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Exercise as an add-on treatment in individuals with schizophrenia: Results from a large multicenter randomized controlled trial

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ABSTRACT

Current treatment methods do not achieve recovery for most individuals with schizophrenia, and symptoms such as negative symptoms and cognitive deficits often persist. Aerobic endurance training has been suggested as a potential add-on treatment targeting both physical and mental health. We performed a large-scale multicenter, rater-blind, parallel-group randomized controlled clinical trial in individuals with stable schizophrenia. Participants underwent a professionally supervised six-month training comprising either aerobic endurance training (AET) or flexibility, strengthening, and balance training (FSBT, control group), follow-up was another six months. The primary endpoint was all-cause discontinuation (ACD); secondary endpoints included effects on psychopathology, cognition, functioning, and cardiovascular risk.

In total, 180 participants were randomized. AET was not superior to FSBT in ACD and most secondary outcomes, with dropout rates of 59.55% and 57.14% in the six-month active phase, respectively. However, both groups showed significant improvements in positive, general, and total symptoms, levels of functioning and in cognitive performance. A higher training frequency additionally promoted further memory domains. Participants with higher baseline cognitive abilities were more likely to respond to the interventions.

Our results support integrating exercise into schizophrenia treatment, while future studies should aim to develop personalized training recommendations to maximize exercise-induced benefits.

Clinical Trials Registration: The study was registered in the International Clinical Trials Database, ClinicalTrials.gov (NCT number: NCT03466112, https://clinicaltrials.gov/ct2/show/NCT03466112?term=NCT03466112&draw=2&rank=1) and in the German Clinical Trials Register (DRKS-ID: DRKS00009804).

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1. Introduction

"Walking is man's best medicine" according to Hippocrates. Can exercise also be used as an effective add-on treatment in individuals with schizophrenia?

Schizophrenia is a severe disorder that represents a substantial burden for affected individuals. Its typical onset is in late adolescence or early adulthood and its course is usually characterized by recurrent episodes of positive symptoms, such as hallucinations or delusions, which can be treated effectively with antipsychotics. However, in most patients other features of the disorder, such as cognitive impairments and negative symptoms, persist despite guideline-based medication, result in low levels of clinical recovery and continuously affect individuals' daily lives (Fusar-Poli et al., 2015; Nielsen et al., 2015). Both cognitive impairments and negative symptoms have a severe impact on occupational and social functioning and therefore are the primary contributors to the poor outcomes of schizophrenia (Green, 2016). Overall, current treatment methods do not achieve favorable functional outcomes in the majority of people with schizophrenia. Functional recovery is a multidimensional concept covering psychosocial aspects such as living independently, being able to work and engage relationships (Jääskeläinen et al., 2013; Liberman et al., 2002) and is usually considered as a cornerstone for personal recovery (ie, the subjectively evaluated process of coping with symptoms over time, quality of life, confidence and hope) (Roe et al., 2011; Vita and Barlati, 2018). To address these outcome measures, psychosocial interventions such as social skills training, psychoeducation or family interventions have been developed. Exercise could be another add-on therapy to improve not only clinical symptoms but also to facilitate recovery in schizophrenia.

Another unmet need in individuals with schizophrenia is their greatly increased risk for physical comorbidities. Individuals with schizophrenia generally engage in lower levels of physical activity and consequently have lower fitness levels than the general population (Vancampfort et al., 2017). Physical inactivity and antipsychotic-associated weight gain contribute to a markedly increased prevalence of metabolic syndrome, diabetes, and cardiovascular diseases in individuals with schizophrenia (Firth et al., 2019). In turn, metabolic syndrome, diabetes, and cardiovascular diseases have a strong influence on premature morbidity in individuals with schizophrenia, whose life expectancy is at least ten years less than that of the general population (Laursen et al., 2019). Therefore, novel treatment options are needed to further improve the outcome of individuals with schizophrenia.

In the general population, exercise has long been established as one of the main ways to promote physical and mental health. Animal models have also contributed to our understanding of the cognition-enhancing and neurotrophic effects of exercise (van Praag et al., 2005). The potential beneficial impact of exercise on both physical health and psychiatric symptoms has led to increasing interest in exercise as a novel add-on therapeutic approach in individuals with schizophrenia, and a growing number of clinical trials have investigated this topic. In 2010, our group conducted a first landmark study in which eight male patients with schizophrenia performed a 12-week endurance training consisting of three 30-min sessions per week on a bicycle ergometer. The control group consisted of eight male patients with schizophrenia playing table soccer for the same amount of time. We assessed neurocognitive performance before and after the training and found improvements in short-term memory and negative symptoms in the intervention group only (Pajonk et al., 2010). In a subsequent study from 2015, 21 patients with schizophrenia took part in a similar exercise intervention combined with additional cognitive training after six weeks. Again, we observed increases in psychosocial function and cognitive performance (Malchow et al., 2015). Several studies have identified improved aerobic fitness as an important moderator of the beneficial effects of exercise in people with schizophrenia (Maurus et al., 2022a,b; Sabe et al., 2019). Summarizing previous findings, meta-analyses have concluded that exercise may have the potential to improve symptom severity, cognition, quality of life, and global functioning (Dauwan et al., 2021; Shimada et al., 2022).

Although aerobic exercise has been the most widely studied type of intervention, the literature is inconclusive on which type of exercise may be the most beneficial (Yu et al., 2022). With respect to physical outcomes, exercise alone did not reliably improve cardiovascular risk factors across trials (Firth et al., 2019). However, most meta-analyses indicated that only preliminary conclusions can be drawn because of the design of the underlying studies. Previous exercise trials in schizophrenia were often small in sample size and heterogeneous regarding participant characteristics, duration, exercise modalities, and outcome measures. Many studies also lacked exact training parameters, an appropriate control group or randomization and blinding procedures. Moreover, all exercise trials to date have been monocentric, further limiting the generalizability of study results. Thus, despite some promising findings, it remains unclear whether exercise is an effective add-on treatment in individuals with schizophrenia.

To this end, we performed the largest multicenter randomized controlled clinical trial so far on this topic. Our study implements an adequate sample size recruited at several sites, an external monitoring and organizational structure, a validated training methodology, and lactate testing to determine exercise parameters. Building on our previous studies on this topic (Malchow et al., 2015; Pajonk et al., 2010), the interventions under investigation were adapted to present evidence-based knowledge and recommendations regarding the weekly exercise amount (Garber et al., 2011). The total exercise duration was furthermore extended to six months and the subsequent 6-month follow-up will allow us to analyze the long-term effects of exercise interventions.

The main aim of this trial was to investigate the efficacy of aerobic endurance training (AET) performed up to three times a week for six months by the intervention group and flexibility, strengthening, and balance training (FSBT) performed for the same amount of time by the control group by comparing all-cause discontinuation (ACD) between groups as the primary endpoint. Secondary outcomes were psychopathological symptoms, cognitive performance, level of functioning, and quality of life. Additionally, we explored exercise-induced effects on cardiovascular risk factors. We hypothesized that AET would be superior to FSBT in improving physical and mental health outcomes in individuals with schizophrenia. Showing that aerobic endurance exercise can alleviate disease impairment and contribute to a more favorable disease outcome would provide support for this type of exercise as an effective add-on treatment in schizophrenia.

2. Methods

2.1. Study design

The ESPRIT (Enhancing Schizophrenia Prevention and Recovery through Innovative Treatments) C3 study presented here was a multicenter, rater-blind, parallel-group, two-arm randomized controlled clinical trial. See Supplement (S) 1 for details on the ESPRIT network. In the present study, participants were randomly assigned to either AET on bicycle ergometers as the intervention or FSBT as the control (study design displayed in S2).

The study was conducted at five tertiary hospitals in Germany (LMU Munich, ZI Mannheim, Charité Berlin, HU Dusseldorf, and RWTH Aachen University). Participant screening and enrolment were performed by medical sub-investigators at the individual study centers. Before starting the study, participants provided written informed consent. All study procedures complied with the Declaration of Helsinki and were approved by the local ethics committees of the participating centers. For details on the randomization process and databank management see S3.

2.2. Participants

The study included male and female in- and outpatients aged 18 to 65 years with a primary diagnosis of schizophrenia as assessed by the Mini-International Neuropsychiatric Interview (Version 6.0.0) (Sheehan et al., 1998). Further inclusion criteria were a total Positive and Negative Syndrome Scale (PANSS) score less than or equal to 75, indicating a post-acute disease phase and stable psychopathology; and stable treatment with one or two antipsychotics. Exclusion criteria included severe comorbidities that prevented regular participation in the study procedures or current drug abuse. Further details can be found in the publication of the study protocol (Maurus et al., 2020) and in S4.

2.3. Exercise protocol

Before randomization, study participants completed the baseline assessments, which included lactate threshold tests on bicycle ergometers to assess aerobic fitness levels and determine exercise intensity in the intervention group. After randomization, the participants performed the six-month AET or FSBT training and were subsequently followed up for another six months. In both groups, training duration and frequency were based on current recommendations from the American College of Sports Medicine (ACSM) (Garber et al., 2011) and on our experience from previous exercise trials (Malchow et al., 2015; Pajonk et al., 2010).

Both groups participated in up to three training sessions per week for six months. To reduce the risk of injury, each session included a five-minute warm-up and five-minute cool-down phase at 80% intensity of the main training session. Additionally, the total duration of the training sessions increased gradually from 40 min in weeks one to six to 45 min in weeks seven to 12 and 50 min in weeks 13 to 26. In both groups, a maximum of three participants attended the exercise sessions, which were led by trained study staff and supervised by a sports scientist. During each session, study staff documented participants' heart rate and subjective exertion with the Borg scale (Borg, 1982).

2.3.1. Intervention group

The intervention group performed AET on bicycle ergometers. Participants cycled constantly at the wattage level determined by the baseline individual lactate threshold test. The wattage level was chosen such that study participants had a blood lactate concentration of approximately 2 mmol/L, indicating a predominantly aerobic metabolic exercise intensity. In general, participants should have found this exercise intensity slightly strenuous but should have still been able to talk without being short of breath. Every four weeks, lactate concentrations were measured and the training intensity was adjusted, if necessary.

2.3.2. Control group: FSBT

The control group performed FSBT according to Liu-Ambrose et al. (2010). As described in a standardized catalog, FSBT combined exercises targeting flexibility/mobility, stability, balance, and relaxation. Unlike in the intervention group, exercise intensity was not defined by the baseline lactate threshold test. Instead, participants were encouraged to perform the exercises as correctly as possible. If a participant was able to perform an exercise constantly with only little effort, the training staff modified the exercise to increase its difficulty (e.g., crunches with arms on the chest was modified to crunches with arms folded behind the head). Furthermore, confounders were minimized by using the same training frequency, duration, setting, documentation, and professional supervision as in the intervention group.

2.4. Outcomes

In all ESPRIT trials, the primary endpoint is ACD, evaluated at each study visit. Five different sub-criteria were specified: relevant worsening of schizophrenia symptoms (total PANSS score $>$ 75 for more than 14 days), occurrence of severe adverse events, non-adherence with the training program for more than six weeks, withdrawal of consent to participate in the training, or inability to reach the participant (see S5 for details on the choice of primary outcome and S6 for sample size calculation).

Secondary outcomes were assessed at baseline (BL), after three months of exercise training (3 m), after six months of exercise training (6 m), and after the six-month follow-up period (12 m). As summarized in Table 1, they included ratings of schizophrenia symptoms, cognitive performance, level of functioning, quality of life, cardiovascular risk factors, and physical fitness (determined in lactate threshold tests, see S7 and (Maurus, 2022)). To facilitate interpretation of the results, neurocognitive ratings that comprised subtests assessing the same cognitive domain were summarized as sum scores. Additionally, a global cognition score was generated (for details on cognitive tests and sum scores, see S8).

2.5. Safety assessment

The safety of both types of exercise was assessed by recording adverse events.

2.6. Statistical analyses

Data were analysed with IBM SPSS Statistics for Windows Version 28 (28.0.1.1), Rstudio V4.2.1 (RStudio Team, 2020) and Stata 17.0 (StataCorp LLC, College Station, TX, USA). The primary endpoint (ACD) was evaluated in the intention-to-treat 1 (ITT1) sample, which included all randomized study participants. To examine group differences in the ACD rate at a two-sided significance level of 5%, Kaplan-Meier curves were created by a log rank test and a stratified Cox regression with the main effects group (AET vs. FSBT), chlorpromazine equivalents, age, and sex was calculated across study sites.

All analyses of secondary outcomes were performed in the ITT2 sample and in the per-protocol (PP) sample. The ITT2 sample included all randomized patients who had participated in at least one training and one of the following main visits after three, six months or twelve months. The PP sample included all patients who received at least 50% of the randomized study treatment, had participated in at least one of the main visits and experienced no significant protocol violations.

To investigate effects of exercise on secondary outcomes, linear mixed effect models for repeated measures with the corresponding change from baseline score as dependent variable and the factors group (AET vs. FSBT), time (3 m, 6 m, and 12 m), study site (Munich, Mannheim, others), sex, age, chlorpromazine equivalents, number of training sessions up to the respective visit, years of education, outcome score at baseline, and time x group interaction were calculated. As predefined in the study protocol, data from study sites with fewer than eight participants were pooled. P values of the factor group were corrected with the false discovery rate (FDR) method (Benjamini and Hochberg, 1995). In case of a significant group effect after FDR correction, one-sample t-tests on the marginal means of the change scores were performed within groups for each timepoint. Similarly, the marginal means of the change scores for each time point across both exercise groups were evaluated to assess the effectiveness of the exercise training in general. Statisticians were blinded to group assignments while transforming and analyzing the data.

Several additional exploratory analyses were calculated. We used multiple linear regressions to examine the influence of baseline participant characteristics on exercise adherence (S21).

Moreover, we investigated whether improvements in fitness levels mediated the effects of exercise on secondary outcomes using mediation analyses. To further explore the relationship between both the number of training sessions completed and improvements in fitness levels, and the extent of improvements in secondary outcomes during the trial we used multiple linear regressions (S22, S23).

Last, we also analyzed the proportion of participants that had at least

Table 1
Secondary outcomes.

	Abbreviation	Details of assessed domains
Clinical symptom ratings		
Positive and Negative Syndrome Scale (1)	PANSS	Positive, negative, general, and total symptoms
Calgary Depression Scale for Schizophrenia (2)	CDSS	
Clinical Global Impression (3)	CGI	
Neurocognitive ratings		
Rey Auditory Verbal Learning Test (4)	VLMT	Verbal declarative memory
Digit Span Test (5)	DST	Short-term and working memory
Brief Cognitive Assessment Tool for Schizophrenia (6)	B-CATS	Verbal fluency
Digit Symbol Substitution Test (7)	DSST	Processing speed, learning, and memory
Pictures of Facial Affect Recognition Test (8)	PFA	Emotion recognition
Trail Making Tests A and B (9)	TMT-A,-B	Visual scanning, processing speed, cognitive flexibility, and working memory updating
Functioning in daily life		
Functional Remission of General Schizophrenia (10)	FROGS	
Social and Occupational Functioning Assessment Scale (11)	SOFAS	
Personal and Social Performance Scale (12)	PSP	
Global Assessment of Functioning scale (13)	GAF	
Quality of life		
World Health Organization Quality of Life-Bref (14)	WHOQOL	Life satisfaction, health satisfaction, social, psychological, physical, and environmental quality of life
Cardiovascular risk and protective factors		
Body mass index, kg/m^2	BMI	
Waist circumference, cm		
Aerobic fitness level, watt/kg		Achieved wattage at aerobic threshold divided by body weight
International Physical Activity Questionnaire (15)	IPAQ	
Laboratory assessments:		
Triglycerides, mg/dL		
Total cholesterol, mg/dL		
High-density lipoprotein cholesterol, mg/dL	HDL	
low-density lipoprotein cholesterol, mg/dl	ldl	
hemoglobin a1c,%	hba1c	
Fasting glucose, mg/dL		

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a 25% improvement in the PANSS total score (responders at the symptom level (Leucht et al., 2007)) and an improvement of at least ten points on the GAF scale (responders at the functional level (Endicott et al., 1976)) from the baseline visit to the visit after six months of exercise. In addition, we used linear regressions to investigate whether responders at the symptom or functional level could be distinguished from non-responders by baseline characteristics (S24).

3. Results

Study participants were recruited between 22 July 2016 and 15 December 2021, and data acquisition, including follow-up, was completed on 15 December 2022. In total, 180 individuals diagnosed with schizophrenia were randomly assigned to either the AET intervention group (89 participants) or the FSBT control group (91 participants; CONSORT Flow Diagram in S9). Participant baseline demographic and clinical characteristics are displayed in Table 2.

Table 2
Demographic characteristics.

		AET		FSBT	
n		89	49.44%	91	50.56%
Sex	Female	36	40.45%	41	45.05%
	Male	53	59.55%	50	54.95%
Age, y		m	SD	m	SD
		36.84	11.83	37.90	12.15
Site	Munich	51	28.33%	54	30.00%
	Mannheim	26	14.44%	25	13.89%
	Berlin	7	3.89%	7	3.89%
	Aachen	2	1.11%	1	0.56%
	Dusseldorf	3	1.67%	4	2.22%
Education years, y		m	SD 3.54	m	SD 3.94
		14.23		14.34	
Disorder duration, y		m	SD	m 8.73	SD 9.60
		10.44	10.03		
CPZ		m	SD	m	SD
		466.26	297.77	464.59	295.92
BMI, kg/m^2		m	SD 5.78	m	SD 5.41
		28.61		28.19	
BMI category	Normal	26	29.55%	32	35.16%
	Overweight	30	34.09%	25	27.47%
	Obese I	16	18.18%	25	27.47%
	Obese II	16	18.18%	9	9.89%
Waist circumference, cm	Women	m	SD	m	SD
		98.24	18.82	104.90	13.25
	Men	m	SD	m	SD
		106.12	14.45	105.81	18.36

Table 2 shows demographic characteristics of the ITT1 sample (all randomized participants).
AET, aerobic endurance training; BMI, body mass index; CPZ, chlorpromazine equivalents; Education years, school years and vocational training in total; FSBT, flexibility, strengthening and balance training; m, mean.

All 180 individuals were included in the ITT1 sample and analyzed for the primary outcome. ACD over the 12-month study was not significantly different in the AET and FSBT groups (29.21% vs. 35.16%, respectively; hazard ratio [HR] 1.06, 95% CI 0.74–1.53). During the 12-month study period, 67.78% of participants met one of the ACD criteria (Fig. 1). Furthermore, 59.55% of the AET group and 57.14% of the FSBT group dropped out of the study during the six-month active study phase. A high number of participants dropped out in the early phase of the study, but the number of participants remained more stable as the study progressed. For details on the number of training sessions performed, see S10.

All analyses of secondary outcomes were performed in the ITT2 sample ($n = 92$, all randomized patients who had participated in at least one training and at least one of the following main visits), and in the per-protocol sample ($n = 45$, patients who received at least 50% of the randomized study treatment and were assessed in at least one of the following main visits).

As secondary outcomes, we investigated changes in clinical symptomatology during the six-month active study phase and after another six months of inactive follow-up.

At baseline, individuals in our sample had a mean PANSS total of 50.26 (SD 11.81), which indicates a stable phase of the illness. During the subsequent study course, we observed a tendency for a group effect of change in the PANSS positive subscale for the FSBT group (F (1.57, 57) = 6.83, $p = 0.015$, p(FDR) = 0.059). Thus, the FSBT group seemed to be superior to the AET intervention in improving schizophrenia positive symptomatology. There were no other statistically significant differences between the groups (S11, S13). However, we saw significant time effects across both groups (Table 3, S12, S14).

In the ITT2 sample, positive, general, and total symptom scores improved significantly from baseline to the follow-up (Table 3, Fig. 2), accompanied by trends for the positive, general and total PANSS scores at the end of the six-month active study phase and for the PANSS negative scores from baseline to follow-up. In the PP sample, time effects were significant already at earlier study visits.

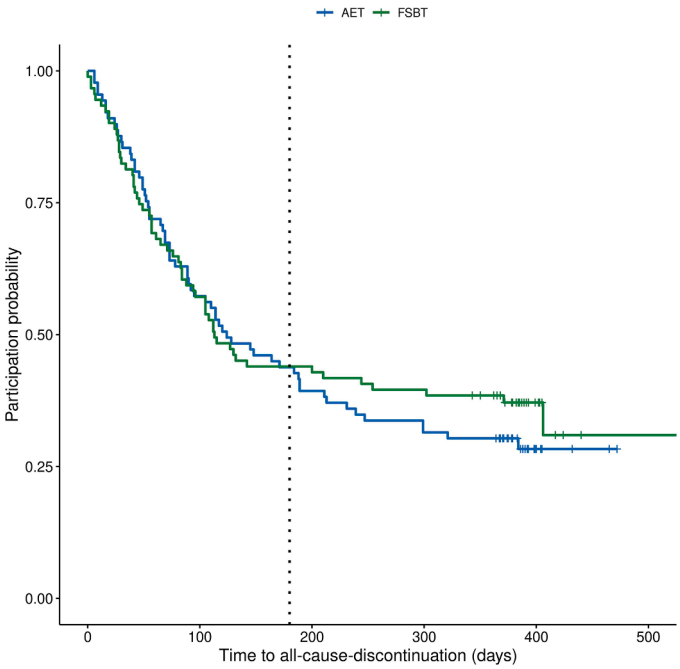

Fig. 1. All-cause discontinuation rates.
Fig. 1 shows the Kaplan-Meier curves regarding all-cause discontinuation (ACD) rates in the intention-to-treat 1 sample (all randomized participants). Results from the aerobic exercise training group are shown in blue and results from the flexibility, strengthening, and balance training control group in green. The x-axis represents the time until ACD in days and the y-axis, the participation probability. The dotted line depicts the end of the six-month active study phase.

The improvements in PANSS total corresponded to an absolute change of 6•4 points (95% CI 1•02-11•83) in the AET and 6•9 points (95% CI 2•50-11•30) in the FSBT group. In conclusion, participants in both exercise groups showed improvements in symptomatology beyond their already stable state at baseline.

By contrast, we found no significant changes in Calgary Depression Scale for Schizophrenia or Clinical Global Impression scores in any group (S11-S14, S15).

Further secondary outcomes included neurocognitive ratings. We found no significant group effects of change that would indicate a superiority of AET or FSBT in enhancing cognitive performance in individuals with schizophrenia (S11, S13). At the same time, participants across both groups achieved significant improvements in several ratings (Table 3). Taken together, our results showed an improved performance in cognitive flexibility (Trail Making Test global), verbal declarative short-term memory (Verbal Learning and Memory Test short-term memory), and global cognition (global cognition composite score) in the ITT2 sample from baseline to the end of both the active study phase and the follow-up period (Fig. 3).

In the PP sample, we found additional improvements in working memory (Digit Span Test working memory), long-term memory (Verbal Learning and Memory Test long-term and difference score) and a tendency for additional improvements in processing speed (Digit Symbol Substitution Test).

There were no robust changes in emotion recognition (Pictures of Facial Affect recognition test), short-term memory (Digit Span Test short-term memory), or verbal fluency (Brief Cognitive Assessment Tool for Schizophrenia).

While we found no significant group effects of change, the ITT2 and PP sample also improved in assessments of daily functioning. Participants achieved significantly higher scores in the Global Assessment of Functioning and Functional Remission of General Schizophrenia scales at the end of both the active study phase and the follow-up period (Table 3, S16).

In the Personal and Social Performance scale and in the Social and Occupational Functioning Assessment, we found no significant effects in neither the ITT2 nor PP sample (S12, S14). Although almost all subscales of the WHOQOL-Bref showed slight increases (S17), there were also no statistically significant group effects of change nor time effects (S11-S14). In conclusion, neither AET nor FSBT resulted in robust increases in quality of life.

To investigate effects on physical health, we assessed several cardiovascular risk factors. The mean body mass index in our sample was 28.40 kg/m^2 (SD 5.58), signifying overweight (Table 2), and the mean waist circumference was also elevated (men, 106.21 cm [SD 16.51]; women, 101.35 cm [SD 16.14]), a key sign of metabolic syndrome. We found neither statistically significant group effects of change nor time effects in any of the behavioral or metabolic risk factors (S11-S14, S18).

However, Mediation analyses showed that participation in the AET group led to enhancements in aerobic fitness levels, which in turn led to improvements in PANSS general (average causal mediation effect [ACME] = −1.26, $p = 0.006$, p [FDR] = 0.040) and total scores (ACME = −0.99, $p = 0.010$, p [FDR] = 0.040).

Moreover, multiple linear regressions revealed a significant positive relationship between improvements in fitness and social and occupational functioning as assessed with the SOFAS ($p = 0.001$). In addition, we found a trend for a positive relationship between improvements in fitness and general functioning as assessed by the GAF ($p = 0.087$) (S22).

Between training adherence and the secondary outcomes, there was a positive relationship between the number of training sessions completed and improvements in DST working memory ($p = 0.034$), but we found no evidence of a direct relationship between the number of training sessions and changes in other cognitive assessments, PANSS scores or functioning ratings (S23).

Table 3
Test statistics for significant effects on secondary outcomes across both groups.

Outcome	Contrast	Mean	SE	Df	CI low	CI high	p (t)	p (FDR)
ITT2 SAMPLE								
Clinical variables								
PANSS positive	BL – 3m	−1.10	0.55	105.96	−2.19	−0.02	**0.046**	0.069
PANSS positive	BL – 12m	−1.71	0.44	61.26	−2.58	−0.84	**0.000**	**0.000**
PANSS negative	BL – 12m	−1.43	0.59	62.27	−2.61	−0.26	**0.017**	0.051
PANSS general	BL – 6m	−1.48	0.71	85.01	−2.89	−0.08	**0.039**	0.059
PANSS general	BL – 12m	−2.23	0.78	71.44	−3.79	−0.66	**0.006**	**0.018**
PANSS total	BL – 6m	−2.92	1.36	68.55	−5.63	−0.21	**0.035**	0.053
PANSS total	BL – 12m	−5.22	1.46	63.82	−8.14	−2.30	**0.001**	**0.003**
Cognition								
TMT global	BL – 6m	0.20	0.08	91.87	0.04	0.36	**0.014**	**0.026**
TMT global	BL – 12m	0.18	0.09	96.78	0.00	0.36	**0.017**	0.026
PFA	BL – 3m	0.28	0.14	80.36	0.01	0.55	**0.044**	0.132
VLMT stm	BL – 12m	0.37	0.13	80.09	0.11	0.62	**0.006**	**0.018**
Cognition global	BL – 6m	0.11	0.04	76.89	0.02	0.19	**0.012**	**0.036**
Cognition global	BL – 12m	0.12	0.05	63.26	0.01	0.23	**0.029**	**0.044**
Functioning								
GAF	BL – 12m	4.44	1.79	70.00	0.88	8.00	**0.015**	**0.045**
FROGS	BL – 12m	2.52	1.17	74.00	0.19	4.84	**0.034**	0.080
PP SAMPLE								
Clinical variables								
PANSS positive	BL – 6m	−1.29	0.54	39.98	−2.37	−0.20	**0.021**	**0.032**
PANSS positive	BL – 12m	−1.80	0.60	28.50	−3.04	−0.57	**0.006**	**0.018**
PANSS general	BL – 6m	−1.85	0.85	38.45	−3.57	−0.13	**0.036**	0.062
PANSS general	BL – 12m	−2.26	1.06	30.50	−4.42	−0.10	**0.041**	0.062
PANSS total	BL – 6m	−4.61	1.67	39.01	−7.98	−1.24	**0.009**	**0.015**
PANSS total	BL – 12m	−5.37	1.96	32.39	−9.37	−1.37	**0.010**	**0.015**
Cognition								
TMT global	BL – 6m	0.25	0.11	32.51	0.04	0.47	**0.023**	0.069
DSST	BL – 12m	0.26	0.12	31.23	0.01	0.50	**0.040**	0.120
DST stm	BL – 12m	0.32	0.13	29.44	0.05	0.60	**0.021**	0.063
DST wm	BL – 3m	−0.46	0.20	40.92	−0.86	−0.06	**0.024**	**0.050**
DST wm	BL – 12m	0.26	0.11	30.33	0.02	0.49	**0.033**	**0.050**
VLMT stm	BL – 12m	0.62	0.19	31.98	0.24	1.00	**0.002**	**0.006**
VLMT ltm	BL – 12m	0.52	0.13	31.90	0.26	0.78	**0.000**	**0.001**
VLMT diff	BL – 12m	0.60	0.20	25.33	0.18	1.01	**0.007**	**0.021**
Cognition global	BL – 6m	0.12	0.05	31.33	0.02	0.22	**0.025**	**0.038**
Cognition global	BL – 12m	0.23	0.06	22.21	0.10	0.36	**0.001**	**0.003**
Functioning								
GAF	BL – 12m	5.68	2.39	30.43	0.80	10.56	**0.024**	0.072
FROGS	BL – 6m	3.95	1.35	37.01	1.22	6.68	**0.006**	**0.018**

Table 3 shows test statistics from the significant one-sample t-tests of the marginal means between session and across groups based on the ITT2 sample ($n = 92$; all randomized patients who had participated in at least one training and at least one of the following main visits) and PP sample ($n = 45$, patients who received at least 50% of the randomized study treatment and were assessed in at least one of the following main visits).
CI: 95%-confidence interval; Df: degrees of freedom; DSST: Digit Symbol Substitution test; DST wm: Digit Span Test working memory; FROGS: Functional Remission of General Schizophrenia; GAF: Global Assessment of Functioning Scale; p (FDR), p values corrected using the False Discovery Rate method; PANSS: Positive and Negative Syndrome Scale; SE: standard error; TMT global: Trail Making Test global score; VLMT stm, ltm, diff: Verbal Learning and Memory Test short-term memory, long-term memory, and difference score.

We also explored whether patient characteristics at baseline predicted drop-out probability. Our results indicated that especially levels of functional remission as assessed with the FROGS had a significant influence on training participation and study completion. Thus, participants with lower levels of functioning were more likely to drop out during the study course (S21).

Similarly, we investigated whether responders at the symptom or functional level differed from non-responders in baseline characteristics. Overall, the percentage of PANSS responders (at least a 25% improvement in the PANSS total score) to the exercise interventions studied in our current trial was 49.32% (AET 47.06%, FSBT 52.28%) and the percentage of GAF responders (improvement of at least 10 points) was 30.00% (AET 27.27%, FSBT 32.43%).

PANSS responders showed a better performance in the TMT at baseline ($p = 0.024$), indicating superior abilities in processing speed, inhibition and working memory. PANSS responders also had higher DSST scores at baseline ($p = 0.003$) for which the cognitive domains of short-term memory and processing speed are decisive.

GAF responders were characterized by a higher level of education ($p = 0.023$), a better performance in the DST working memory ($p = 0.036$) and again, in the TMT at baseline ($p = 0.037$). GAF responders were also more likely to exercise regularly before the study ($p = 0.018$). See S24 for more details.

In terms of intervention safety, both AET and FSBT were well tolerated, and no statistically significant differences in adverse events were observed between the groups (S19).

4. Discussion

This multicenter study is the largest to date to investigate the efficacy of exercise as an add-on treatment in stable schizophrenia. We found no superiority of AET over FSBT in our primary outcome ACD or in any of the secondary outcomes regarding psychopathology, cognition, functioning in daily life, quality of life, and cardiovascular risk factors. However, across the six-month active and six-month follow-up period, both exercise groups showed significant improvements in several of the secondary outcomes, i.e., in PANSS positive, general, and total scores, in levels of global and occupational functioning, and in the cognitive domains of cognitive flexibility, verbal declarative short-term memory, and global cognition. When only participants with a higher training

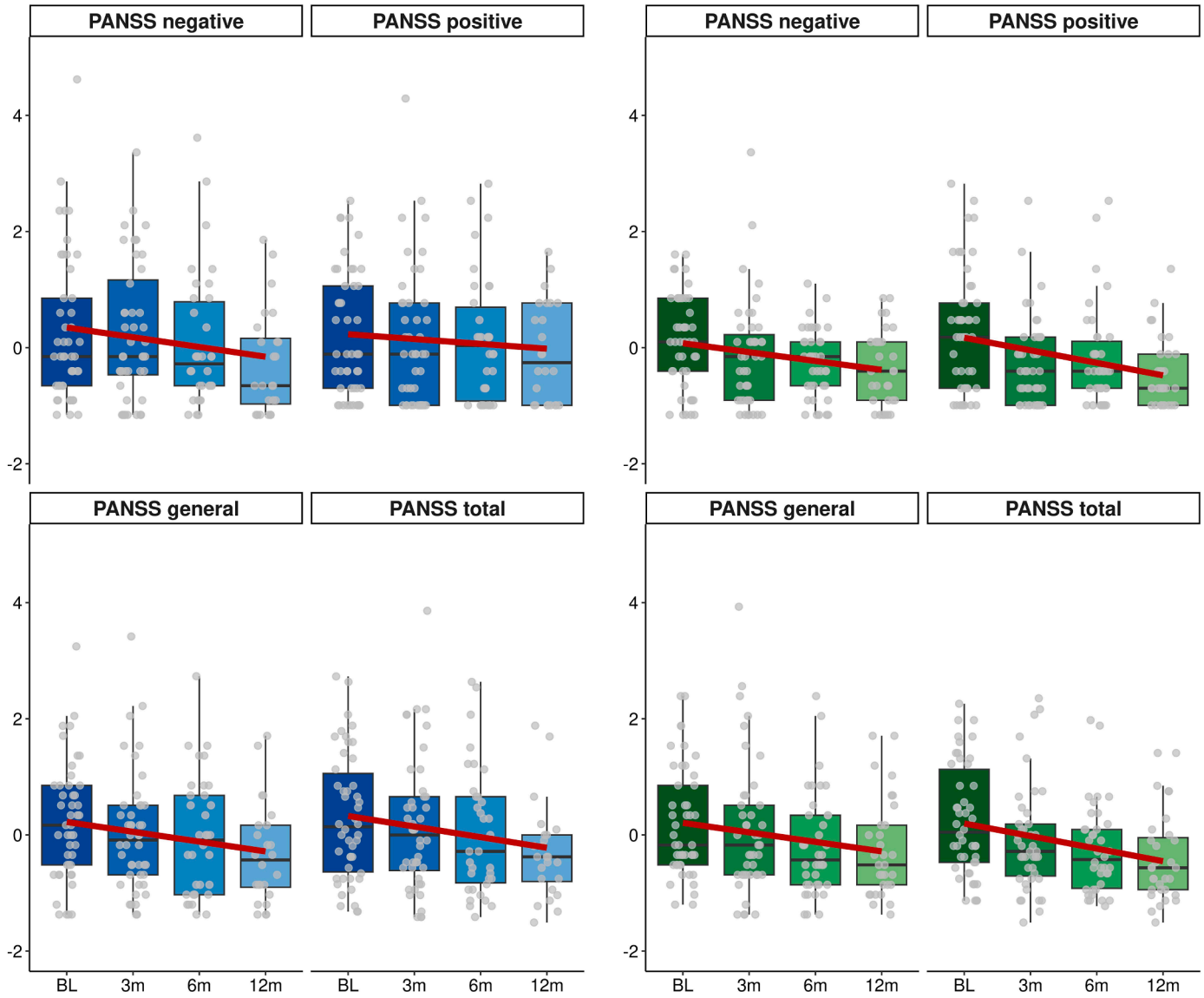

Fig. 2. Changes in clinical symptoms.
Fig. 2 shows z-standardized Positive and Negative Syndrome Scale results in the aerobic exercise training group (left-hand side, blue boxes) and in the flexibility, strengthening, and balance training control group (right-hand side, green boxes) in the ITT2 sample (randomized participants who performed at least one training session and one main visit) at individual study visits.
3 m, 6m: visit after three and six months of the active study phase; 12m: visit after another six months of inactive follow-up; BL: baseline visit.

frequency were considered, we saw additional improvements in the cognitive domains of working memory, long-term memory and processing speed.

During the six-month active study phase we found a similar drop-out rate of about 60% in both groups. This rate is considerably higher than the mean of 26.7% determined in a systematic review of exercise interventions (Vancampfort et al., 2016); however, the mean duration of the studies included in the review was only half that in our trial and studies with a longer duration showed attrition rates similar to ours (Scheewe et al., 2013). In general, both study and sample characteristics can affect drop-out. For example, larger sample sizes, a higher number of intervention sessions, and treatment in an outpatient setting were found to be inversely associated with adherence levels in non-pharmacological schizophrenia trials (Sedgwick et al., 2021; Szymczynska et al., 2017; Villeneuve et al., 2010). In terms of sample characteristics, our findings indicated that especially levels of functioning in daily life had a significant influence on study discontinuation (S21).

Previous study results pointed to the beneficial effects of exercise, so it would have been unethical to include an inactive control group. Instead, we designed the FSBT to enable control group participants to exercise according to ACSM recommendations and in the same setting as the AET intervention group. As suggested before (Bredin et al., 2021), also this kind of exercise showed broad positive effects on mental health outcomes in people with schizophrenia. Thus, in both groups, we identified improvements in psychopathology and cognition in our sample of individuals in a stable phase of schizophrenia. Even though our sample had less severe disease, mean improvements in PANSS total exceeded the mean placebo response of 6.25 in antipsychotic trials (Leucht et al., 2018).

In addition, we compared our results with the control groups from our two previous studies of exercise in people with schizophrenia (Malchow et al., 2015; Pajonk et al., 2010). Both studies involved three months of table soccer as control group, which is much less physically demanding than our FSBT training and is not regarded as exercise per se. In the second trial, participants received additional standardized cognitive training after six weeks (Malchow et al., 2015).

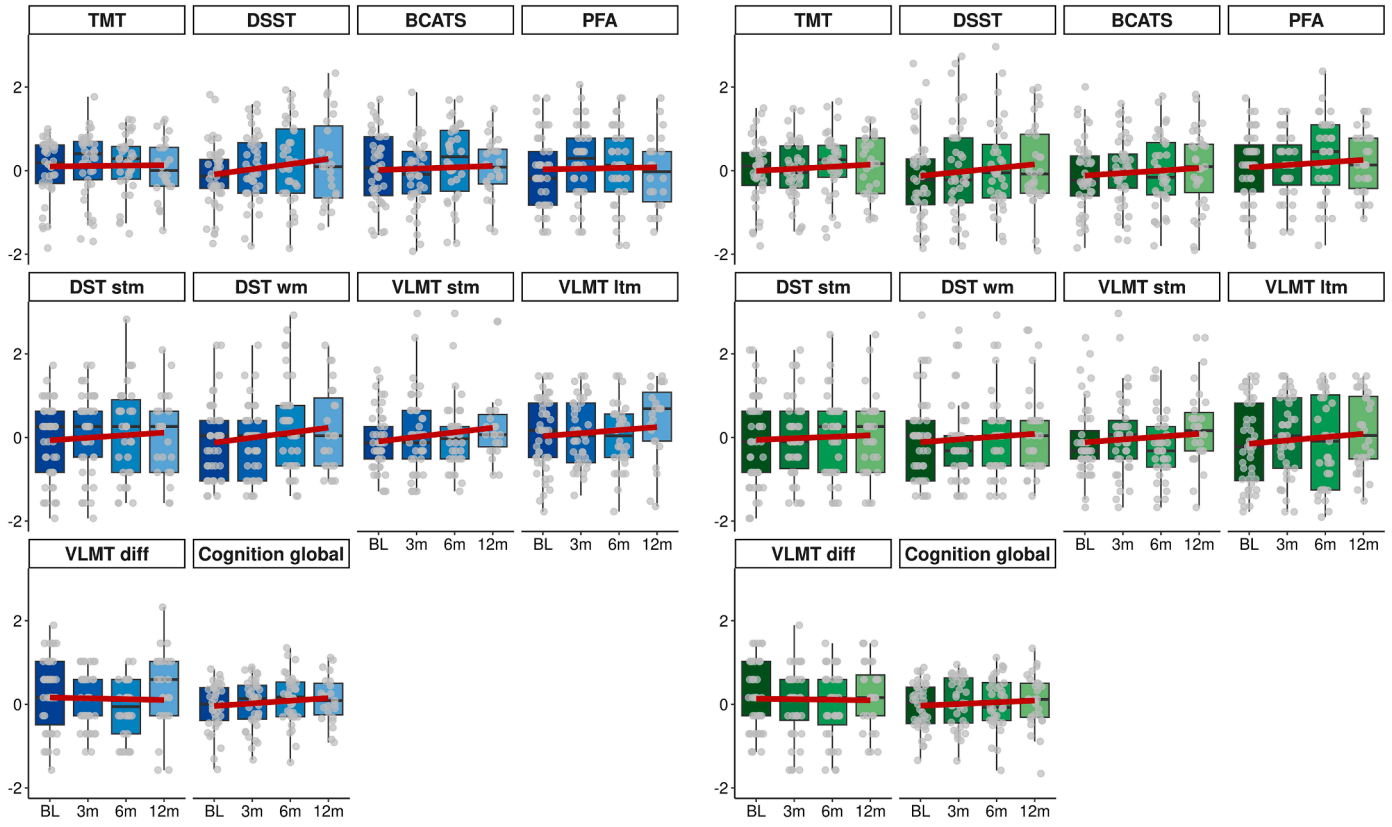

Fig. 3. Changes in cognitive performance.

Fig. 3 shows z-standardized cognitive ratings and sum and composite scores in the aerobic exercise training group (left-hand side, blue boxes) and in the flexibility, strengthening, and balance training control group (right-hand side, green boxes) in the ITT2 sample (randomized participants who performed at least one training session and one main visit) at individual study visits.

3 m, 6m: visit after three and six months of the active study phase; 12m: visit after another six months of inactive follow-up; B-CATS global: Brief Cognitive Assessment Tool for Schizophrenia global score; BL: baseline visit; DSST: Digit Symbol Substitution Test; DST stm, wm: Digit Span Test short-term memory and working memory; PFA: Pictures of Facial Affect Recognition Test; TMT global: Trail Making Test global score; VLMT stm, ltm, diff: Verbal Learning and Memory Test short-term memory, long-term memory, and difference score.

In the first exercise study, participants of the control group worsened in PANSS negative and total scores and their verbal long-term memory performance declined significantly during the three months of table soccer. Other ratings remained unchanged. In the second exercise study, the control group (with additional cognitive training) showed significant improvements only in the cognitive assessments TMT and DST wm, but not in other cognitive scores, PANSS scores or general functioning (more details in S25).

Thus, we conclude that the PANSS improvements found in our current study are not to be expected in non-exercising controls groups and can be attributed to the exercise interventions. None of the cognitive assessments (except two tests after additional cognitive training) showed a significant improvement in the previous studies and VLMT ltm performance even worsened. Therefore, we assume that cognitive performance in people with schizophrenia tends to be stable or declining under control group conditions. This further supports the notion that the improvements we observed in our current study are attributable to the exercise interventions.

Strikingly, we did not find significant reductions in BMI, waist circumference or laboratory parameters related to metabolic syndrome in either group of our current trial. Combining exercise with additional interventions, such as diet modifications, might obtain larger effects on cardiovascular risk parameters (Daumit et al., 2013).

While there were also no statistically significant improvements in aerobic fitness levels across both groups, mediation analyses showed that participation in the AET group led to greater increases in aerobic fitness levels, which in turn led to improvements in the PANSS general. In addition, we investigated whether changes in fitness levels were associated with improvements in secondary outcomes and found a positive relationship between fitness levels and functioning scores (S22). However, we identified a significant positive relationship between the number of training sessions completed and improvements in secondary outcomes only in case of the DST working memory. We conclude that, at a group level, exercise adherence and fitness improvements may not necessarily translate directly into symptom benefits in all individuals with schizophrenia. Instead, exercise induced effects may vary among individuals with schizophrenia and should also be investigated at an individual level as previously proposed (Rethorst et al., 2017; Suterwala et al., 2016). We therefore focused on gaining a better understanding of exercise response by comparing the baseline characteristics of study participants who achieved a notable improvement in PANSS or GAF scores with those who did not. In this context, socio-demographic and clinical variables have been suggested as preferable indicators for treatment response because they can be easily obtained and promise clinical utility (Chekroud et al., 2021).

In general, the proportions of responders in our study are comparable to those in other exercise trials, mostly conducted in people with depression (Falkai et al., 2021; Rethorst et al., 2017; Schuch et al., 2016). Whereas in previous studies the outcomes of exercise interventions were most frequently associated with baseline symptom severity (Herring et al., 2012; Rethorst et al., 2017; Wang et al., 2018), we identified higher baseline cognitive abilities in processing speed and working memory in exercise responders (possibly also reflected in higher levels of education) (S24). Furthermore, responders were more

likely to exercise regularly before entering the study, perhaps because they perceived greater benefits from exercise.

Previous work by our group already indicated that a higher polygenic risk burden might negatively influence neuroplasticity-related responsiveness to exercise interventions (Papiol et al., 2017). Accordingly, a similar effect may be present at the symptom level, resulting not only in more severe baseline cognitive impairments, but also in a reduced ability to benefit from exercise interventions.

Future exercise trials need to further consider and investigate the predictive role of participant characteristics and exercise modalities. Identifying the predictors of (non-)response is essential not only to optimize resource allocation but also to develop personalized treatment recommendations, that include interventions tailored to the individual needs of each patient.

Several limitations should be taken into account when interpreting the findings of this study. First, the social effects of the supervised group setting and training effects regarding cognitive tests should be considered. Because we had no inactive control group for direct comparison, we cannot rule out that these aspects might have contributed to some extent to the positive effects we found. Second, our trial had a high attrition rate (but comparable to other trials of similar duration). In general, high attrition rates reduce study power and introduce a risk of bias. Therefore, we used a statistical model that analyzed only cases with at least one further follow-up visit. Moreover, we investigated drop-out characteristics and identified levels of functioning at baseline as a factor that negatively influenced study continuation (S21). Future trials should focus on ways to foster ongoing exercise participation in individuals at risk of attrition. Third, insufficient adherence with the recommended amount of exercise (e.g., due to the COVID pandemic, S20) was a major challenge in our trial. We also examined the effects of both trainings in a sub-sample with higher levels of training adherence. Indeed, our results indicated that participants with at least 50% training attendance showed more robust improvements in symptom severity and cognition, as previously suggested (Dauwan et al., 2021).

Last, our study only provided group sessions conducted on site, and the changing constraints from the COVID pandemic led to interruptions in the training sessions and had an impact on training adherence. To meet this challenge in the future, exercise trials should consider offering optional, professionally supervised online trainings.

In summary, we conclude that AET and FSBT can both be used as add-on treatments in individuals with schizophrenia and have beneficial effects on clinical symptoms and cognitive performance in a stable phase of their disease. Thus, both training programs resulted in improvements even in symptom domains that are usually difficult to treat with standard therapeutic approaches.

Future trials should focus on further identifying factors that influence the beneficial effects of exercise, and on gaining in-depth knowledge of how individual and training characteristics mediate or moderate the effects of exercise.

Furthermore, we need to expand our understanding of how to optimize participant adherence to interventions; according to our findings, this could be achieved by providing support especially to participants with low levels of functioning. To improve cardiovascular risk profiles of individuals with schizophrenia, exercise as implemented in our trial does not seem to be effective enough and should be combined with additional lifestyle or pharmacological measures.

In conclusion, our findings support the integration of exercise into the treatment of people with schizophrenia in general, but future studies should aim to develop personalized training concepts to maximize the benefits of exercise.

Ethics approval and consent to participate

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved by the local ethics committees of the participating centres (project no. 706–15, date May 18, 2016). All participants provided written informed consent.

Data availability statement

Scripts for the whole analysis, and deidentified participant demographic, clinical, cognitive, and physical data will be published on OSF with publication of the manuscript. Additional data can be made available upon reasonable request (email to Isabel.maurus@med.uni-muenchen.de).

CRediT authorship contribution statement

Isabel Maurus: Data curation, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Lukas Roell:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Moritz Lembeck:** Investigation, Writing – review & editing. **Irina Papazova:** Investigation, Writing – review & editing. **David Greska:** Investigation, Writing – review & editing. **Susanne Muenz:** Investigation, Writing – review & editing. **Elias Wagner:** Investigation, Writing – review & editing. **Mattia Campana:** Investigation, Writing – review & editing. **Rebecca Schwaiger:** Investigation, Writing – review & editing. **Thomas Schneider-Axmann:** Formal analysis, Writing – review & editing. **Kerstin Rosenberger:** Data curation, Writing – review & editing. **Martin Hellmich:** Formal analysis, Writing – review & editing. **Eliska Sykorova:** Investigation, Writing – review & editing. **Cristina E. Thieme:** Investigation, Writing – review & editing. **Bob O. Vogel:** Investigation, Writing – review & editing. **Carolin Harder:** Investigation, Writing – review & editing. **Sebastian Mohnke:** Investigation, Writing – review & editing. **Charlotte Huppertz:** Investigation, Writing – review & editing. **Astrid Roeh:** Investigation, Writing – review & editing. **Katriona Keller-Varady:** Conceptualization, Methodology, Writing – review & editing. **Berend Malchow:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Henrik Walter:** Funding acquisition, Supervision, Writing – review & editing. **Bernd Wolfarth:** Methodology, Supervision, Writing – review & editing. **Wolfgang Wölwer:** Funding acquisition, Supervision, Writing – review & editing. **Karsten Henkel:** Funding acquisition, Supervision, Writing – review & editing. **Dusan Hirjak:** Project administration, Supervision, Writing – review & editing. **Andrea Schmitt:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Alkomiet Hasan:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Andreas Meyer-Lindenberg:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Peter Falkai:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

AS: honorary speaker for TAD Pharma and Roche, member of Roche advisory boards. **AH**: editor of the German (DGPPN) schizophrenia treatment guidelines, first author of the WFSBP schizophrenia treatment guidelines; on advisory boards of and speaker fees from AbbVie (speaker fees only), Advanz (speaker fees only), Janssen-Cilag, Lundbeck, Recordati, Rovi, and Otsuka. **PF**: co-editor of the German (DGPPN) schizophrenia treatment guidelines, co-author of the WFSBP schizophrenia treatment guidelines; on advisory boards and speaker fees from Janssen, Lundbeck, Otsuka, Servier, and Richter. **AML**: consultant fees from Boehringer Ingelheim, Elsevier, Brainsway, Lundbeck Int. Neuroscience Foundation, Lundbeck A/S, Sumitomo Dainippon Pharma Co., Academic Medical Center of the University of Amsterdam, Synapsis

Foundation-Alzheimer Research Switzerland, IBS Center for Synaptic Brain Dysfunction, Blueprint Partnership, University of Cambridge, Dt. Zentrum für Neurodegenerative Erkrankungen, Zürich University, Brain Mind Institute, L.E.K. Consulting, ICARE Schizophrenia, Science Advances, Fondation FondaMental, v Behring Röntgen Stiftung, The Wolfson Foundation, and Sage Therapeutics; speaker fees from Lundbeck International Foundation, Paul-Martini-Stiftung, Lilly Deutschland, Atheneum, Fama Public Relations, Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Janssen-Cilag, Hertie Stiftung, Bodelschwingh-Klinik, Pfizer, Atheneum, University of Freiburg, Schizophrenia Academy, Hong Kong Society of Biological Psychiatry, Fama Public Relations, Spanish Society of Psychiatry, Italian Society of Biological Psychiatry, Reunions I Ciencia S.L., and Brain Center Rudolf Magnus UMC Utrecht; awards from the Prix Roger de Spoelberch grant and the CINP Lilly Neuroscience Clinical Research Award 2016. **IM, LR, ML, IP, DG, SMu, EW, MC, RS, TSA, KR, MH, ES, ET, BV, CHa, SMo, CHu, AR, KKV, BM, HW, BW, WW, KH,** and **DH** report no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115480.

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