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ORIGINAL PAPER

High-intensity interval training and active video gaming improve neurocognition in schizophrenia: a randomized controlled trial

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Abstract

There is a need for treatments targeting neurocognitive dysfunctions in schizophrenia. The aim of this study was to investigate the neurocognitive effect of aerobic high-intensity interval training (HIIT). A comparison group performed sport simulating active video gaming (AVG). We anticipated that HIIT would improve neurocognition beyond any effect of AVG, due to engagement in higher intensity cardiorespiratory demands. Recent research on the beneficial neurocognitive effect of AVG challenges this expectation but added new relevance to comparing the two interventions. This is an observer-blinded randomized controlled trial. Eighty-two outpatients diagnosed with schizophrenia were allocated to HIIT ($n=43$) or AVG ($n=39$). Both groups received two supervised sessions per week for 12 weeks. The attrition rate was 31%, and 65% of the participants were defined as protocol compliant study completers. Intention-to-treat analyses showed significant improvements in the neurocognitive composite score from baseline to post-intervention and from baseline to 4 months follow-up in the total sample. The same pattern of results was found in several subdomains. Contrary to our hypothesis, we found no interaction effects of time and group, indicating equal effects in both groups. Separate within-group analysis unexpectedly showed trends of differential effects in the learning domain, as HIIT showed post-intervention improvement in verbal but not visual learning, while AVG showed improvement in visual but not verbal learning. HIIT and AVG improve neurocognition equally, suggesting that both interventions may be applied to target neurocognition in schizophrenia. Future research should investigate trends towards possible differential effects of exercise modes on neurocognitive subdomains. NCT02205684, 31.07.14.

Keywords Randomized controlled trial · Schizophrenia · Cognition · Exercise, High-intensity interval training · Active video gaming

Introduction

Neurocognitive dysfunction is a core feature in schizophrenia [1] affecting daily living and predicting long-term functional outcome [2–6]. It is, therefore, an important target for treatment [7, 8]. Although neurocognitive functions appear relatively stable across months or years in schizophrenia [1, 9–12], they respond to interventions targeting these functions [13]. Despite this, efficient and effective treatment options are limited. Cognitive remediation (CR) shows small to moderate neurocognitive effects, but these appear task-specific and do not necessarily generalize to untrained tasks or across situations [14–16]. Antipsychotic pharmacotherapy has insufficient neurocognition-enhancing effects and may have neurocognitive side effects [17–19]. Consequently, there is a need for new interventions targeting

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neurocognitive function in schizophrenia [20] with broader and more generalizable effects [14].

Neurocognition in schizophrenia ranges from normal functioning to severe dysfunction (mostly presenting as moderate), with processing speed, attention, executive function, verbal learning and memory most often affected [5, 6, 21–24]. Due to the strong associations with outcome, verbal memory, processing speed and attention are important targets for treatment [4, 6, 25]. The neurocognitive dysfunction in schizophrenia is linked to structural and functional brain abnormalities [26], typically of the hippocampus [27].

Aerobic exercise (AE) improves neurocognition across age in both non-clinical and clinical populations [8, 28–30]. Putative underlying mechanisms are improved cardiorespiratory fitness (CRF) and induction of neuroplastic processes such as neurotrophin upregulation, neurogenesis, neuroprotection and angiogenesis [20, 31–35]. The hippocampus is among the most responsive structures to AE-induced neuroplasticity, along with improvements in functions such as learning and memory [31, 33, 36–39]. In schizophrenia, Pajonk found an increase in hippocampal volume following AE, correlating with improved verbal memory and increased CRF [37]. AE is a promising intervention targeting neurocognition in schizophrenia [32, 34] and could potentially have broad neurocognitive effects. However, given the responsiveness of the hippocampus, additional effects on learning and memory are hypothesized.

Meta-analyses and reviews on the neurocognitive effects of physical exercise in schizophrenia have arrived at promising but also diverging results [8, 40–43]. The meta-analysis by Firth et al. [8], specifically studying the effect of AE in schizophrenia, found a moderate effect on global cognitive functioning. For the subdomains, the largest effects were found in working memory, attention/vigilance and social cognition.

Single studies investigating the effect of AE on neurocognition in schizophrenia are scarce. Kimhy et al. [48] found a larger effect on global cognition following an intervention combining traditional AE and AVG than following usual treatment. Nuechterlein et al. [44] reported an effect on a cognitive composite score when comparing combined AE and CR to CR alone. Effects on neurocognitive subdomains are inconsistent, possibly because of methodological differences, such as outcome measures and cognitive subdomains assessed, intervention type and choice of control or comparison intervention. Oertel-Knochel et al. [45] reported the effect of AE on working memory, processing speed and visual learning but not verbal learning. Notably, their AE intervention included choreography, motor coordination tasks and cognitive training. Su et al. [46] found an effect on processing speed and attention when comparing AE to stretching and toning. Lin et al. [47] reported differential effects, as both AE and yoga had an effect on working memory, while yoga had an additional effect on processing speed.

There is a need for larger randomized controlled trials (RCT) to replicate earlier studies before conclusions can be drawn, with well-described and supervised interventions, active comparison-conditions matched for time and personal contact, blinded assessment, standardized tools and complete outcome data analysed as intention-to-treat (ITT) [8, 41]. The current study was designed to meet methodological challenges in the field and to complement existing research.

The aim of this study was to investigate the neurocognitive effects of aerobic high-intensity interval training (HIIT) in schizophrenia. HIIT, consisting of high-intensity bursts alternating with recovery phases of lower intensity, is documented to increase CRF more efficiently than moderate intensity continuous AE [49, 50] and to improve CRF in both inpatients and outpatients with schizophrenia [51, 52]. HIIT is time efficient, easily standardized, associated with low rates of adverse events and shown to reduce psychopathology in schizophrenia [53–55]. Neurocognitive effects following HIIT are described in adolescents and older adults [56, 57]. A recent study compared the effects of two different levels of AE intensity on neurocognition in older adults and found HIIT to be more effective in improving neurocognition than moderate continuous training [58]. The effect of HIIT on neurocognitive functions in schizophrenia has not been previously investigated.

A comparison group performed active video gaming (AVG), consisting of interactive computerized sport simulations (bowling, golf or tennis) using the Nintendo Wii console and Wii Sports software. This activity was intended to control for time and personal contact in an attempt to extract engagement in high-intensity interval training as the main difference.

We hypothesized that HIIT would enhance neurocognition beyond the effect in the comparison group, based on an expectancy of higher intensity cardiorespiratory demands while engaging in HIIT. Increased CRF is considered one of the putative mechanisms underlying improved neurocognition. However, studies on the association between CRF and neurocognition are conflicting, and the necessity of increased CRF following engagement in AE to achieve neurocognitive effects has not been established [59, 60].

The effect of physical exercise on neurocognitive function in schizophrenia has primarily focused on AE [8]. AVG, also called exergaming, is described as the playing of interactive video games, where responding to visual stimuli with body movements induces virtual actions on a screen [61, 62]. It combines physical and cognitive exercise [63], described as dual-task training [64]. While conducting the current study, meta-analyses on AVG have emerged and show moderate neurocognitive improvements across populations, including schizophrenia, equal to the effect of physical exercise

[30, 62, 63, 65]. In schizophrenia research, studies have shown the feasibility, adherence, acceptability and safety of AVG [66–71]. Campos et al. [68] compared AVG to TAU in schizophrenia but failed to find an effect on neurocognition. Kimhy et al. [48] combined traditional AE and AVG and found larger improvements in neurocognition than with TAU, but the design did not allow for comparisons of the neurocognitive effects of AVG versus AE.

Different types of AVG encompass exercise modes ranging from cardiorespiratory training (moderate continuous AE and HIIT) to motor coordination training [63], and accordingly, activity level and energy expenditure may differ [72]. AVG type was a moderator for the effects on energy expenditure in a meta-analysis by Peng et al. [73]. However, the type of AVG could not explain inconsistencies in neurocognitive effects between single studies in a meta-analysis by Stojan and Voelcker-Rehage [63].

Nintendo Wii Sports simulates golf, tennis or bowling, described as low intensity activities [72, 73] primarily demanding motor coordination and visuospatial function [65]. Interestingly, motor coordination training aimed at improving motor fitness may increase hippocampal volume and enhance neurocognition in elderly individuals in the absence of increased CRF, and studies comparing AE and motor coordination training indicate that these exercise modes have differential effects on brain and neurocognition [74–77].

Not only AE, but also motor coordination training and AVG may improve neurocognition and are associated with neuroplastic processes [64, 77]. This challenges our original hypothesis but nevertheless adds new relevance to the study. To our knowledge, this is the first RCT to compare the neurocognitive effects of HIIT and AVG in schizophrenia.

Materials and methods

This study reports the primary outcome data from the Effects of Physical Activity in Psychosis Study (EPHAPS), prereported in ClinicalTrials.gov (NCT02205684, first posted 31.07.14) and approved by the regional ethical committee of Southern and Eastern Norway (2014/372/REK SØR-ØST). For details on study design see Engh et al. [78], as well as publications on baseline data [79–83]. There were no important changes in methods after trial commencement, but the recruitment period was extended by one semester to increase the sample size.

Participants

Individuals meeting the Diagnostic and Statistical Manual of Mental Disorders version five (DSM-V, American Psychiatric Association, 2013) diagnostic criteria for a schizophrenia spectrum disorder confirmed by the Structured Clinical Interview for DSM-IV (SCID), aged 18–67 and understanding and speaking a Scandinavian language were eligible for the study. The exclusion criteria were pregnancy, chest pain during exercise, unstable angina pectoris, recent myocardial infarction, uncontrollable cardiac arrhythmia, severe hypertension (> 180/110 mm/Hg), comorbid diagnosis of mild mental retardation or other medical conditions incompatible with participation.

Participants were recruited from two out-patient clinics at the Division of Mental Health and Addiction, Vestfold Hospital Trust, Norway. The clinical staff informed 171 outpatients diagnosed with schizophrenia about the study, assuring that participation was voluntary and that neither declining nor consenting to participate would affect their clinical treatment. One hundred and two outpatients consented to participate and received oral and written information from the EPHAPS group. If they understood the nature of the research project and wanted to take part, written consent was obtained, and baseline testing was performed. Eighty-two participants were included and randomly allocated to HIIT ($n = 43$) or AVG ($n = 39$) (Fig. 1) by a study coordinator using concealed envelopes. The allocation sequence, generated by a computerized random number generator, kept treatment assignment unpredictable by varying the size of the stratification blocks. Allocation was performed blinded for baseline assessment results, but equal distribution of baseline CRF in the two groups was obtained by stratification on the expected median peak VO_2 based on the results from the feasibility study ($n = 10$) [84]. Allocation, interventions and assessments were conducted separately, and participants from the two groups never met. Due to the study design, the participants could not be blinded. The research team performed all the psychiatric and neurocognitive assessments blinded for allocation. If one assessor was off-blinded, another performed the assessment. An intervention team (a physiotherapist, a nurse with a master's degree in sport education and four mental health care workers) was trained to supervise both interventions and could not be blinded.

Attrition and protocol violation

The attrition rate was 13% ($n = 11$) at the post-intervention assessment. Including patients lost to follow-up, the total attrition rate at the end of the study was 31% ($n = 25$) (HIIT 33% ($n = 14$)/AVG 28% ($n = 11$), $p = 0.67$). Protocol violation was defined as either less than 60% session attendance, no participation for two successive weeks or more than 2 weeks delay before assessing CRF following the last session. If absent from a session, participants were given another opportunity within the same week. Protocol violations were registered for ten participants. They were allowed

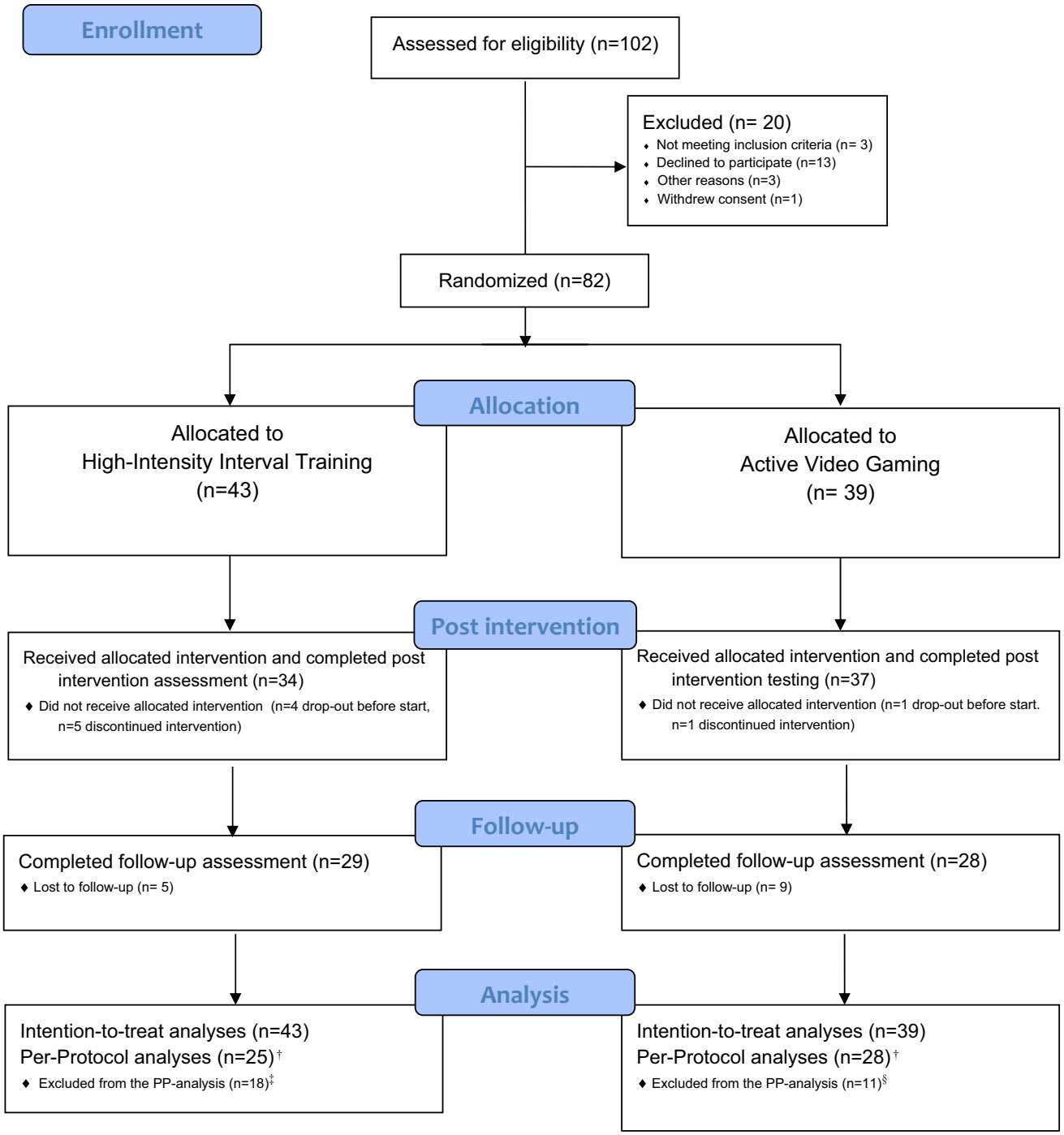

Fig. 1 Consort flow diagram. Note: †PP analyses included protocol compliant study completers, and excluded 29 participants due to drop-out and protocol violation ($n=6$); drop out only ($n=4$) and protocol violation only ($n=19$), respectively. ‡Excluded participants in the HIIT group due to dropout and protocol violation ($n=4$); dropout only ($n=10$) and protocol violation only ($n=4$). §Excluded participants in the AVG group due to protocol violation and drop out ($n=2$); drop-out only ($n=9$) and protocol violation only ($n=0$). Spontaneous participant-reported reasons for drop-out were; not motivated ($n=6$), not motivated for more assessments ($n=5$), high psychosis symptom load ($n=1$), drug intake ($n=1$), psychiatric inpatient treatment needs ($n=2$), somatic inpatient needs ($n=1$), moved ($n=2$), holiday ($n=1$); prison ($n=1$), not possible to combine with work ($n=2$), did not have time ($n=1$), family issues ($n=1$) and unknown ($n=1$). Protocol violation was registered in ten participants (more than 14 days delay before VO_{2max} assessment following last intervention session ($n=4$), less than 60% attendance to session ($n=2$) and both ($n=4$))

to stay in the study to reduce missing data and to enable both ITT analyses of all randomized participants and per-protocol (PP) analyses. Sixty-five percent ($n=53$) (HIIT $n=25$/AVG $n=28$) were defined as "protocol compliant study completers" and included in the PP analyses (Fig. 1).

Interventions

Both intervention groups separately received two supervised sessions per week for 12 weeks. The interventions were provided individually or in groups of two to three participants.

The aerobic HIIT intervention consisted of 8 min of warm-up followed by four times 4 min intervals of treadmill running or walking (cycling if unable to walk or run, $n=1$) at 85–95% of maximum HR alternating with 3 min of pauses of walking/running at 70% of maximum HR. Finally, there was a 5 min cool-down period. In-session heartrate was measured by a digital watch and a chest-strap (Polar RCX3 heart monitor) to assure engagement at the right intensity. The level of intensity is in line with the study by Brobakken and colleagues on aerobic interval training, alternating 85–95% and 70% of maximum HR [52], while a narrower range of 90–95% during intervals has been used in other aerobic HIIT studies [49, 50].

The AVG group performed 45 min of computerized interactive sport simulation using the Nintendo Wii console and the Wii Sports software, intended to control for time and personal contact. The participants stood in front of a TV screen. Moving the arm and body while holding the console controller induced virtual motion on the screen simulating sport performance. Each session offered a choice between bowling, tennis or golf, described as low-intensity activities [72, 85] and primarily demanding motor coordination and visuospatial function [65].

The mean (SD, percentage) session attendance (maximum $n=24$) in the total ITT sample was 17 (6, 71%), ranging from 0 to 24 sessions (HIIT group 16 (7, 65%); AVG group 18 (5, 76%), $p=0.06$). For the PP sample, the mean session attendance was 20 sessions (2, 82%; HIIT 83%; AVG 81%, $p=0.35$). Within the HIIT group, the mean attendance to the 96 possible intervals (four per session) was 70 (19, 73%) for the ITT sample and 77 intervals (12, 80%) for the PP sample.

Harm

There were no observed or reported episodes of adverse effects.

Data collection

For baseline clinical and functional descriptions, psychosis symptoms were assessed using PANSS [86], psychosocial functioning was assessed using the Global Assessment of Functioning [87] and split into the symptoms (GAF-s) and function (GAF-f) scales to improve psychometric properties [88]. Medication was obtained from medical journals and interviews. Intellectual functioning was assessed using subtests included in the General Ability Index (GAI) from the Wechsler Adult Intelligence Scale (WAIS-IV) [89]. Baseline CRF was assessed as the highest measured maximum oxygen uptake (peak VO_2) [79] using a modified Balke protocol [90].

The primary outcome, neurocognition, was measured at baseline, post-intervention and at the 4 months follow-up using the MATRICS Consensus Cognitive Battery (MCCB) [91]. It is designed for repeated measures of neurocognition in clinical trials on cognitive enhancement in schizophrenia and has good psychometric properties, such as sensitivity to the severity of neurocognitive dysfunction at baseline, good test–retest reliability and minimal practice effects by use of parallel test versions [92]. An international reference study for the Norwegian standardization of the MCCB concludes that it is well suited for research purposes in Norway [93], with the possible exception of the social cognition subdomain [94]. This subdomain was excluded, and for the purpose of investigating neurocognition, age- and gender-corrected *T* scores from the following neurocognitive subdomains were included: processing speed, attention/vigilance, working memory, verbal learning, visual learning and reasoning/problem solving. A neurocognitive composite score was calculated as the mean *T* score of all observed subdomains.

Statistical analysis

Statistical analyses were run in IBM SPSS Version 25. Group differences in baseline measures were analysed using ANOVA, *t* test or Pearson's Chi-squared as applicable. To examine possible effects of attrition rate and protocol violation on the results, baseline differences between all randomized participants in the ITT sample and between the protocol compliant study completers in the PP sample were analysed by comparing the means and 95% confidence intervals (CI) of the chosen baseline characteristics.

Prior to the ITT analysis, the normality of the distributions of the neurocognitive composite score and scores on the six subdomains were assessed using Kolmogorov–Smirnov's test. The seven variables were examined separately for the two groups at each time point for a total of 42 tests. Six of the tests for normality yielded a *p* value below 0.05. Visual inspection of the distributions deviating from normality revealed that the scores were approximately normally distributed. As no extreme outliers were detected (absolute *Z* scores outside the range ± 3), the assumption of normality was considered fulfilled. Levene's test performed

separately for the seven variables at each point in time showed no significant differences in variance between the groups. For the main outcome, intention-to-treat analyses of neurocognition, all variables satisfied the criteria for parametric statistics without transformation. Missing data mainly resulted from attrition (Fig. 1). Intermittent missing data were few [baseline visual learning ($n=1$), post-intervention visual learning ($n=2$), follow-up attention ($n=1$) and visual learning ($n=1$)]. Missing data were not replaced or imputed.

The effects of the interventions were estimated using the repeated measures linear mixed model (LMM) "model 2d", recommended by Twisk et al. [95]. We confirmed the assumption of a normal distribution of residuals in each of the neurocognitive outcomes. For all analyses, significance was set at $p<0.05$ (two-tailed).

All analyses were based on age- and gender-adjusted *T* scores having a standard deviation of 10 in the norm group. The change in *T* scores divided by 10 was used as a measure of effect size, enabling generalizability beyond the sample. Thus, an average increase in the *T* score in the present sample of 2, 5 and 8 points corresponds to an increase of 0.2, 0.5 and 0.8 standard deviations, respectively. These values correspond to a small (0.2), medium (0.5) and large (0.8) effect size according to Cohen [96].

Results

Baseline results

There were no significant baseline differences between the HIIT and AVG groups on any of the presented demographic, clinical, intellectual or functional characteristics, except for lower GAF function scores and higher defined daily antipsychotic medication doses in the HIIT group (Table 1). For the PP sample, the HIIT group scored higher on negative symptoms, lower on GAF function and symptoms and had higher defined daily antipsychotic medication doses (Table 1 in supplementary). There were no significant baseline differences in neurocognition or CRF (peak VO_2) between the HIIT and AVG groups in either the ITT or the PP sample.

Table 1 Baseline demographics and clinical characteristics of all randomized participants

	Total intention-to-treat sample, $n=82$		High-intensity interval training, $n=43$	Active video gaming, $n=39$	Baseline group differences
	Mean (SD)	CI (95%)	Mean (SD)	Mean (SD)	*p* value
Age (years)	37.0 (14.0)	33.95–40.10	36.6 (14.3)	37.5 (13.8)	0.78
Gender, male (%)	61.0		60.5	61.5	0.92
PANSS[a] positive subscale	15.1 (5.1)	13.95–16.20	15.7 (5.1)	14.4 (5.0)	0.22
PANSS[a] negative subscale	18.3 (7.0)	16.78–19.90	19.3 (7.2)	17.3 (6.7)	0.19
GAF[b]-symptom	42.9 (8.0)	41.17–44.69	41.6 (7.6)	44.5 (8.2)	0.11
GAF[b]-function	43.9 (7.8)	42.15–45.58	42.2 (7.4)	45.7 (8.0)	0.04*
Duration of illness (years)	13.8 (11.4)	11.06–16.45	12.9 (10.3)	14.6 (12.6)	0.55
Antipsychotic medication (DDD[c])	1.6 (1.0)	1.42–1.85	1.8 (1.1)	1.4 (0.7)	0.04*
WAIS-IV GAI[d]	87.3 (15.5)	83.91–90.74	85.8 (14.2)	89.0 (16.9)	0.36
MCCB[e] composite score	33.9 (8.4)	32.08–35.79	32.8 (8.4)	35.2 (8.4)	0.19
MCCB speed	29.8 (12.0)	27.14–32.42	27.6 (12.7)	32.2 (10.9)	0.08
MCCB attention	29.5 (11.4)	27.01–32.01	28.5 (10.5)	30.6 (12.3)	0.42
MCCB working memory	34.9 (10.5)	32.59–37.19	34.2 (10.5)	35.7 (10.5)	0.53
MCCB verbal learning	35.0 (8.6)	33.13–36.92	33.8 (7.1)	36.3 (10.0)	0.19
MCCB visual learning	33.7 (14.3)	30.56–36.87	33.6 (15.6)	33.9 (13.0)	0.93
MCCB reasoning/problem solving	40.7 (10.2)	38.41–42.88	38.8 (9.5)	42.7 (10.6)	0.08
CRF[f]	29.7 (11.1)	27.28–32.19	29.9 (11.5)	29.5 (10.8)	0.87

*$p<0.05$

[a] *PANSS* Positive And Negative Syndrome Scale, positive subscale ($n=81$) and negative subscale ($n=80$)

[b] *GAF* Global Assessment of Functioning, symptoms ($n=81$) and function ($n=81$)

[c] *DDD* defined daily doses

[d] *WAIS-IV* Wechslers Adult Intelligence Scale-Fourth Edition General Ability Index

[e] *MCCB* MATRICS Consensus Cognitive Battery (visual learning $n=81$)

[f] *CRF* cardiorespiratory fitness, highest measured maximum oxygen uptake (peak VO_2) ($n=81$)

To check whether attrition and protocol violations affected the results, we compared the baseline demographic, clinical, intellectual or functional characteristics between participants in the ITT sample and those in the PP sample. Only small differences in mean values were found, and for all variables, the mean of the PP sample was within the 95% confidence interval of the corresponding mean value in the ITT sample.

Efficiency analyses of the primary outcome neurocognition

The results from the main ITT LMM analyses (ITT) (Table 2) showed that there was a significant increase in the neurocognitive composite *T* score for the total sample from baseline to post-intervention ($b = 2.71$, SE = 0.64, $p < 0.001$) and from baseline to follow up ($b = 4.35$, SE = 0.72, $p < 0.001$), corresponding to *d* values of 0.27 and 0.44, respectively. The time × group interaction effect was not significant at either post-intervention or follow-up, indicating an equal increase in score over time for the HIIT and AVG groups.

For the subdomains, there was a significant increase in mean *T* scores from baseline to post-intervention in processing speed, attention, working memory and visual learning in the total sample, ranging from 3.17 to 4.28 and corresponding to *d* values between 0.32 and 0.43. We found no significant time × group interactions. From baseline to follow-up, there was a significant increase in mean *T* scores in the subdomains processing speed, attention, visual learning and reasoning for the total sample ranging from 2.93 ($d = 0.29$) for reasoning, 5.35 ($d = 0.54$) for attention, 7.67 ($d = 0.77$) for visual learning and 7.69 ($d = 0.77$) for processing speed. We found no significant time × group interactions.

PP analyses gave only trivial differences in estimates compared to the ITT analyses, and thus, the same conclusion was reached as in the main analysis (Table 2 in supplementary materials).

Within-group changes in neurocognition

From baseline to post-intervention, the LMM within-group analyses (ITT) (Table 3) showed a significant mean increase in the neurocognitive composite score corresponding to $d = 0.32$ ($b = 3.19$, SE = 0.66, $p < 0.001$) in the HIIT group and $d = 0.26$ ($b = 2.58$, SE = 0.66, $p < 0.001$) in the AVG group. For the subdomains, both groups showed a significant mean increase in *T* scores corresponding to the following effect sizes in the following subdomains: processing speed (HIIT $d = 0.38$/AVG $d = 0.28$), attention (HIIT $d = 0.36$/AVG $d = 0.40$) and working memory (HIIT $d = 0.37$/AVG $d = 0.33$). In the learning domains, HIIT had an increase in the mean *T* score corresponding to $d = 0.48$ in verbal learning, while AVG had an increase in the mean *T* score corresponding to $d = 0.34$ in visual learning.

From baseline to follow-up, there was a significant increase in the neurocognitive composite score corresponding to $d = 0.48$ ($b = 4.83$, SE = 0.70, $p < 0.001$) for the HIIT group and $d = 0.42$ ($b = 4.22$, SE = 0.74, $p < 0.001$) for the AVG group. For the subdomains, there were increased mean *T* scores in all subdomains in the HIIT group corresponding to $d = 0.52$ for processing speed, $d = 0.53$ for attention, $d = 0.36$ for working memory, $d = 0.30$ for verbal learning, $d = 0.71$ for visual learning and $d = 0.49$ for reasoning/problem solving. In the AVG group, there were increased mean *T* scores corresponding to $d = 0.74$ in processing speed, $d = 0.51$ in attention and $d = 0.76$ in visual learning.

PP analysis gave only trivial differences in estimates compared to the ITT analysis, except for the lack of a main effect of time on processing speed at post-intervention in the AVG group and on working memory and verbal learning at follow-up in the HIIT group (Table 3 in supplementary materials).

Discussion

We compared the effects of HIIT and AVG on neurocognitive function in outpatients with schizophrenia. From baseline to post-intervention, the total sample showed improvement in overall neurocognition and the processing speed, attention, working memory and visual learning subdomains. From baseline to follow-up, there was improvement in overall neurocognition and in the processing speed, attention, visual learning and reasoning subdomains. Contrary to our hypothesis, there were no significant differences between HIIT and AVG in neurocognitive improvement.

The lack of group differences in neurocognitive improvement is discordant with several single studies within the field. A meta-analysis by Firth et al. [8] found effect of AE on neurocognition compared to different control conditions. However, none of the included studies compared AE to AVG. The mean *T* score increases within the current HIIT group are comparable to or larger than those described in recent RCTs on AE and neurocognition in schizophrenia using MCCB as an outcome measure [46, 48]. The mean *T* score increases in the AVG intervention, originally intended to control for time and personal contact, were higher than we expected. We interpret this as a plausible explanation for the lack of group differences, leading to the main conclusion that HIIT and AVG show equivalent small to moderate improvements in neurocognition.

Interestingly, our results are in accordance with meta-analyses concluding that AVG improves neurocognition equally to physical exercise interventions [62, 63]. Stanmore et al. [62] found improvements in global cognition

Table 2 Primary outcome results, intention-to-treat analysis

	Baseline			Post-intervention						Follow-up					
	Intercept			$Time_1$[a]			$Time_1$ and group[b]			$Time_2$[c]			$Time_2$ and group[b]		
	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*
Neurocognitive composite score	33.93 (0.96)	32.02–35.85	**< 0.001**[d]	2.71 (0.64)	1.45–3.98	**< 0.001**	0.36 (0.91)	− 1.45–2.17	0.696	4.35 (0.72)	2.94–5.76	**< 0.001**	0.36 (1.00)	− 1.61–2.33	0.719
Processing speed	29.78 (1.43)	26.94–32.63	**< 0.001**	3.17 (1.16)	0.88–5.46	**0.007**	0.33 (1.64)	− 2.92–3.58	0.840	7.69 (1.29)	5.14–10.25	**< 0.001**	− 2.83 (1.79)	− 6.37–0.72	0.117
Attention	29.51 (1.20)	27.13–31.90	**< 0.001**	4.28 (1.15)	2.02–6.54	**< 0.001**	− 0.87 (1.61)	− 4.05–2.31	0.590	5.35 (1.28)	2.83–7.88	**< 0.001**	− 0.29 (1.78)	− 3.80–3.22	0.870
Working memory	34.89 (1.27)	32.37–37.41	**< 0.001**	3.46 (1.24)	1.01–5.91	**0.006**	0.01 (1.74)	− 3.43–3.45	0.996	2.19 (1.38)	− 0.55–4.92	0.116	1.21 (1.91)	− 2.55–4.98	0.525
Verbal learning	35.02 (1.01)	33.04–37.01	**< 0.001**	1.98 (1.35)	− 0.68–4.64	0.144	2.29 (1.83)	− 1.31–5.89	0.211	1.83 (1.50)	− 1.14–4.80	0.225	0.61 (2.01)	− 3.36–4.58	0.762
Visual learning	33.72 (1.56)	30.63–36.80	**< 0.001**	3.40 (1.42)	0.58–6.21	**0.018**	− 2.22 (2.04)	− 6.25–1.80	0.277	7.67 (1.59)	4.52–10.81	**< 0.001**	− 0.51 (2.21)	− 4.89–3.87	0.818
Reasoning and problem solving	40.65 (1.13)	38.40–42.89	**< 0.001**	1.13 (1.15)	− 1.15–3.41	0.328	0.13 (1.61)	− 3.10–3.31	0.937	2.93 (1.29)	0.39–5.47	**0.024**	1.51 (1.77)	− 1.97–5.00	0.392

Linear mixed model (LMM) with random intercept and three repeated measurements. Covariance matrix of within subject measurements was variance components. $N = 82$. At baseline, 39 participants were in the AVG group and 43 participants were in the HIIT group. At post-intervention, 37 participants were in the AVG group and 34 participants were in the HIIT group. At follow-up, 28 participants were in the AVG group and 29 participants were in the HIIT group

[a]Post-intervention = 1, else = 0

[b]AVG = 0, HIIT = 1

[c]Follow-up = 1, else = 0

[d]Bold values indicate significant $p < 0.05$

Table 3 Within-group change in neurocognition, intention-to-treat analysis

	Baseline						Post intervention						Follow-up					
	Intercept AVG			Intercept HIIT			$Time_1$[a] AVG			$Time_1$[a] HIIT			$Time_2$[b] AVG			$Time_2$[b] HIIT		
	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*	Estimate (SE)	95% CI	*p*
Neurocognitive composite score	35.23 (1.41)	32.39–38.07	**< 0.001**[c]	32.75 (1.31)	30.11–35.39	**< 0.001**	**2.58** (0.66)	1.25–3.91	**< 0.001**	**3.19** (0.66)	1.88–4.50	**< 0.001**	**4.22** (0.74)	2.74–5.70	**< 0.001**	**4.83** (0.70)	3.44–6.22	**< 0.001**
Processing speed	32.21 (2.03)	28.13–36.28	**< 0.001**	27.58 (2.00)	23.57–31.59	**< 0.001**	**2.81** (1.40)	0.01–5.60	**0.049**	**3.82** (0.93)	1.96–5.68	**< 0.001**	**7.38** (1.55)	4.27–10.48	**< 0.001**	**5.18** (1.00)	3.21–7.16	**< 0.001**
Attention	30.60 (1.89)	26.80–34.38	**< 0.001**	28.54 (1.52)	25.48–31.59	**< 0.001**	**4.04** (1.29)	1.47–6.62	**0.003**	**3.61** (1.09)	1.44–5.78	**< 0.001**	**5.12** (1.43)	2.26–7.98	**0.001**	**5.26** (1.17)	2.93–7.60	**< 0.001**
Working memory	35.67 (1.79)	32.08–39.26	**< 0.001**	34.19 (1.82)	30.54–37.84	**< 0.001**	**3.30** (1.14)	1.02–5.57	**0.005**	**3.65** (1.45)	0.75–6.54	**0.014**	2.00 (1.27)	−0.53–4.52	0.120	**3.58** (1.54)	0.51–6.65	**0.023**
Verbal learning	36.33 (1.54)	33.26–39.41	**< 0.001**	33.84 (1.30)	31.24–36.44	**< 0.001**	1.37 (1.50)	−1.63–4.37	0.366	**4.81** (1.39)	2.04–7.58	**0.001**	1.22 (1.66)	−2.10–4.53	0.465	**2.99** (1.47)	0.05–5.92	**0.046**
Visual learning	33.87 (2.09)	29.69–38.06	**< 0.001**	33.57 (2.32)	28.91–38.24	**< 0.001**	**3.36** (1.45)	0.45–6.27	**0.024**	1.15 (1.56)	−1.97–4.26	0.466	**7.64** (1.62)	4.41–10.86	**0.000**	**7.14** (1.64)	3.86–10.43	**< 0.001**
Reasoning and problem solving	42.72 (1.65)	39.40–46.03	**< 0.001**	38.77 (1.53)	35.71–41.82	**< 0.001**	0.62 (1.24)	−1.87–3.10	0.622	1.71 (1.17)	−0.62–4.04	0.147	2.43 (1.38)	−0.33–5.18	0.083	**4.89** (1.24)	2.42–7.36	**< 0.001**

Linear mixed model (LMM) with random intercept and three repeated measurements. Covariance matrix of within subject measurements was variance components. Neither group nor interaction time × group was in the model. $N = 82$. At baseline, 39 participants were in the AVG group and 43 participants were in the HIIT group. At post intervention, 37 participants were in the AVG group and 34 participants were in the HIIT group. At follow-up, 28 participants were in the AVG group and 29 participants were in the HIIT group

[a]Post intervention = 1, else = 0

[b]Follow-up = 1, else = 0

[c]Bold values indicate significant $p < 0.05$

and the subdomains executive functions, attentional processing and visuospatial skills across different populations, including schizophrenia. According to Stojan and Voelcker-Rehage [63], AVG was not inferior to any of the control or comparison groups in the included studies. In line with our results, most single studies comparing AVG to physical exercise describe within-group improvements but fail to find between-group effects [63]. Guimarães et al. [97] compared AE to AVG in healthy elderly individuals and found comparable within-group neurocognitive improvements but no between-group effects. The current study replicates these findings.

One challenge when interpreting equal improvement in both groups is differentiating treatment effects from practice effects. The practice effect is calculated to be $z = 0.17–0.18$ for the MCCB composite score and ranges from $d = 0.09$ (reasoning/problem solving) to $d = 0.18$ (processing speed) for the subdomains, just below what is considered small effects and below the detection of meaningful clinical changes [92, 98, 99]. In the absence of interventions, the MCCB shows minimal changes in *T* scores over time [12]. The effect sizes in the current study indicate treatment effects in both groups beyond pure practice effects. Whether the neurocognitive improvements are clinically meaningful is a challenging question. On an individual level, an increase in the MCCB composite *T* score of 10 or more is needed to be considered a reliable change, and for some subdomains, an even larger change is needed [100]. In the current study, the frequency of two sessions per week for 12 weeks resulted in statistically significant changes ranging from small to medium effect sizes. Further research should investigate dose–response issues [43]; for instance, whether a higher frequency or longer duration of interventions is necessary to achieve larger and more reliable clinical changes.

Equal neurocognitive effects demand a discussion of whether the putative underlying mechanisms are shared or different. The current study may be perceived as comparing two different exercise modes: HIIT aimed at improving CRF and motor coordination training aimed at improving motor fitness. Cardiorespiratory training, motor coordination training and AVG are associated with neuroplasticity, which may occur both in the presence and absence of increased CRF [37, 64, 77]. Studies comparing cardiorespiratory training (AE) and motor coordination training suggest that these exercise modes have differential effects on neurocognition in elderly individuals that are supported by differential effects on brain structure, thus indicating that the mechanisms underlying neurocognitive improvement may differ depending on the intervention [74–77]. Hötting et al. [101] found differential neurocognitive effects when comparing AE and stretching/coordination. Compared with sedentary controls, both interventions improved verbal memory, but stretching and coordination unexpectedly had a larger effect on attention than AE. Koutsandréou et al. [102] studied the differential effect of cardiovascular exercise and motor exercise in children and found that both groups had increases in working memory, but the largest increase was found in the motor exercise group. Moreau et al. [103] compared AE, complex motor training and cognitive training in healthy adults and found the largest neurocognitive effect following complex motor training.

The main analyses in the current study failed to identify differential neurocognitive effects when comparing HIIT to AVG; however, separate within-group analyses unexpectedly showed trends towards possible differential effects within the learning domain, as HIIT improved verbal but not visual learning and AVG improved visual but not verbal learning. We cannot exclude that larger statistical power in the study could have resulted in time-group interaction effects and reveal differential neurocognitive effects. We chose to comment on this, because these described differential trends are supported by Niemann et al. [104], who found a double dissociation in the sense that AE (named cardiovascular training) was associated with an increase in left hippocampal volume, and motor coordination training was associated with an increase in the right hippocampus. In accordance with this, Firth et al. [105] found that AE had a specific effect on left hippocampus volume retention. Verbal and spatial memory performance are primarily associated with the left and right hippocampal volumes, respectively [39, 106]. Both Pajonk et al. [37] and Su et al. [46] found improved verbal learning following AE. Holmen et al. [81] found that CRF was associated specifically with a verbal factor in a cross-sectional study on baseline data from the current RCT. In line with this, Hötting et al. [101] suggested that improved CRF specifically enhances memory functions, measured as verbal learning in their study, rather than a wide range of cognitive subdomains in elderly participants. However, there are inconsistencies. Lin et al. [47] compared yoga and AE to waiting-list controls in schizophrenia and found that both exercise modes improved working memory, but yoga additionally improved verbal learning and attention.

Despite being the hitherto largest RCT investigating the effect of AE on neurocognition in schizophrenia ($n = 82$), the current study was underpowered due to recruitment challenges. Based on pre-study power calculations, the targeted sample size was 126 participants, allowing for 15% dropout and resulting in a sample size of $n = 55$ per group at study end [84]. In combination with large inter-individual heterogeneity, this may have affected the possibility of detecting significant between-group effects. With equal neurocognitive improvements in both groups, a non-intervention control group would enable more definitive differentiation between practice effects and treatment effects. In-session HR was not registered in the comparison group while performing AVG, because this activity

was initially intended to control for time and interpersonal contact. With the emerging recognition of AVG as a combined physical and cognitive intervention with neurocognitive effects, the lack of in-session HR registration in this group represents a limitation in this study.

The strengths of the current study were a larger sample size than in previous studies, follow-up assessments and complete outcome data (ITT/PP). The primary outcome measure, MCCB, is designed for clinical trials on neurocognitive enhancement in schizophrenia. The interventions were supervised and standardized. The attrition rate was similar to other AE studies in schizophrenia [8]. To facilitate generalizability of the results beyond the sample, we calculated effect sizes using the change in *T* scores divided by a population-based standard deviation of 10, not sample-based standard deviations. Furthermore, we included a broad age span and a heterogeneous sample according to clinical characteristics. The duration of illness ranged from first episode to chronic phase. Baseline scores on neurocognitive functioning appeared consistent with previous studies in schizophrenia [107], indicating a representative sample of the population of outpatients with schizophrenia.

HIIT and AVG show equal neurocognitive effects but also trends of possible differential effects on neurocognitive subdomains. In line with our emerging interest in both the shared and differential effects of exercise modes on neurocognitive function, reviews by Falkai et al. [43] and Jahshan et al. [20] call for investigations of different modes of exercise in addition to length and dose questions and underlying neuroplastic mechanisms. Inspired by research on elderly individuals [108], we suggest that this may contribute to overcoming inconsistent results between studies on the effect of AE on neurocognitive subdomains in schizophrenia. Furthermore, future research should further explore the neurocognitive effects of AVG, combining different modes of physical exercise with cognitive exercise.

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Author contributions Study conception and design were initiated by JE and JAE. GB-K, JE, TLH, TTB, EA, JM, and JAE contributed to data collection, preparation of the data base and to the analyses of the data and interpretation of the results. PU contributed to the analyses of the data and interpretation of the results. GB-K wrote the manuscript as first author. All authors contributed to and critically reviewed previous versions of the manuscript and approved the final version.

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Data availability Data are sensitive in nature and as such availability is restricted and regulated by Norwegian Laws and EC laws (GDPR).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics of Southern and Eastern Norway (file number 2014/372/REK SOER-OEST).

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