Effects of Cognitive Training and Exergaming in Pediatric Cancer Survivors—A Randomized Clinical Trial

VALENTIN BENZING[1,2,3], JANINE SPITZHÜTTL[3,4], VALERIE SIEGWART[2,3], JÜRG SCHMID[1], MICHAEL GROTZER[5], THEDA HEINKS[3], CLAUDIA M. ROEBERS[4], MAJA STEINLIN[3], KURT LEIBUNDGUT[2], MIRKO SCHMIDT[1], and REGULA EVERTS[2,3]

[1]Institute of Sport Science, University of Bern, Bern, SWITZERLAND; [2]Division of Pediatric Hematology and Oncology, University Children's Hospital Bern, Inselspital, Bern University Hospital, University of Bern, Bern, SWITZERLAND; [3]Division of Neuropaediatrics, Development and Rehabilitation, University Children's Hospital Bern, Inselspital, Bern University Hospital, University of Bern, Bern, SWITZERLAND; [4]Institute of Psychology, University of Bern, Bern, SWITZERLAND; [5]Division of Pediatric Oncology, University Children's Hospital Zurich, Zurich, SWITZERLAND

ABSTRACT

BENZING, V., J. SPITZHÜTTL, V. SIEGWART, J. SCHMID, M. GROTZER, T. HEINKS, C. M. ROEBERS, M. STEINLIN, K. LEIBUNDGUT, M. SCHMIDT, and R. EVERTS. Effects of Cognitive Training and Exergaming in Pediatric Cancer Survivors—A Randomized Clinical Trial. *Med. Sci. Sports Exerc.*, Vol. 52, No. 11, pp. 2293–2302, 2020. **Purpose:** Although most pediatric cancer patients survive, those who undergo anticancer treatments like chemotherapy and/or radiotherapy are at a high risk for late effects, such as cognitive deficits. To counteract these deficits, feasible and effective interventions are needed. The aim of this study was to compare the effects of working memory training, exergaming, and a wait-list control condition on cognitive functions in pediatric cancer survivors. **Methods:** In a parallel-group randomized trial, 69 pediatric cancer survivors aged 7–16 yr (mean = 11.35, SD = 3.53) were randomly assigned to 8-wk working memory training, exergaming, or a wait-list control group. Each training course consisted of three 45-min training sessions per week. The primary outcome comprised the core executive functions (visual working memory, inhibition, switching), and the secondary outcomes included other cognitive domains (intelligence, planning, memory, attention, processing speed), motor abilities, and parent rating on their children's executive functions. Assessments were conducted both before and immediately after the interventions, and at 3-month follow-up. **Results:** Linear mixed models revealed that participants in the working memory training group showed a linear improvement in visual working memory after training and at follow-up compared with the control group. No other intervention effects of either type of training could be detected. **Conclusion:** This study presents evidence that working memory training improves visual working memory in pediatric cancer survivors. Results show that near-transfer, but no far-transfer effects can be expected from working memory training. Multiple-component interventions tailored to fit the individual's cognitive profile are needed to best support cognitive development after cancer and its treatment. **Key Words:** COGNITIVE TRAINING, PHYSICAL EXERCISE, COGNITION, MOTOR ABILITIES

Already in childhood and adolescence, physical activity seems to benefit physical and mental health (1). These health benefits associated with physical activity are highly relevant for pediatric cancer survivors because they are at risk for a variety of late effects (2). Therefore, physical activity is increasingly investigated as intervention to counteract the actual and late effects on physical and mental health. However, there is only limited research investigating the effects of physical activity intervention on the cognitive dimension of mental health (3), even though an increased risk for cognitive difficulties is a common consequence of both cancer and its treatment (4).

Prevalence estimates indicate that cognitive difficulties occur in around one-third of pediatric cancer survivors (5). Severe cognitive impairments were found in 8%–57% depending on the performance measures applied (6). The severity of these impairments largely depends on the type of tumor and treatment.

The three domains in which impairments are most salient, intelligence, memory, and executive functions (EFs) (6,7), are the focus of this study.

EFs are higher-order cognitive functions required for performing and monitoring goal-oriented, adaptive, and flexible behavior, and are therefore needed in unfamiliar, complex, and challenging situations (8). EFs are thought to embrace three core components, namely working memory, inhibition, and switching. They are of particular importance for predicting a wide range of developmental outcomes, such as mental and physical health (8). Furthermore, EFs are tightly linked to academic achievement throughout childhood and adolescence (9). Children with poor EFs have an increased risk of behavioral problems and poor academic performance, and are more likely to drop out of school (10).

Finding ways to train EFs to increase academic success and general cognitive development has thus been a frequent focus in recent psychological research in typically developing children and adolescents (8). This endeavor is particularly important in populations with a higher probability of EF impairments, such as pediatric cancer survivors, because strengthening EFs is crucial to support rehabilitation and facilitate the achievement of developmental milestones of these children. However, only few intervention studies have so far been carried out on this population.

Home-based computerized working memory training programs are feasible and effective in improving cognitive skills in pediatric cancer survivors (11,12). Attention, processing speed, and working memory have been shown to improve immediately after the intervention, and long-term effects have been documented even at 6-month follow-up (except for improvements in attention) (13,14). Considering the importance of working memory for academic achievement and the finding of transfer effects of computerized working memory training on nonverbal IQ, improving children's working memory capacity is of high relevance (15). However, because of working memory trainings with high specificity, recent reviews and meta-analyses have questioned the transfer effects of such training to untrained tasks, and additionally to EFs in a real-world context (16,17). A potential explanation for limited transfer effects is that most computerized cognitive trainings train specific EFs in isolation (17).

Physical exercise has recently been gaining increased attention in research, because it has been shown to improve cognitive functions in children and adolescents (18,19). It is thought that these beneficial effects are driven by quantitative and qualitative exercise characteristics. The quantitative characteristics include physical demands (e.g., the intensity and duration) of physical exercise and the physiological response, which is reported to enhance neurogenesis and angiogenesis (20). The qualitative characteristics (i.e., exercise type or modality) include cognitive demands (e.g., whether EFs are triggered and challenged during physical exercise), which is reported to enhance learning processes (19,21). Therefore, interventions including both physical and cognitive demands are needed.

Exergaming is increasingly used for health promotion, enabling a home-based training with both physical and cognitive challenges (22,23). Exergaming (or active video gaming) is a portmanteau derived from "exercise" and "gaming." It has shown to benefit EFs in clinical and nonclinical populations (24). Exergaming frequently has a broad focus and triggers multiple cognitive domains within one training (23). Furthermore, because in cognitive trainings, novelty and diversity are often ignored, it has been suggested that exergaming might be able provide these important factors (in a flexible and controllable fashion) and consequently increase transfer effects on cognitive functions (25). However, to our knowledge, only two studies so far have investigated the effects of physical exercise or exergaming on cognitive functions in pediatric cancer survivors, finding beneficial effects (26,27).

Against this background, we conducted a bicentric randomized clinical trial in pediatric cancer survivors to investigate whether a computerized training program specifically targeting working memory or an exergame including physical and cognitive challenges (targeting EFs more broadly) can strengthen cognitive functions. Our primary objective was to investigate the effects of both training approaches on the core EFs (working memory, inhibition, switching). We expected near-transfer effects (i.e., effects on the trained cognitive domain) for both types of training when compared with a wait-list control group: For the working memory condition, we expected a positive effect on working memory; for the exergaming condition, we expected a positive effect on all three core EFs (working memory, inhibition, switching).

Our secondary objective was to investigate potential far transfer effects (i.e., effects on less trained or untrained domains) of the training on further cognitive functions (nonverbal IQ, planning, memory, attention, and processing speed) and parent ratings on their children's EFs in real-world context. Again, positive effects were expected from both training programs. For motor abilities, however, we expected a positive intervention effect only in the exergaming condition; furthermore, we expected a change in motor abilities to be associated with a change in EFs in this condition.

MATERIALS AND METHODS

Participants. Children and adolescents were recruited at two specialized pediatric university hospitals in Bern and Zurich, Switzerland. Medical data of potentially eligible participants were provided by the Swiss Childhood Cancer Registry. Inclusion criteria were as follows: participants had to be age between 7 and 16 yr; they had to be diagnosed with cancer and cancer treatment had to be terminated at least 12 months before participation. Because the purpose of this study was to investigate interventions to improve EFs, the prerequisite for inclusion was that all participating children had direct damage to the central nervous system (CNS), or indirect consequences due to radiotherapy or chemotherapy. Children and adolescents with or without CNS involvement, in the past 10 yr, were included. If the cancer did not involve the CNS, treatment had to include either radiation or chemotherapy in addition to surgical removal of the tumor. Children and adolescents

with unstable health status or physical conditions were excluded. In addition, potential participants who were unable to follow the study procedures, for example, because of language problems, were excluded. A total of 69 children and adolescents met the inclusion criteria.

Random allocation of the 69 participants resulted in 24 children in the working memory training, 22 in the exergaming, and 24 in the control group (see Fig. 1 for details on recruitment and allocation). Two children in the working memory training group did not receive the allocated intervention because of technical difficulties, and one had a relapse of cancer (discovered at pretest); three participants were lost to posttest and five were lost to follow-up. In the exergaming group, one participant was lost to posttest and two were lost to follow-up. In the control group, two participants were lost to posttest and five were lost to follow-up. Reasons given for dropping out were noncompliance with the training, and lack of time and motivation to participate in the assessments.

According to the initial study protocol (28), a total sample size of 150 participants was planned. Despite having access to the Swiss Childhood Cancer Registry for recruitment, we did not reach this number of children during the 3 yr of study duration (recruitment rate, 26.71%). The reasons given for not participating in the study included the following: a) no interest; b) the considerable effort to follow the study procedure; c) no perceived need for action from the parents, being unaware of present late effects; and d) the long travel distance to the hospital (although the intervention was home-based, participants were supposed to come to the hospital to perform the pretest, posttest, and follow-up test). Nevertheless, for the current sample size, power calculation using G*Power revealed a power of 0.74–0.93 for the primary outcome calculated for a within-between interaction in a general model with repeated measures ($1 - \beta$ error probability = 0.80; α error probability = 0.05; small to medium effect size $f = 0.14$; number of groups = 3, number of measurements = 3).

Design and procedures. This clinical trial (see Table S1, Supplemental Digital Content 1, CONSORT checklist, http://links.lww.com/MSS/C132) was conducted in the cantons of Bern and Zurich, Switzerland, between January 2017 and December 2018. It was granted ethical approval by the respective cantonal ethics committees (Bern: KEK-NR. 196/15;
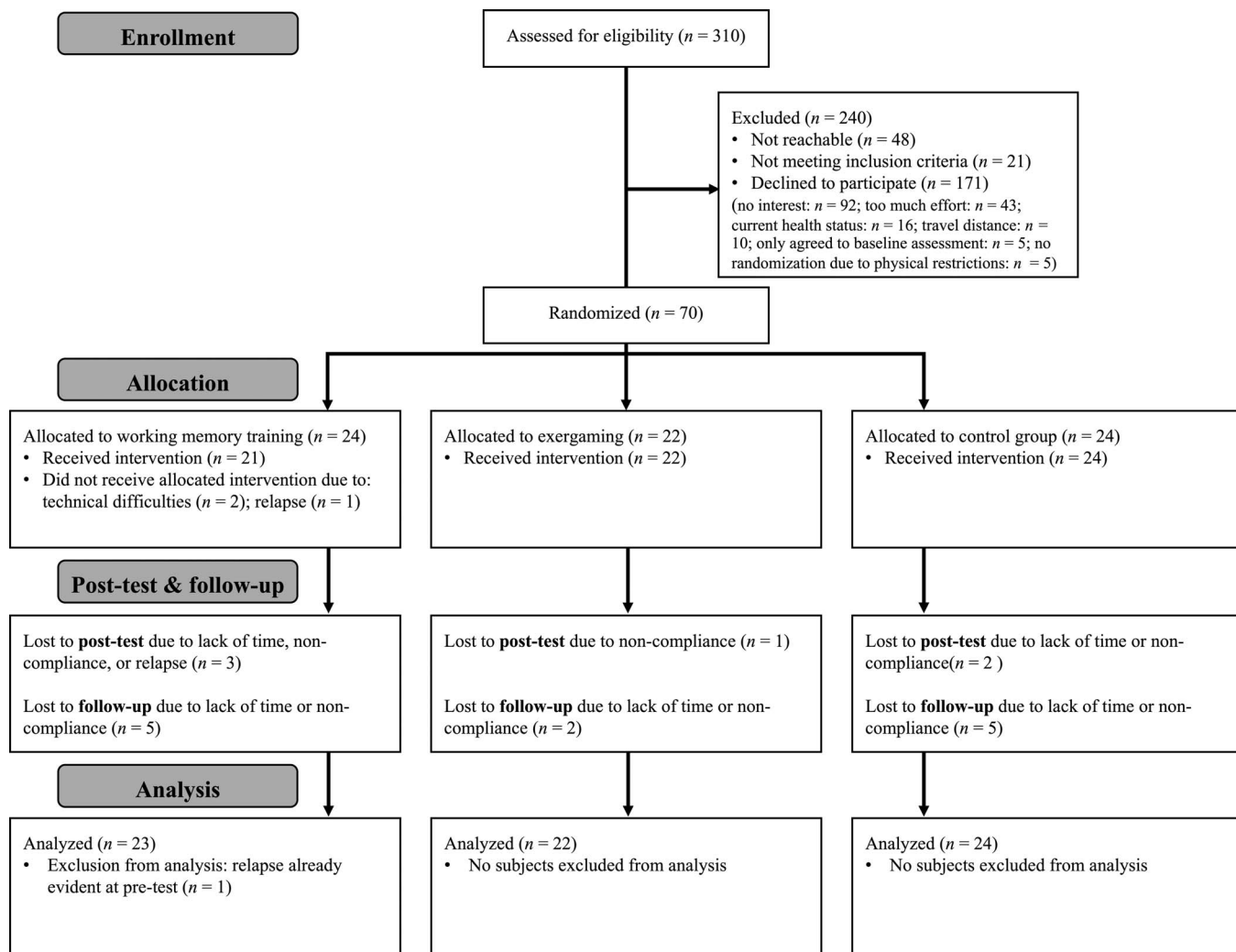

FIGURE 1—CONSORT diagram. Enrollment, allocation, completion of assessment, and training.

Zurich: ZH2015-03997) and was registered at ClinicalTrials. gov (NCT02749877). The study protocol was previously published (28). The legal guardians of all participants provided written informed consent, and the children provided assent to participate. The preinterventional assessment (pretest) measured cognitive and motor performance. Using a parallel pre–post study design, participants were assigned by a randomized and concealed allocation process until enrollment to an intervention (working memory training, exergaming) or a wait-list control group after the pretest. Randomization was performed in SecuTrial by the principal investigator (R.E.) using the minimization algorithm entering age, sex, nonverbal IQ, study center, and CNS involvement as stratification factors. Only investigators conducting the assessments were blinded to group assignment, as supervised intervention studies cannot be double-blinded. In addition, participants were blinded to the specific study hypotheses. After randomization, the interventions were set up at the participant's home, and a supervised first training session was conducted. During the interventions, a coach (psychologist or trained postgraduate student) provided weekly supervision via phone calls to address questions and increase motivation for the training. Cognitive and motor performance was assessed immediately after the 8-wk period of intervention or control (posttest), and again after 12 wk (follow-up). The assessments took place in a quiet room at the children's hospital in Bern or Zurich. After each assessment and after completing the follow-up tests, the participants received a gift and travel reimbursement.

Intervention. Parents of pediatric cancer survivors spent a lot of time in the hospital or at treatment and rehabilitation sites during and after the acute phase of their children's illness. Therefore, both interventions were designed to be conducted at the participants' home. The first intervention session in each group was supervised by specifically trained research assistants. The parents were asked to assist and support the children throughout the interventional period. Children agreed to train for 8 wk (three times a week for approximately 45 min) with either Cogmed RM® Working Memory Training (www.cogmed.com) (29) or Shape UP (Ubisoft, Montreal, Canada).

Cogmed is an adaptive working memory training program accessed via a laptop computer. It includes 13 adaptive tasks taxing the storage and manipulation of visual and verbal working memory, mostly presented in visual format. Seven of these tasks are visuospatial tasks in which children have to recall positions of a moving (dynamic) or static object, for example. The other six tasks are letter and digit span tasks targeting the storage and processing of verbal components. The exercises are presented as games ensuring motivation and enjoyment. The level of difficulty is adjusted continuously based on previous performance. The training program was monitored online by trained psychologists. In previous studies, Cogmed has been shown to improve working memory in children with attention deficit hyperactivity disorder and is frequently used in clinical practice (29).

Shape UP is an adaptive exergame, which runs on the Xbox Kinect (Microsoft, USA, Redmond, WA), a game console that includes a motion-sensing input device. Users control and interact with the console through their body movements. The user is projected directly into the virtual reality on the screen by integrated cameras. In Shape UP, physical activity is conducted playfully in the form of games. The performance during each session is recorded by the computer and participants can compete to beat their own high scores (records of old performances) in order to ensure a continuous adaptation to their level of performance. In previous studies, Shape UP has been shown to be physically (moderate-to-vigorous intensities) and cognitively challenging (22), and positive effects on EFs and motor abilities have been reported in children with attention-deficit/hyperactivity disorder (30,31).

Within Shape UP, there are six different "workouts," which incorporate physical (strength, coordination, and endurance) and cognitive demands (EFs). All of them are presented in an adaptive manner. The integration of cognitive demands seems to be crucial for beneficial effects on EFs (21) and might (to some degree) provide a simultaneous motor–cognitive training (32). The following exercises are examples for a successful integration of both characteristics. "Waterfall Jump" (inhibition, selective attention): the player stands on the edge of a waterfall and jumps onto a series of oncoming pieces (footprints) of wood without falling down. The player directs his attention to jump in the correct rhythm to hit the footprints, which vary in frequency, size, and order. "Knee up splash" (working memory): the player tries to remember a color span. Then, the player picks colored melons in the order of the given color span (e.g., green, red, blue). As soon as he starts picking up the melons, the depicted color span disappears and the participant has to rely on his memory. "Derby Skate" (working memory, shifting): comparable to aerobics or dancing, the player imitates and remembers new sequences of movements and is therefore challenged to shift the focus of attention back and forth from oneself to the physical activity instructor.

Characteristics of study participants and manipulation check variables. The following background variables were logged: a) age and sex were recorded from questionnaires; b) height and weight were measured; c) information about socioeconomic status and physical activity behavior came from the family affluence scale, completed by the parents (33), and the physical activity, exercise, and sport questionnaire (34); and d) age at diagnosis, cancer type, treatment duration/type were derived from clinical records.

During the supervised first training session, the omnibus perceived exertion scale was used as a measure of physical exertion (35). The arousal dimension of the self-assessment manikin (36) and an adapted version of it were used as a subjective measure of arousal and cognitive engagement, respectively. In addition, the feeling scale was applied to find out whether participants perceived the interventions differently (37). During the intervention, participants filled out training diaries, reporting how many training sessions they performed. Adherence was indirectly assessed from the diaries, which were part of a token system, which entitled the children to receive an additional gift if they reached at least 20 training sessions.

Primary outcome. The neuropsychological assessment was done in random order. The three core EFs (visual working memory, inhibition, switching) were measured before and after the intervention using the Block Recall Test of the Working Memory Test Battery for Children (38) and the Color-Word Interference Test of the Delis-Kaplan Executive Function System (39). An acceptable retest reliability (Block Recall Test: $r = 0.62$; Color–Word Interference Test: $r = 0.77$) has previously been demonstrated for both tests (38,39).

Secondary outcome. The secondary outcome measures comprised the following *neuropsychological assessments*. Fluid intelligence was assessed using the Test of Nonverbal Intelligence (40). Verbal working memory (subtests: Number Recall, Word Order), planning (subtest: Rover), and verbal memory performance (subtests: Atlantis, Atlantis Recall) were measured using the German version of the Kaufman Assessment Battery for Children—Second Edition (41). Selective attention (subtest: Cancellation) and processing speed (subtests: Coding, Symbol search) were assessed using the German Version of the Wechsler Intelligence Scale for Children, Fourth Edition (42). EFs in a real-world context were assessed using the behavioral regulation and working memory scales of the parent version of the Behavior Rating Inventory of Executive Functions (43). The clinical validity and an acceptable retest reliability ($r = 0.81$) have previously been demonstrated for this questionnaire (43,44). Age-normed scores were derived for the analyses (Test of Nonverbal Intelligence: mean = 100, SD = 15; Wechsler Intelligence Scale for Children, Fourth Edition; Kaufman Assessment Battery for Children—Second Edition: mean = 10, SD = 3; Behavior Rating Inventory of Executive Functions: mean = 50, SD = 10).

Motor ability was assessed using six of eight test items of the German Motor Test (45). This test measures five basic motor abilities, namely, endurance, speed, strength, coordination, and flexibility (45). In our study, strength, coordination, and flexibility were assessed (coordination: balancing backwards, jumping sideways; strength: sit-ups, push-ups, long-jump; flexibility: stand and reach). An acceptable validity and reliability ($r = 0.82$) has previously been demonstrated for the German Motor Test (45). For the present study, raw scores were transformed to age-normed z-scores. The total score (calculated from the mean z-scores of the six test items) was considered as a dependent variable (mean = 100, SD = 10). An acceptable validity (see manual) and reliability ($r = 0.82$) has been demonstrated for the German Motor Test (45).

Statistical analyses. For pre-specified data analysis plan see study protocol (28). Preliminary analyses were conducted to ensure that randomization was successful. Characteristics of the study participants (age, sex, socioeconomic status, physical activity, nonverbal IQ, CNS involvement, age at diagnosis, cancer type, treatment duration, treatment type) were compared using ANOVAs (continuous variables) or χ^2 tests (categorical variables). For feasibility analyses, ANOVAs were also used to compare participants' perception of the supervised first training session.

The main analyses for primary and secondary outcome were conducted using linear mixed models, including the main effect of time and the group–time interaction. These models were specified accordingly in order to adjust for potential baseline imbalances (46). The reported results include the control as reference group for the models; the pattern of results did not change when using the exergaming group instead. As the period between the data collection waves was not exactly equal for all participants, the individual time interval in months was used to increase the precision with which a child's growth trajectory was measured. For each dependent variable, the optimal model was determined using likelihood-ratio tests for nested models and Akaike information criterion for nonnested models. In particular, a random intercept model was compared with a fixed effects model and a model including random intercepts as well as fixed effects. The model with the best fit was subsequently chosen. Although linear mixed models are comparably robust in handling missing data, to provide an intention-to-treat analysis (see CONSORT guidelines), data were subsequently analyzed using a multiply imputed data set (10 imputations) with full conditional specification (predictive mean matching). The pattern of results did not change when the same analyses were conducted with or without the imputed data; reported results refer to multiply imputed data.

In addition to the intention-to-treat analyses, two series of per-protocol analyses were performed. The first series included only children who received the respective trainings (excluding the two children in the Cogmed condition who did not receive the training because of technical difficulties). The second series did only include participants who completed at least 10 training sessions with the respective trainings. The pattern of results did not change with the two per-protocol analyses; reported results refer to intention-to-treat analyses.

For supplementary analyses, we explored whether participants' characteristics were associated with intervention effects. Therefore, for significant group–time interactions, differential variables (age, sex, socioeconomic status, CNS involvement, age of diagnosis) were added sequentially as fixed effects to the model, including two-way (differential variable–time, differential variable–group) and three-way (differential variable–group–time) interactions. In addition, to find out whether children with poor baseline performance showed a larger improvement, for outcomes with significant group–time interactions, baseline performance was correlated to gain scores using Pearson correlations. In the exergaming condition, change in motor abilities was additionally correlated to change in core EFs. For all analyses, the significance level was set at $P < 0.05$. For the primary outcome, a Bonferroni correction was applied to account for multiple comparisons ($n = 3$).

RESULTS

Preliminary and feasibility analyses. Characteristics of study participants (Table 1) did not differ between groups ($P > 0.05$). Participants indicated that they enjoyed the interventions (Table 2), and level of enjoyment did not differ

TABLE 1. Characteristics of study participants.

	Cogmed (n = 23), Mean (SD)	Exergaming (n = 22), Mean (SD)	Control (n = 24), Mean (SD)
Age (yr)	10.71 (2.48)	11.81 (2.41)	11.13 (2.47)
Sex (% female)	11	12	8
Height (cm)	141.61 (13.69)	147.91 (14.44)	144.27 (14.66)
Weight (kg)	37.84 (12.69)	43.00 (13.47)	42.89 (15.34)
Socioeconomic status (0–9)	6.60 (1.19)	6.39 (1.93)	6.48 (1.53)
Physical activity behavior (min·month^{-1})	621.42 (549.22)	659.82 (434.62)	623.39 (735.21)
Nonverbal IQ[a]	105.87 (13.49)	106.27 (10.96)	105.46 (9.92)
Age at diagnosis (yr)	5.02 (3.17)	5.88 (3.16)	5.59 (3.14)
Leukemia and lymphomas	15	11	12
CNS tumors and neuroblastomas	4	7	5
Other cancer diagnoses	4	4	7
Treatment duration (yr)	1.32 (0.87)	1.36 (1.06)	1.33 (0.87)
Surgery	0	1	0
Radiotherapy	2	2	1
Chemotherapy	10	9	10
Surgery and radiotherapy	2	3	0
Surgery and chemotherapy	4	5	6
Chemotherapy, radiotherapy and surgery	5	2	7

[a]Age-normed score: mean = 100, standard deviation = 15; a higher score is better.

between groups ($Ps > 0.05$). Similarly, their perceived arousal and cognitive exertion were comparable ($Ps > 0.05$). Not surprisingly, exergaming was perceived more physically exerting than the Cogmed training ($P < 0.0005$).

According to the participants' diaries, they performed on average 15.13 sessions (min. = 0; max. = 25; SD = 9.59) of 45 min each with Cogmed and 18.10 sessions (min. = 4; max. = 25; SD = 8.18) of 45 min each with exergaming. The adherence rate did not significantly differ between the two groups ($P > 0.05$). Although weekly phone calls and a token system (which entitled children to an additional gift) were applied, only 47.8% in the Cogmed and 47.6% in the exergaming condition reached the prescribed amount of at least 20 training sessions. In addition, during the intervention, several children did voluntarily discontinue the study (Cogmed: $n = 3$; exergaming: $n = 1$, control: $n = 2$) because of lack of time, noncompliance, or relapse (see Fig. 1 for further details).

Main analyses for primary and secondary outcome. Analysis of the primary outcome (Table 3) revealed a significant group–time interaction for visual working memory performance. Visual working memory performance of the participants in the Cogmed group showed a statistically significant improvement over time when compared with the control group ($P = 0.012$). The estimated effect size indicates an increase of 6.6 points immediately after training and 16.5 points at follow-up when comparing the Cogmed group with the control group. However, analysis of the effects on inhibition and switching showed no significant group–time interactions ($Ps > 0.02$). For secondary outcome variables (Table S2, Supplemental Digital Content, linear mixed models for secondary

outcomes, http://links.lww.com/MSS/C133), no significant group–time interactions were detected ($Ps > 0.05$).

Supplementary analyses. When investigating differential effects of the significant group–time interaction, inclusion of additional variables (age, sex, socioeconomic status, CNS involvement, age of diagnosis) did not improve the model fit or serve as a significant predictor ($Ps > 0.05$). However, the baseline performance in the Cogmed group was negatively correlated with gain scores immediately after the intervention ($r = -0.46$, $P = 0.034$) and at follow-up ($r = -0.51$, $P = 0.044$), indicating that low baseline performers were high gainers. The change in motor abilities was not associated with change in core EFs in the exergaming condition ($Ps > 0.05$).

DISCUSSION

In the current study, we investigated whether a home-based computerized working memory or an exergame training program would be effective in improving EFs in pediatric cancer survivors. We present evidence that the working memory training improved visual working memory performance in pediatric cancer survivors when compared with the exergaming and the control condition. These findings are important given that pediatric cancer survivors frequently have deficits in the domain of working memory (7). However, besides this beneficial effect on visual working memory, neither the working memory training nor the exergame improved other cognitive functions, motor abilities, or EFs observed in a real-world context.

Given these unexpected results, the question is, why was a positive effect detected in the working memory training group

TABLE 2. ANOVAs comparing participants' evaluation of the training.

Variable	Cogmed (n = 23), Mean (SD)	Exergaming (n = 22), Mean (SD)	Control (n = 24), Mean (SD)	P	η^2_p
Enjoyment (0–4)	2.54 (0.58)	2.68 (0.41)	2.17 (0.54)	0.119	0.07
Cognitive exertion (0–10)	3.05 (2.63)	3.30 (2.15)	2.20 (1.80)	0.196	0.05
Physical exertion (0–10)	1.06[b] (1.44)	4.35[a,c] (2.23)	0.78[b] (1.42)	<0.0005	0.48
Feeling scale (–5 to 5)	3.60 (1.19)	4.14 (1.06)	2.94 (1.64)	0.013	0.13
Arousal (1–9)	6.43 (2.13)	5.00 (2.36)	5.85 (2.20)	0.127	0.06

Significant differences in *post hoc* comparisons (LSD) are indicated by superscript letters ([a]Cogmed, [b]exergaming, [c]control).

TABLE 3. Fixed and random effects for the linear mixed models—primary outcomes.

Random Effects

Level	Parameter Estimate	SE	P	95% Confidence Intervals Lower	Upper
Working Memory—WMTB-C: Block Recall Test[a]					
AR1 diagonal	272.61	98.08	0.006	79.08	466.14
AR1 ρ	0.33	0.24	0.171	−0.14	0.80
Intercept	49.27	95.59	0.607	−139.18	237.72
Inhibition—D-KEFS: Color Word Interference Test[b]					
AR1 diagonal	3.12	0.71	<0.0005	1.67	4.57
AR1 ρ	−0.12	0.22	0.586	−0.56	0.32
Intercept	3.53	0.86	<0.0005	1.84	5.21
Shifting—D-KEFS: Color Word Interference Test[b]					
AR1 diagonal	3.87	1.69	0.025	0.49	7.25
AR1 ρ	0.14	0.32	0.659	−0.52	0.80
Intercept	3.95	1.95	0.046	0.07	7.84

Fixed Effects

Effects	Parameter Estimate	SE	t Ratio	P	95% Confidence Intervals Lower	Upper
Working Memory—WMTB-C: Block Recall Test[a]						
Intercept	99.38	2.20	45.10	<0.0005	95.05	103.71
Months	0.07	1.01	0.07	0.943	−1.91	2.06
Cogmed × months	3.30	1.30	2.53	0.012	0.74	5.85
Exergaming × months	−0.46	1.32	−0.35	0.730	−3.04	2.13
Control × months	0.00	—	—	—	—	—
Inhibition—D-KEFS: Color Word Interference Test[b]						
Intercept	9.78	0.34	28.75	<0.0005	9.11	10.45
Months	0.32	0.14	2.26	0.026	0.04	0.59
Cogmed × months	0.23	0.18	1.31	0.193	−0.12	0.58
Exergaming × months	0.00	0.17	0.01	0.996	−0.34	0.34
Control × months	0.00	—	—	—	—	—
Shifting—D-KEFS: Color Word Interference Test[b]						
Intercept	10.31	0.35	29.71	<0.0005	9.63	10.99
Months	0.39	0.14	2.82	0.005	0.12	0.66
Cogmed × months	−0.23	0.18	−1.28	0.200	−0.59	0.12
Exergaming × months	−0.05	0.18	−0.29	0.775	−0.40	0.30
Control × months	0.00	—	—	—	—	—

D-KEFS = Delis–Kaplan Executive Function System; WMTB-C, Working Memory Test Battery for Children.
[a]Age-normed score: mean = 100, SD = 15; a higher score is better.
[b]Age-normed score: mean = 10, SD = 3; a higher score is better.

yet there was no effect in the exergame training group? One explanation might relate to the training contents. Visual working memory is the major training component in the working memory training, making a near-transfer effect on this cognitive domain likely. In exergaming, not all exercises include specific demands on the EFs, and these exercises do not necessarily target all core EFs simultaneously. Hence, the training intensity on each core EF was lower compared with the working memory training where mostly only one core EF (working memory) is trained. Although discussed as an intervention potentially providing broader benefits (25), our results suggest that effects on EFs might only occur when the exergame training includes higher demands on the core EFs.

In addition, Riggs et al. (26) found effects on attention, processing speed, and short-term memory, as well as on physical fitness, and white matter and hippocampal volume. Compared with the current study, however, the exercise training protocol used in the study by Riggs et al. (26) consisted of longer sessions over a longer period (3 × 45 min for 8 wk vs 3 × 90 min for 12 wk). Furthermore, Riggs et al. (26) did not use an exergame but an exercise training program, which was provided either in a group setting or a combined setting (group and home) and therefore included social interactions. Although a previous exergaming intervention using a similar protocol as the present study promoted physical and cognitive benefits in children with attention-deficit/hyperactivity disorder (31), one could speculate that the conducted exergaming intervention was not stimulating enough with regard to quantitative (duration) and qualitative characteristics (cognitive demand, social interaction) to provide benefits in pediatric cancer survivors.

The near-transfer effect in the working memory training condition, however, is to some extent in line with previous studies in pediatric cancer survivors. Using the same computerized working memory training program, these studies revealed promising effects on cognitive outcomes including visual working memory, attention, and processing speed (12,13). These improvements were maintained 6 months after the intervention (14). The results of the current study are in keeping with regard to benefits for visual working memory, which were maintained 3 months after the intervention. Working memory is known to be an important predictor of achievement in math (47) and is thought to be central to many cognitive operations (48). Because working memory impairments are frequently observed in children who have had cancer, computerized working memory training seems to be an effective means for the rehabilitation of such specific cognitive functions.

Besides this beneficial effect on visual working memory, the interventions did not improve other cognitive functions.

This finding is in contrast to Conklin et al. (13), who reported increased attention and processing speed after the same computerized working memory training. It is noteworthy that Conklin et al. (13) only included participants with working memory impairments, whereas in the current study, working memory impairments were not a requirement to participate. The finding that baseline working memory performance was inversely linked to gain scores, however, seems in line with the aforementioned study. The influence of performance level on the training effect has been shown in previous studies of working memory training (15). Working memory training seems thus beneficial for leveling out the interindividual variety in visual working memory and reducing the achievement gap between lower and higher performing children.

Besides the near-transfer effect on visual working memory, there was no evidence for a far transfer. The extent of transfer effects derived from working memory training is a controversial subject in the cognitive training literature (16). Recent meta-analyses and empirical studies showed that working memory training rarely promotes transfer effects to less trained or untrained cognitive domains (17). Findings of the current study give further empirical evidence that there are limited benefits for other cognitive domains or EFs observed in a real-world context in pediatric cancer survivors. We therefore claim that similar circumstances apply to pediatric cancer survivors as to what the authors of a recent meta-analysis have concluded regarding neuropsychological disorders (17): training EFs in isolation has limited practical relevance in pediatric cancer survivors because of the missing transfer effects.

When interpreting the study results, the recruitment and adherence rate have to be considered. Eligible participants were recruited via phone calls; nevertheless, only a small percentage (26.71%) finally participated in the study. This low recruitment rate is comparable to other studies in pediatric cancer survivors (3), and nonparticipation was often justified by the effort (including travel times to the hospital), which would be too much for the participants. In addition, the adherence of participating pediatric cancer survivors was suboptimal. Only around half of the participating children reached the desired number of 20 sessions. Although this randomized controlled trial was designed as a home-based intervention including weekly phone calls and a token system to ensure compliance, the considerable effort needed to follow the training regime might have decreased participation and the adherence rate.

From the results of the current study, some important recommendations for clinical practice can be derived. First, for pediatric cancer survivors, a training intervention over a period of 8 wk is a difficult undertaking. Adherence was limited, even though participants were guided with weekly phone calls and a token system. It seems that pediatric cancer survivors have to be guided very closely during training interventions, and a systematic inclusion of parents might be an option to increase adherence. Second, a home-based computerized working memory training program promotes improvements in visual working memory and could therefore serve as an intervention for individuals with specific impairments in this domain. However, given the limited transfer effects, a thorough neuropsychological assessment of cancer survivors should be made before identifying children with working memory deficits. Consequently, it may not be generally applicable as an intervention fostering cognitive development of pediatric cancer survivors but should be considered on a case-by-case basis. Third, currently available home-based exergaming is not stimulating enough to promote cognitive changes in pediatric cancer survivors. Therefore, longer and more stimulating training programs including, for example, a combination of physical and cognitive challenges as well as social interactions in team games (49), should be considered as part of the aftercare of these children.

In conclusion, given the increasing number of pediatric cancer survivors, it is crucial to find evidence-based interventions for targeting late effects on cognitive functions. In the current study, two interventions aiming to improve EFs were examined. A beneficial near-transfer effect on visual working memory was obtained after the working memory training, but no far-transfer effects to less trained or untrained cognitive functions were achieved by either of the interventions. Therefore, it seems that other forms of interventions tailored to the individual's cognitive profile are needed to improve cognitive functions more broadly. Because physical exercise is thought to promote transfer effects of cognitive training (25), future interventions could systematically integrate simultaneous cognitive and physical training. Such an intervention should continuously assess the cognitive and physical profile, allowing for adjustment of the training according to each individual's needs.

Limitations. The current study is not without limitations. First, a very heterogenous sample was included in the current study. Children differed with regard to time since diagnosis, type of oncological disease, and treatment type, duration, and intensity. Although intervention groups were comparable in regard to influencing factors, the heterogeneity of the sample still increases the risk for bias. Given the comparably small number of pediatric cancer survivors in Switzerland, we aimed to include as many children as possible in our study. Second, several children dropped out during the study. Although missing data were completed by multiple imputation, this procedure cannot exclude a potential bias (condition of not missing at random). Third, even though the sample size was large enough to detect small to medium effects of the intervention, the statistical power was too low to investigate differential effects of the training. With larger sample sizes, one could investigate how differences in participant characteristics (e.g., time passed since diagnosis) affect training gains from a differential point of view. Fourth, although the exergaming intervention was previously shown to be physically challenging (moderate-to-vigorous intensities) (22,30,31), in the current study, heart rate was not assessed throughout the interventional period. It therefore might be possible that some children did not reach moderate-to-vigorous intensities at all times during exergaming. This could have reduced intervention effects.

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