1.48	0.98	2.21	1.37	1.608	1, 25	0.216
CSP120, ms	26 (14/12)	145.16	46.33	139.53	41.80	143.08	36.35	158.36	48.32	1.148	1, 24	0.295
CSP150, ms	21 (10/11)	167.21	51.30	203.16	39.52	195.67	49.12	209.40	52.79	1.358	1, 19	0.200
Right hemisphere												
S1mV, %	19 (7/12)	61.57	10.21	65.71	11.97	66.17	14.90	68.83	15.64	0.201	1, 17	0.660
RMT, %	19 (7/12)	53.43	8.32	56.71	11.71	55.33	12.11	58.00	12.81	0.028	1, 17	0.869
1-mV MEP, mV	26 (14/12)	0.95	0.54	1.14	0.70	0.76	0.34	0.96	0.54	<0.001	1, 24	0.989
Rel 3 ms	26 (14/12)	0.88	0.80	0.61	0.47	0.37	0.25	0.44	0.35	1.351	1, 24	0.257
Rel 7 ms	24 (12/12)	1.53	0.69	1.32	0.66	1.20	0.68	1.48	0.47	1.895	1, 22	0.183
Rel 15 ms	25 (13/12)	1.73	0.79	1.69	0.62	1.54	0.66	1.96	1.30	0.863	1, 23	0.363
CSP120, ms	21 (9/12)	142.72	29.34	150.98	57.40	143.35	38.48	151.11	35.95	0.001	1, 19	0.978
CSP150, ms	17 (7/10)	202.79	14.85	203.71	50.21	195.60	59.62	206.45	41.72	0.206	1, 15	0.656

TMS, transcranial magnetic stimulation; SZ, schizophrenia patients; HC, healthy controls; S1mV, stimulator intensity to evoke an MEP of ~1 mV in peak-to-peak amplitude; RMT, resting motor threshold; MEP, motor-evoked potential; Rel 3/7/15 ms, conditioned/unconditioned ratios at different interstimulus intervals (see main text for details); CSP20 and CSP150, cortical silent period at 120 and 150% RMT, respectively.

tween the after/before ratios of those dependent variables and the respective ratios of clinical variables were calculated. Tables 1 and 2 show mean values and SD.

Results

Baseline Comparison

Baseline values are displayed in Table 2. There were no significant differences between schizophrenia patients and healthy controls regarding the demographic data, including age, gender, handedness, and education level. The TMS measurements of the baseline visit showed no significant differences between the 2 groups. At baseline, schizophrenia patients showed a moderate psychopathology (with $PANSS_{positive}$ = 11.35 ± 4.96, $PANSS_{negative}$ = 18.00 ± 6.36, and $PANSS_{general}$ = 26.00 ± 10.54), were moderately to markedly ill (with Clinical Global Impression [CGI] score = 4.59 ± 0.80), and had a moderate symptom burden with (Global Assessment of Functioning [GAF] score = 59.53 ± 13.76). All of the patients were treated with antipsychotics and the mean CPZ equivalents were 860.80 ± 887.65 at baseline and 860.00 ± 853.81 at the end of the intervention ($t_{[16]}$ = –0.002, p = 0.998). Healthy controls showed higher PWC130 and PWC150 values (W/kg) compared to schizophrenia patients at baseline (Table 2) and after the intervention (PWC130: schizophrenia patients, 1.20 ± 0.46; healthy controls, 1.58 ± 0.27; $t_{[20.7]}$ = 2.715, p = 0.013; PWC150: schizophrenia patients, 1.64 ± 0.50; healthy controls, 2.09 ± 0.32, $t_{[22.1]}$ = 2.824, p = 0.01). Both groups showed an increase in PWC130 ($F_{[1, 26]}$ = 11.319, p = 0.002) and PWC150 ($F_{[1, 26]}$ = 27.404, p < 0.001) over time. This is in line with our previously reported findings and further details can be found elsewhere [23].

Excitability Changes Over Time

Repetitive measures ANOVA revealed no significant "time × group" interaction as displayed in Table 1. For S1mV over the left hemisphere, analyses showed a significant effect of time ($F_{1, 17}$ = 5.334, p = 0.034; observed power = 0.586, η^2 = 0.239) but no effect of group ($F_{1, 17}$ = 0.374, p = 0.549). Descriptive statistics indicated higher S1mV values in both groups after the intervention period

Table 2. Baseline values of the schizophrenia patients and healthy controls

	N (SZ/HC ratio)	SZ		HC		SZ vs. HC		
						LR	df	*p*
Demographics								
Patients	33 (17/16)							
Gender (male/female ratio)		12/5		13/3		0.515	1	0.473
Handedness (right/left ratio)		16/1		16/0		1.356	1	0.244
Smoking (yes/no ratio)		6/11		6/10		0.017	1	0.895
		mean	SD	mean	SD	*t*	df	*p*
Age, years	33 (17/16)	36.82	12.14	37.25	11.83	0.102	31	0.919
Education, years	33 (17/16)	15.56	4.13	16.31	4.44	0.505	31	0.617
BMI	33 (17/16)	26.06	5.67	23.29	3.49	1.681	31	0.103
Training attendance, %	33 (17/16)	88.23	11.00	91.32	7.09	0.951	27.52	0.344
PWC130, W/kg	32 (16/16)	1.04	0.33	1.41	0.33	3.142	30	0.004
PWC150, W/kg	32 (16/16)	1.41	0.38	1.84	0.35	3.362	30	0.002
TMS measurements (left hemisphere)								
S1mV, %	31 (15/16)	62.27	11.50	60.75	14.91	0.316	29	0.755
RMT, %	31 (15/16)	52.87	8.86	51.31	11.16	0.427	29	0.672
1-mV MEP, mV	33 (17/16)	0.99	0.53	1.05	0.61	0.293	31	0.771
Rel 3 ms	33 (17/16)	0.44	0.29	0.43	0.48	0.027	31	0.979
Rel 7 ms	33 (17/16)	1.38	0.83	1.20	0.66	0.665	31	0.511
Rel 15 ms	33 (17/16)	1.67	0.83	1.60	0.90	0.227	31	0.822
CSP control 120%, ms	33 (17/16)	150.33	48.03	148.38	34.11	0.134	31	0.894
CSP control 150%, ms	27 (14/13)	176.66	49.11	197.19	44.99	1.130	25	0.269
TMS measurements (right hemisphere)								
S1mV, %	31 (15/16)	62.53	9.11	64.44	16.06	0.402	29	0.691
RMT, %	32 (16/16)	51.75	7.69	54.38	12.34	0.476	30	0.476
1-mV MEP, mV	32 (16/16)	1.02	0.55	0.80	0.35	1.390	30	0.175
Rel 3 ms	32 (16/16)	0.79	0.77	0.48	0.32	1.497	20	0.150
Rel 7 ms	31 (15/16)	1.36	0.73	1.24	0.63	0.494	29	0.625
Rel 15 ms	32 (16/16)	1.65	0.79	1.54	0.58	0.465	30	0.645
CSP control 120%, ms	28 (12/16)	138.14	35.21	148.63	35.93	0.711	26	0.448
CSP control 150%, ms	23 (10/13)	200.27	32.55	196.75	53.66	0.183	21	0.857

SZ, schizophrenia patients; HC, healthy controls; PWC130 and 150, physical working capacity at 130 and 150 beats/min, respectively; MEP, motor-evoked potential; S1mV, stimulator intensity to evoke an MEP of ~1 mV in peak-to-peak amplitude; RMT, resting motor threshold; Rel 3/7/15 ms, conditioned/unconditioned ratios at different interstimulus intervals (see main text for details); CSP, cortical silent period; LR, likelihood ratio.

as displayed in Table 1. For CSP150 over the left hemisphere, a significant effect of time ($F_{1, 19} = 8.795$, $p = 0.008$; observed power = 0.803, $\eta^2 = 0.316$) could be found, but again there was no significant effect of group ($F_{1, 19} = 0.791$, $p = 0.385$). As displayed in Table 1, the duration of CSP150 increased in both groups over time. S1mV over the right hemisphere showed a trend towards an effect of time ($F_{1, 17} = 4.273$, $p = 0.054$) but no main effect of group ($F_{1, 17} = 0.201$, $p = 0.660$). All other main effect analyses showed no significant effects. Regarding the reported significant main effects, cautious interpretation is warranted because these results would not survive a multiple comparison correction for the extent of all performed repeated measures ANOVA.

As both S1mV and CSP150 over the left hemisphere showed a group-independent increase over time, we calculated the after/before ratios of both variables and tested for a possible correlation. This analysis showed no significant Pearson correlation for the complete sample ($n = 17$, overlap between both variables, $r = 0.002$, $p = 0.994$).

Moreover, we calculated the correlation between the after/before ratios of S1mV (n = 7) and CSP150 (n = 10) over the left hemisphere and the after/before ratios of all PANSS subscales, GAF, CGI, and CPZ equivalents in the schizophrenia patients, but we could not detect any significant correlation (all $p \geq 0.127$). Finally, we analyzed whether the PWC130 and PWC150 ratios (after/before) correlated with the left-hemisphere S1mV and CSP150 ratios, but we could not find a significant correlation for the complete study group (n = 18 for S1mV and n = 20 for CSP, all $p \geq 0.249$).

Missing Values

We had 2 dropouts in the schizophrenia group and 4 dropouts in the control group in the TMS part of the exercise study [14]. 1 of the schizophrenia patients stopped the complete trial due to a high workload and 1 patient completed the trial but did not complete the TMS experiments. These 2 patients had a moderate disease severity, with CGI = 4/GAF = 60 and CGI = 4/GAF = 71. One of the healthy controls became pregnant and stopped the complete trial, 1 stopped the trial for other reasons, and the 2 remaining subjects completed the trial but did not complete the TMS experiments. Due to missing entries in the database for S1mV and RMT at T1, the sample sizes are lower than for the other variables. The sample sizes for the physiological experiments of the right hemisphere were slightly lower compared to those of the left hemisphere, as experiments were first conducted on the left and then on the right hemisphere and as some subjects were not able to complete the full protocol. Lacking data for CSP150 can possibly be explained by the discomfort related to the high stimulation intensity. We have indicated the sample sizes for each investigated item at T0 and T1 in Tables 1 and 2.

Discussion

This is the first study investigating the impact of aerobic endurance training performed for 3 months on motor cortical excitability measures in healthy subjects and schizophrenia patients. While we were not able to detect a group-specific impact of the exercise intervention, our analyses showed an increase in S1mV and CSP150 over the left hemisphere in both groups. These findings indicate an increase in motor inhibition, which is in line with previous studies investigating the impact of different types of exercise between active and sedentary/nontrained subjects [18–20]. However, we could not detect an effect of our intervention on TMS paired-pulse measures like SICI of ICF and our sample size in the longitudinal analyses was limited. The most important difference to previous studies is that we investigated the effects of endurance training on motor cortical excitability over time before and after an intervention while other studies tested active versus nonactive subjects. Despite several limitations as indicated below, our study shows that the motor system of both sedentary healthy controls and schizophrenia patients is capable of showing adaptation to a long-term exercise/plastic stimulus. This is in line with other findings derived from this trial showing a clinical response, as well as cardiovascular and structural brain adaptations to our combined exercise and cognitive training intervention [13, 14, 23].

S1mV can be understood as a parameter reflecting the complex and transsynaptic network activation of corticospinal neurons, and several neurotransmitters (like glutamate, GABA, or serotonin) have been discussed to be involved [2]. The observed higher threshold to induce an MEP of approximately 1 mV after endurance training may point to either increased inhibitory or decreased facilitatory functions in the respectively involved interneuron networks. Unfortunately, we did not record recruitment curves, but this increase in S1mV may be cautiously interpreted a rightward shift of the recruitment curve. The increase in CSP150 over time can be interpreted as an increase in GABAergic (especially $GABA_B$) functions [2], pointing towards an increased inhibitory mechanism after endurance training. CSP is moreover considered as a parameter reflecting inhibitory motor cortical postsynaptic mechanisms within a cortical-striatal-pallidal-thalamical-cortical loop [2, 28], a network which has been shown to be deficient in schizophrenia patients and which is thought to be important for sensory gating and information processing [29, 30]. The increase in CSP can thus hypothetically be understood as an improvement of this network. CSP has been found to be unchanged, increased, and decreased in schizophrenia patients, depending on the disease stage, treatment aspects, and the intensity of stimulation [3, 29], and our findings add novel information to this variability. We could not detect this effect of aerobic endurance training on CSP120 (only a numeric increase in the healthy control group). We know that the duration of CSP is critically dependent on TMS intensity [31, 32], and one could speculate that the here displayed effect on CSP150 is a secondary effect of the increased S1mV. To test this hypothesis, we correlated the after/before ratios of both variables, but we detected no significant correlation; this allowed us to speculate that 2 differ-

ent adaptation mechanisms had been induced by the endurance training. The lacking correlations between cortical excitability measures and changes in PWC130/150 point towards different mechanisms for cardiovascular and neuronal adaptation to exercise, but due to the small sample sizes of these analyses these results must be interpreted with caution.

However, while interpreting these findings, the reader should be aware that: (1) we did not detect any baseline differences in cortical excitability between groups, (2) our findings were limited to the left hemisphere, and (3) we did not find an effect of the training intervention on paired-pulse measures. Moreover, one could hypothesize that the higher stimulation intensity reduced the well-established intersubject differences in CSP duration and resulted in more stable recordings, especially in our long-term longitudinal design. Especially the lacking baseline differences are surprising, because a reduced SICI in schizophrenia patients has been established in one meta-analysis [33] and because inhibitory deficits are one core feature of the motor-cortex physiology in this population [6]. However, as outlined in a systematic review, not all studies comparing motor cortical excitability between healthy controls and schizophrenia patients detected differences between groups [3] – reasons might be differences in target variables, stimulation parameters, medication patterns, comorbid substance abuse, and disease stages. Reviewing descriptive data of our study, ICF of both hemispheres and SICI of the right hemisphere seemed to be (as expected) lower in healthy controls without being significantly different between groups. This pattern could be understood as motor cortical disinhibition and the lacking differences may be due to the modest sample size of our trial. Moreover, we choose a relatively high conditioning pulse of 80% RMT for paired-pulse measures to allow for stable measurements over time that could have resulted in floor and ceiling effects revoking group differences. Further limitations need to be considered with regard to our findings. Our long-term design as part of a controlled study is on the one hand an advantage, allowing for the first time investigation of the impact of a long-term plastic stimulus on motor cortex excitability in schizophrenia patients. However, longitudinal TMS measures have the risk of high outcome variability, and the 3-months period between baseline and follow-up may explain in parts our results (especially the increase in S1mV). Due to the long follow-up period, we lost several patients and items over time, leading to a reduced sample size in the linear models (Table 1). Thus, this limits the power of our analyses and may explain parts of the negative findings. Moreover, our reported significant effects of S1mV and CSP150 of the left hemisphere are based on a reduced number of subjects with longitudinal data. Thus, these effects need to be interpreted with caution. Next, this is a secondary analysis as part of a clinical trial and therefore our results should be considered as exploratory. We also did not investigate the table soccer group of the original study as we assumed that table soccer will be a strong plastic stimulus for the motor system and as we did not have a healthy table soccer control group. From the perspective of the intervention, we did not test motor cortex excitability after 6 weeks. As endurance training was combined with cognitive remediation from week 6 to week 12 and as we tested motor cortex excitability after week 12, we cannot disentangle whether the here observed findings could be allocated to the endurance training alone or whether the combination of both interventions resulted in the adaptive brain changes. Next, we had several missing variables due to the clinical trial setting of our physiological experiments, resulting in modest sample sizes for each analysis. We tested the observed power and the effect sizes for our 2 significant findings, indicating a sufficient sample size for the here presented analyses. Finally, one should note that our findings would not survive correction for the number of RM-ANOVA performed here.

To conclude, we showed for the first time that endurance training over 3 months can induce adaptive changes in the motor cortex of healthy subjects and schizophrenia patients. The latter effect is remarkable as single-session studies inducing plasticity using noninvasive brain stimulation could not show such an adaptation process in schizophrenia patients [6]. However, structural brain plasticity has been established following different exercise interventions in schizophrenia patients [15] and our findings could also be interpreted as a plastic response to long-term aerobic endurance training in schizophrenia patients.

Disclosure Statement

The authors deny any potential conflict of interests as it relates to the subject of this report. A.R., B.M., K.L., M.L., K.K.V., T.S.-A., and A.S. do not report any conflict of interests. T.W. has received paid speakerships from Alpine Biomed, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, I3G, Janssen-Cilag, Novartis, Lundbeck, Roche, Sanofi-Aventis, Otsuka, and Pfizer, has accepted travel or hospitality not related to a speaking engagement from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, and Sanofi-Synthelabo, and has received restricted research grants from AstraZeneca, Cerbomed, I3G, and AOK (health insurance company). P.F. was an honorary speaker for Janssen-Cilag, AstraZeneca, Eli

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