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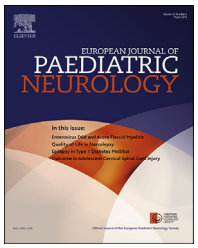

Original article

Motor function in survivors of pediatric acute lymphoblastic leukemia treated with chemotherapy-only

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ABSTRACT

Background: Up to 43% of survivors of pediatric acute lymphoblastic leukemia (ALL) may exhibit fine-motor problems. Information on manual dexterity in this cohort is still limited.
Objectives: We tested survivors of childhood ALL treated with chemotherapy-only for fine-motor function in terms of drawing and handwriting abilities using a *Digitizing Tablet* (*DT*) with three tasks for drawing and handwriting of varying complexity, for ataxia using the *International Cooperative Ataxia Rating Scale* (*ICARS*), and for tremor and hand-eye coordination using the *Nine Hole Steadiness Tester* (*NHST*).
Results: We examined a cohort of non-irradiated survivors (n = 31) after a median time of 3.5 years after end of therapy. In all tasks of the *DT* the cohort demonstrated significant ($p < 0.05$) impairment of speed, automation, and variability in at least two tasks and significantly more pressure. Impaired speed (SPV) inversely correlated with lag time since end of therapy. Dexterity performance of six survivors (19%) lay below the 5th percentile. No survivor exhibited ataxia, tremor, or impaired hand-steadiness.
Conclusion: Despite the absence of gross ataxia, tremor, and impaired hand-eye coordination, we nevertheless detected significant fine-motor impairment in a relevant number of survivors of childhood ALL. Prospective studies are needed to reveal the pathophysiological underpinnings and genetic risk factors for development of such deficits due to ALL and its treatment.

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Abbreviations

ALL	Acute Lymphoblastic Leukemia
CIPN	Chemotherapy-Induced Polyneuropathy
CNS	Central Nervous System
DT	Digitizing Tablet
HSCT	Hematopoietic Stem Cell Transplantation
ICARS	International Cooperative Ataxia Rating Scale
IT	Intrathecal
Movement ABC	Movement Assessment Battery for Children
MTX	Methotrexate
NHST	Nine Hole Steadiness Tester
PNS	Peripheral Nervous System
PP	Perdue Pegboard test
VCR	Vincristine

Kinematic parameters (DT)

F	Frequency of strokes
SPV	Arithmetical Mean of Stoke Peak Velocity
NCV	Number of Changes of y-axis Velocity
VARPV	Variation Coefficient of Stroke Peak Velocity
P	Writing and Drawing Pressure

1. Introduction

Acute lymphoblastic leukemia (ALL), the most common cancer in the pediatric age group[34] is treated by systemic and intrathecal (IT) chemotherapy with known neurotoxic adverse effects. Now, since overall survival rates have risen to around 90%,[34] attention has shifted to quality of survival. Despite replacement of cranial irradiation in the treatment protocols, neurologic deficits are still present in chemotherapy-only treated survivors of pediatric ALL, which in large parts affect fine- and gross-motor function.[22,25,26,59,73]

While several studies about incidence and progression of motor deficits after chemotherapy-only treated ALL patients were inconclusive,[24,29,30,33,37,50,58–60] even less is known in this cohort about the occurrence of ataxia,[9–11,22,46,58,71] tremor,[10] and problems of hand-eye-coordination.[9,23]

Although ataxia is a well-known sequel of cranial irradiation,[36,52] only few studies or case-reports have investigated ataxia or coordination problems in non-irradiated patients or survivors of pediatric ALL.[10,11,22,46,71] Standardized and validated tools such as the *International Cooperative Ataxia Rating Scale* (*ICARS*) have not been used for assessment so far.

Tremor and impaired hand-eye coordination are clinical conditions that impair fine-motor performance[44] and writing abilities.[66] Few studies have investigated these disorders in non-irradiated survivors of childhood ALL and reports on the presence of coordination problems range from nil to 90%[9,10,23,58] leaving uncertainty about exact incidences and the extent of disability in this cohort.

Risk factors for the impairment of motor performance are not yet well defined. While some studies did not find any significant risk factors for motor impairment,[29,59] others mentioned that IT chemotherapy,[15,52] higher dosage of vincristine (VCR),[25] a shorter lag time since end of therapy,[25,26,52] relapse,[22] lower socioeconomic status,[16] and sex[8,10,33,58] were significantly associated with a higher incidence of motor disability, impaired balance, tremor, or peripheral neuropathy.

With regard to ataxia, only one study reported a correlation between young age and upper limb coordination deficits.[23] We did not identify any studies investigating potential risk factors for tremor, hand-eye coordination, or ataxia in non-irradiated survivors of childhood ALL.

In summary, motor deficits as a consequence of ALL and its neurotoxic therapy on the central and peripheral nervous system have been studied mainly in irradiated survivors of ALL, but not sufficiently after chemotherapy-only regimens. Motor abilities are a key element of quality of life. Children and adolescents with motor deficits were shown to have reduced self-assessment of their physical and social competencies, fewer social activities, and reduced academic ambitions for their future.[12,65] Writing abilities are a relevant precondition for a successful child's scholar career, taking into account that pupils spend up to 60% of their school time performing fine motor tasks, of which the proportion of paper-and-pencil tasks is 85%.[47] In particular, manual dexterity is linked to impaired cognitive function and intellectual and scholar achievement such as mathematical and verbal academic performance.[3,20,40,50]

Hence, our aim was to examine and quantify the loss of fine motor skills often reported by children and their parents after chemotherapy-only ALL treatment.[22] We hypothesized that survivors of our ALL cohort, in comparison to their healthy peer group, would have a higher prevalence of impaired manual dexterity and might exhibit ataxia, tremor, and impaired hand-eye coordination more frequently. In addition, we set out to search for risk factors for motor impairment such as age at diagnosis, male or female sex, lag time after end of therapy, cumulative dose of chemotherapeutic agents, and extracurricular fine- and gross-motor activities.

2. Patients and methods

2.1. Participants

This cross-sectional, single-center study of survivors of childhood ALL treated with chemotherapy-only enrolled 31 patients from our pediatric oncology surveillance clinic, who

were followed between 07/2010-03/2011. Inclusion criteria were **(i)** ALL as first malignant disease diagnosed before the age of 18 years and **(ii)** treatment according to protocol. We also included patients, who were positive for blast cells but had less than 5 white blood cells/μl in their cerebrospinal fluid and were thus receiving two additional IT administrations of methotrexate (IT-MTX). All patients had sufficient language skills to understand and perform all tests. Exclusion criteria were **(i)** leukemic Central Nervous System (CNS) involvement of ALL, **(ii)** relapse of ALL, **(iii)** the presence of a neurologic disorder prior to ALL diagnosis, and **(iv)** physical or psychiatric disabilities prior to ALL diagnosis. Thirty-one (22%) patients were recruited from a cohort of 143 eligible pediatric ALL survivors treated between 1993 and 2008 at our department. 66 (46%) patients rejected our request, 26 (18%) were lost to follow-up, and 20 (14%) did not respond.

There were no significant demographic or clinical differences between participants and non-participants of this study. The same experienced pediatrician performed all examinations during a surveillance visit in our outpatient clinic. The whole examination took 60–90 min to complete and was carried out between 10 am and 5 pm. The institutional review board approved this study (EA2/011/10) and we obtained written informed consent for all aspects of this study from participants and in case of minors, from their parents as well.

Table 1 displays the characteristics of our survivor cohort and of the three healthy peer groups. Table 2 describes diagnosis and treatment regimens of our survivor cohort. Five patients below the age of 7 years were examined before they were able to write and further 3 patients before they had learned to write in cursive script. Therefore, only 23 patients performed the high-level tasks 2 and 3 on the *Digitizing Tablet* (*DT*). All patients had undergone chemotherapy according to *the ALL-BFM 90*, *ALL-BFM 95*, or *ALL-BFM 2000* treatment protocols of the *German speaking Society of Pediatric Oncology and Hematology* (*GPOH*). Standard- and medium-risk patients in the *ALL-BFM 2000* protocol had been additionally randomized for prednisone *versus* dexamethasone treatment during induction therapy and in the standard-risk arm additionally for a 50% reduction i.e. 25% reduction of total dose of VCR, doxorubicine, cyclophosphamide, and 30% reduction of dexamethasone in the re-induction phase *versus* normal dosage.[51] In summary, the *ALL-BFM 90*, *95*, and *2000* studies (excluding the less intensive re-induction arm for standard-risk patients) applied identical dosages of neurotoxic chemotherapy and were thus comparable from our perspective.

The number of patients who received prednisone *versus* dexamethasone or additional administrations of IT-MTX, and patients treated with the less intensive protocol during re-induction are described in Table 2. Patients' performances in the tests were compared to three healthy peer groups comprising **(i)** 52 healthy subjects examined with the *International Cooperative Ataxia Rating Scale* (*ICARS*)[7]; **(ii)** 187 healthy subjects examined with a *DT*,[63] and **(iii)** 1142 healthy subjects examined with the *Nine Hole Steadiness Tester* (*NHST*).[54] Age- and sex-matched control subjects were randomly chosen from the respective pool of healthy control subjects.

2.2. Methods

2.2.1. Clinical assessment

Medical records of each patient were reviewed. A standardized history and physical assessment of 15–20 min prior to our study examination excluded current relevant medical conditions that might have interfered with performance in the neurological tests. Children underwent a standardized interview to identify their regular fine- and gross-motor practice, hours per week of PC- or video-play, whether they were practicing two-handed activities (e.g. playing a musical instrument), and to define their laterality (adapted from the *Edinburgh Handedness Inventory* (*EHI*)[53]). A laterality-index was calculated ranging from −100 (strong lateralized left-hander) to +100 (strong lateralized right-hander). Subjects scoring below −40 were defined as left-handed, above +40 as right-handed, and subjects ranging between −40 and + 40 as ambidextrous. Interviews, clinical examinations and motor function tests were performed in a quiet room. All tasks were explained to the patients in a standardized age appropriate manner.

2.2.2. Digitizing tablet (DT)

We used a *DT* (*Wacom® Intouos3*) as an objective, standardized, and validated tool to analyze handwriting and -drawing abilities as an ensemble of fine-motor skills.[28,63,64] Drawing and writing are skills that children and adolescents do often practice in every-day life, and especially at school. The DT yields the possibility to measure age- and gender dependent fine-motor function at different levels of task complexity and to correlate motor impairments to different nervous system structures, i.e. higher impact of cortico-spinal nerve conduction in low complexity task 1 vs. greater involvement of neuronal motor-networks in high complexity task 2 and 3.[61,63]

The task composition, computational projection, and processing of kinematic parameters were identical to previous studies.[63,64] Each survivor was instructed to perform three tasks with the dominant hand. These comprised two complexity levels: *low complexity level*: task 1: drawing a spiral at maximum speed for 30 s; *high complexity level*: task 2: writing repeated letters ("a a a …"), and task 3: writing a predetermined sentence ("Der Ball rollt ins Tor.", translation from German: "The ball is rolling into the goal."), both in cursive script and at normal speed and level of fluency. Children attending the 2nd grade and above (n = 23) wrote in cursive letters. First graders or younger (n = 8) who were mostly unfamiliar with (cursive) writing only performed task 1. The whole examination took 15–20 min.

Identical to earlier studies,[63,64] we categorized several kinematic parameters into four movement domains: **(i) Speed**: frequency of strokes (F) and arithmetical mean of stroke peak velocity (SPV), **(ii) Automation:** number of changes of y-axis velocity (NCV) from acceleration to deceleration and *vice versa*, i.e. number of y-axis velocity maxima and minima, per stroke, **(iii) Variability**: variation coefficient of stroke peak velocity (VARPV), and **(iv) Pressure** of writing and drawing (P). Results were interpreted in an age and sex adjusted fashion. 187

Table 1 – Demographic and clinical characteristics of ALL survivors and healthy peer groups.

	SURVIVORS OF ALL (n = 31)		PEER GROUP *DT* (n = 187)		PEER GROUP *ICARS* (n = 52)		PEER GROUP *NHST* (n = 1142)	
	median	(min/max)	median	(min/max)	median	(min/max)	median	(min/max)
Age [years] at diagnosis	3.7	(1.6/9.8)						
Age [years] at evaluation	9.5	(6.1/18.3)	11.0	(6.0/18.0)	10.5	(4.2/17.0)	12.0	(6.0/25.0)
Lag time [years] since end of therapy	3.5	(0.3/14.0)						
Weeks of intensive chemotherapy	31.2	(28.0/49.0)						
Sex	Total n	(%)	Total n	(%)	Total n	(%)	Total n	(%)
Female	14	(45.2)	102	(54.5)	26	(50.0)	602	(52.7)
Male	17	(54.8)	85	(45.5)	26	(50.0)	540	(47.3)
Handedness								
Right-handed	24	(77.4)	166	(88.8)			1027	(89.9)
Left-handed	3	(9.7)	6	(3.2)			115	(10.1)
Ambidextrous	4	(12.9)	15	(8.0)			n.d.	
	median	(min/max)	median	(min/max)				
Laterality index	80.0	(−100.0/100.0)	87.5	(−100.0/100.0)				
Fine motor exercise [hours/week]	2.8	(0.0/10.0)	1.0	(0.0/40.0)				
Gross motor exercise [hours/week]	0.0	(0.0/10.0)	0.0	(0.0/42.0)				
PC/video game [hours/week]	4.0	(0.0/21.0)	2.0	(0.0/50.0)				
Two-handed activity learned	35.5%	(yes)	65.8%	(yes)				
	51.6%	(no)	34.2%	(no)				
	12.9%	(na)						

ALL, survivors of acute lymphoblastic leukemia; *DT*, *Digital Tablet;* *ICARS*, International Cooperative Ataxia Rating scale; *NHST*, Nine Hole Steadiness Tester. The *Laterality index* was determined for ALL survivors and the DT peer group with the *Edinburgh Handedness Inventory (EHI)*, and with a questionnaire for the *NHST* peer group.

Table 2 – Clinical characteristics of survivors.

	Total n (%)
CNS status	
CNS-infiltration (CNS positive)	0 (0.0)
Cerebrospinal fluid ≤5 white blood cells/μl	3 (9.7)
Cerebrospinal fluid contaminated with blood	3 (9.7)
Extra MTX-IT	6 (19.4)
Type of all	
Immature B-ALL (pro-B-ALL)	1 (3.2)
Common B- ALL (c-ALL)	26 (83.9)
Precursor B-ALL (pre-B-ALL)	4 (12.9)
Protocol	
ALL-BFM-90	1 (3.2)
ALL-BFM-95	2 (6.5)
ALL-BFM-2000	28 (90.3)
Cranial irradiation	0 (0.0)
Induction	
Prednisone	17 (54.8)
Dexamethasone	14 (45.2)
Re-induction	
Less intensive protocol	2 (6.5)
Risk-group	
Standard risk (SR)	20 (64.5)
Intermediate risk (IR)	11 (35.5)

CNS-infiltration was diagnosed if cranial MRI was positive or if cerebrospinal fluid contained more than 5 white blood cells/μl. Extra MTX-IT was applied *via* two additional doses of intrathecal methotrexate during the intensive part of chemotherapy. ALL-BFM protocols were approved by the German speaking Society of Pediatric Oncology and Hematology (GPOH). INDUCTION; number of ALL survivors having received prednisone *versus* dexamethasone during induction therapy. RE-INDUCTION: Less intensive protocol with reduced dosage for VCR, doxorubicine, cyclophosphamide, and dexamethasone during re-induction.

healthy control subjects were examined with the *DT*.[63] Age-group[h] and sex adapted z-scores of ALL survivors' kinematic parameters were calculated using the corresponding section of the healthy reference group.

2.2.3. *The International Cooperative Ataxia Rating Scale (ICARS)*

Patients were examined for the presence and severity of cerebellar ataxia, using the *ICARS*-scores.[69] This scale has 19 items spread out over 4 subscales for assessment of **(i)** gait, postural and balance disorder, **(ii)** limb ataxia, kinetics and limp-coordination, **(iii)** speech, and **(iv)** oculomotor disturbance. Total scores achieved on the *ICARS* range from 0 (no impairment) to 100 (high level of ataxia). The test took 5–10 min to administer. Total *ICARS* and subscale scores were interpreted in an age-adjusted manner. 52 healthy control subjects were examined with the *ICARS*.[7] Age-group[h] and, for speech, sex adapted z-scores of ALL survivors' *ICARS*-scores were calculated using the corresponding healthy reference group.

2.2.4. *Nine Hole Steadiness Tester (NHST)*

A Motor Steadiness Tester (*NHST*)[54] modified for children, measuring postural isometric tremor of the whole upper limb (shoulder, elbow, wrist) in case of physiological or essential tremor, was used to determine the incidence and extent of loss of manual steadiness and to quantify its severity in survivors of pediatric ALL. Furthermore, the *NHST* measures hand-eye coordination, manual dexterity, concentration, and the integrity of proprioception for hand position in space.[43] The whole examination took 10–15 min to administer. The advantage of this tool lies in its noninvasiveness and high compliance in children. The task composition was analogous to the study of Pfuhlmann et al.[54] Subjects held a 32 cm long, 97 g weighing stick with a metal-tip of 2 mm diameter with the dominant hand for 30 s inside 9 holes of varying diameter (50–4 mm) of a metal plate. Numbers of contacts (ST-score) were counted electronically for each hole. More contacts meant a stronger loss of hand steadiness. 1142 healthy subjects between 6 and 25 years of age were examined with the *NHST*.[54] Age and sex adapted z-scores of ALL survivors' ST-scores for the holes of 10 mm (ST10), 7 mm (ST7), and 5 mm (ST5), as well as cumulative ST-scores (total score), and the area under the curve (AUC-score) between the 50 and 5 mm holes were calculated using the cumulative results of the corresponding healthy reference group.

2.2.5. *Statistical analysis*

Descriptive statistics were calculated with the software R Studio.[62] Age and/or sex adjusted z-scores of kinematic-, *ICARS*-, and ST-parameters were calculated using the respective healthy peer group to establish a correction of age and if indicated of sex as well. We pooled patients above 16 years of age into a single group because the influence of age diminishes during adolescence for all tools.[7,54,63] We calculated z-scores for *ICARS* and the *NHST* by adding 0.1 to all data as they are unidirectional and the lowest value is zero. Sixty-two (*DT*, *NHST*) and 31 (*ICARS*) age and sex-matched subjects were randomly chosen from each control group for matched pair analysis. Differences between ALL survivors and matched pairs as well as z-scores between ALL survivors and the respective healthy peer group were tested using the nonparametric Mann–Whitney U-test. Differences of frequency distribution between primary data of ALL survivors and respective peer groups were calculated using the χ^2-test and if indicated the Mann–Whitney U-test. Effect size for functional impairment was calculated using Hedges' g.[27] We tested for potential risk factors that could predict an unfavorable motor performance, which were **(i)** male or female sex, **(ii)** age at diagnosis, **(iii)** length of induction therapy, **(iv)** lag time since end of therapy, **(v)** prednisone *versus* dexamethasone for induction, **(vi)** less intensified protocol for re-induction, **(vii)** additional IT-MTX administration, **(viii)** laterality, **(ix)** laterality-index, and **(x)** fine-motor practice. Spearman correlation was applied to determine the strength of interaction between possible risk factors. Number of patients scoring below the 5th percentile, i.e. z-scores ≤ −1.645 for F, SPV, P, and ICARS- as well as NHST-values or ≥ +1.645 for NCV and VARPV, or 5–15th percentile i.e. z-scores between −1.036 and −1.645 for F, SPV, P, and ICARS- as well as NHST-values or between +1.036 and + 1.645 for NCV and VARPV, were calculated to determine total number and percentage of ALL survivors with *definitive* (≤5th percentile) or *probable* (5–15th percentile) motor impairment. A

[h] Age-groups: 6–7, 8–9, 10–11, 12–13, 14–15, ≥ 16.

Bonferroni-corrected significance level was assumed for $p \leq 0.01$ for z-score analysis of five kinematic parameters. As 10 potential risk factors were correlated with fine-motor z-scores, the Bonferroni-corrected significance level was set to $p \leq 0.005$.

3. Results

3.1. *Demographic and clinical characteristics of patients*

All participants had normal results on clinical neurologic examination at the age of diagnosis. Characteristics of survivors of ALL and of the healthy peer groups are depicted in Tables 1 and 2. Our cohort was significantly younger (−2.2 years; 95% confidence interval −3.6 to −0.5) than the whole group of healthy subjects examined with the *NHST*. There were no significant age differences between survivors of ALL and healthy subjects examined with the *DT* or *ICARS*. Sex-ratio did not differ between groups. Among our cohort we found significantly more lefthanders ($p = 0.04$, effect size, i.e. Hedges' g 0.4, data not shown) and a tendency for less right-handers ($p = 0.08$, data not shown) if compared to healthy peers. Percentage of ambidextrous and absolute-values for laterality index did not differ significantly between our cohort and healthy peers, indicating that survivors of ALL were not less lateralized. ALL survivors performed significantly more often fine-motor exercise in their daily routines (1.5 h per week; confidence interval 0.5–2.0, Hedges' g 0.3), more PC/video-gaming (1.0 h per week; confidence interval 0.0–3.0, Hedges' g 0.2) and significantly less survivors had learned or were learning a two-handed activity. In contrast, there was no difference in time of extra-curricular gross-motor exercise between our cohort and healthy peers. We did not find significant differences of age, sex, handedness, or laterality index between survivors of ALL and matched-pair controls.

3.2. *Fine-motor function, hand-eye coordination, upper limb steadiness and ataxia in ALL survivors*

Fig. 1 displays the box plot of z-scores for all 3 tasks on the *DT*. Table 3 shows results for all 3 tasks on the *DT*, total score and area under the curve between 50 and 5 mm holes for *NHST*, and total score for *ICARS*. In comparison to healthy peers, survivors of ALL performed significantly worse on the *DT*, but not if tested with the *ICARS* or the *NHST*. Compared to the whole healthy peer group, survivors used significantly more pressure (P) in all three tasks with an effect size of Hedges' g 0.6–0.8. Their variability was significantly higher when performing the high complexity tasks 2 and 3 (Hedges' g 0.6), but not when completing the low complexity task 1. Survivors drew with significantly inferior automation in task 1 and 3 (Hedges' g 0.7–1.4). Next, they were often significantly slower (reduced F in task 1 and 3, Hedges' g 0.6–1.0, SPV in task 1, Hedges' g 0.7) but not in all tests. Comparison to age- and sex-matched controls corroborated the above-mentioned results. Supplemental table 1 displays the number of survivors that had critically impaired fine-motor function, i.e. kinematic parameters below 5th and between 5 and 15th percentiles when tested with the *DT*, *ICARS*, and *NHST* as compared to healthy peers. Survivors of ALL had definitive drawing and writing impairment, i.e. at least two kinematic parameters scoring ≤5th percentile in 6 individuals (19.4%), in task 1, 1 individual (4.3%) in task 2, and 4 individuals (17.4%) in task 3.

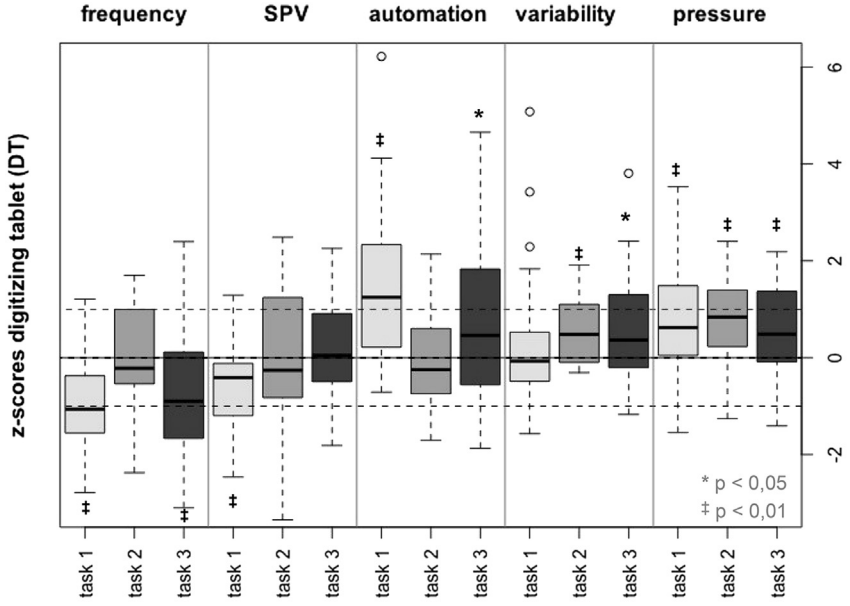

Fig. 1 – Distribution of ALL survivors' kinematic parameters (z-scores). Boxplot of age- and gender-adapted z-scores of survivors' kinematic parameters on the *DT* (task 1–3) as compared to the healthy peer group. Differences of median were calculated using the one-sided non-parametric Mann–Whitney U-test. Significance levels for differences from the control group: *, $p \leq 0.05$; and after Bonferroni correction: ‡, $p \leq 0.01$ level; SPV, Stroke Peak Velocity.

Table 3 – Quantitative assessment of fine-motor impairment, ataxia, and tremor in ALL survivors.

	Z-Score	ALL *vs* peer group	Effect size	ALL *vs* Matched-pairs	Effect size
	Median (SD) mean	P-value	Hedges' g	P-value	Hedges' g
DIGITAL TABLET					
Task 1: Drawing circles					
F	−1.06 (0.94) −0.95	<0.001‡	0.98	<0.001‡	1.05
SPV	−0.41 (0.88) −0.63	0.001‡	0.65	<0.001‡	0.76
NCV	1.25 (1.68) 1.52	<0.001‡	1.38	<0.001‡	1.10
VARPV	−0.07 (1.35) 0.33	0.101	0.32	0.091	0.40
P	0.62 (1.02) 0.74	<0.001‡	0.76	0.038*	0.40
Task 2: Writing repeated letters					
F	−0.22 (1.08) 0.11	0.745	0.11	1.000	0.26
SPV	−0.26 (1.37) −0.02	0.557	0.01	1.000	0.20
NCV	−0.25 (1.08) −0.01	0.562	0.01	<0.001‡	0.26
VARPV	0.48 (0.70) 0.54	0.007‡	0.58	<0.001‡	0.38
P	0.84 (0.91) 0.73	<0.001‡	0.76	<0.001‡	0.57
Task 3: Writing a sentence					
F	−0.90 (1.48) −0.59	0.008‡	0.56	0.013‡	0.53
SPV	0.05 (1.13) 0.09	0.652	0.09	0.187	0.18
NCV	0.46 (1.68) 0.71	0.021*	0.65	0.029*	0.58
VARPV	0.36 (1.21) 0.61	0.016*	0.61	0.018*	0.62
P	0.49 (0.93) 0.59	0.003‡	0.61	0.056	0.44
ICARS					
Total score	−0.12 (2.38) 0.61	0528	0514	098	
NHST					
Total score	0.06 (1.03) −0.13	0.537	0.841	0.32	
AUC-score	−0.54 (0.97) −0.01	0.680	0.680	0.65	

ALL survivors were compared to the whole group of healthy peers (age and sex-adapted z-scores) and additionally to age- and sex-matched-pairs randomly chosen from each peer group (62 healthy subjects for *DT* and *NHST*, 31 healthy subjects for *ICARS*) using the one-sided non-parametric Mann–Whitney U-test. P-values display the level of significance for smaller median values of F and SPV or larger median values of NCV, VARPV, and P. Significance levels for differences from the control group: *, $p \leq 0.05$; and after Bonferroni correction: ‡, $p \leq 0.01$. The effect size (*Hedges g*) was calculated for kinematic parameters taking into account the different group sizes (ALL survivors n = 31 *versus DT* peer group n = 190) and pooled standard deviation.

3.3. *Risk factor analysis for abnormal fine-motor function*

Fig. 2 shows the correlation between the time lag since end of therapy and velocity (z-scores of SPV), as well as the correlation between the duration of the intensive part of therapy and automation (z-scores of NCV). The shorter the time lag the slower survivors of ALL performed on the *DT* in all 3 tasks. If considering only the first 8 years after end of therapy, this correlation was even stronger for task 1 and 3. Survivors who had received prednisone during induction therapy used more drawing- and writing-pressure (Supplemental figure 1). These results might be biased as further analysis revealed that survivors of ALL from the dexamethasone-arm had a significant shorter time lag since end of therapy than those from the prednisolone-arm (prednisolone-group median 4.5 years lag time, dexamethasone-group median 3.3 years lag time, $p = 0.039$). With increasing age at diagnosis only variability increased in task 3 (VARPV, Spearman rho = 0.41, $p = 0.05$, data not shown). Higher laterality-index of ALL survivors correlated with less variability in task 2 (VARPV, Spearman rho = −0.41, $p = 0.05$, data not shown). Correlation of lateralization with lower frequency in task 1 reached only a tendency (F, Spearman rho = −0.35, $p = 0.053$, data not shown). No significant correlation was found for any of the kinematic parameters with additional cofactors such as more intensified IT-therapy, differently intensive protocols during re-induction, or fine-motor practice (data not shown). When taking the Bonferroni-corrected significance level of $p = 0.005$ into account, none of the tested parameters correlated significantly with any impaired kinematic parameter.

4. Discussion

In our cohort of survivors of pediatric ALL having received chemotherapy-only, fine-motor function in terms of drawing and writing abilities in were significantly impaired at a median lag time of 3.5 years since the end of therapy. Up to 19% of the cohort scored below the 5th percentile and a further 29% between the 5–15th percentile for at least 2 kinematic parameters in a simple task on a *DT*. Inferior speed recovered significantly with increasing lag time in all three tasks on the *DT*. Yet, we did neither detect ataxia nor tremor in our cohort of chemotherapy-only ALL survivors.

4.1. *Fine-motor function*

Three and a half years after end of therapy we found loss of fine-motor function in terms of impaired drawing and writing abilities as indicated by altered kinematic parameters, i.e. pressure in all tasks and speed, variability and automation in almost all tasks tested with the *DT*. The mean effect size of all impaired kinematic parameters was high (Hedges' g 0.8).

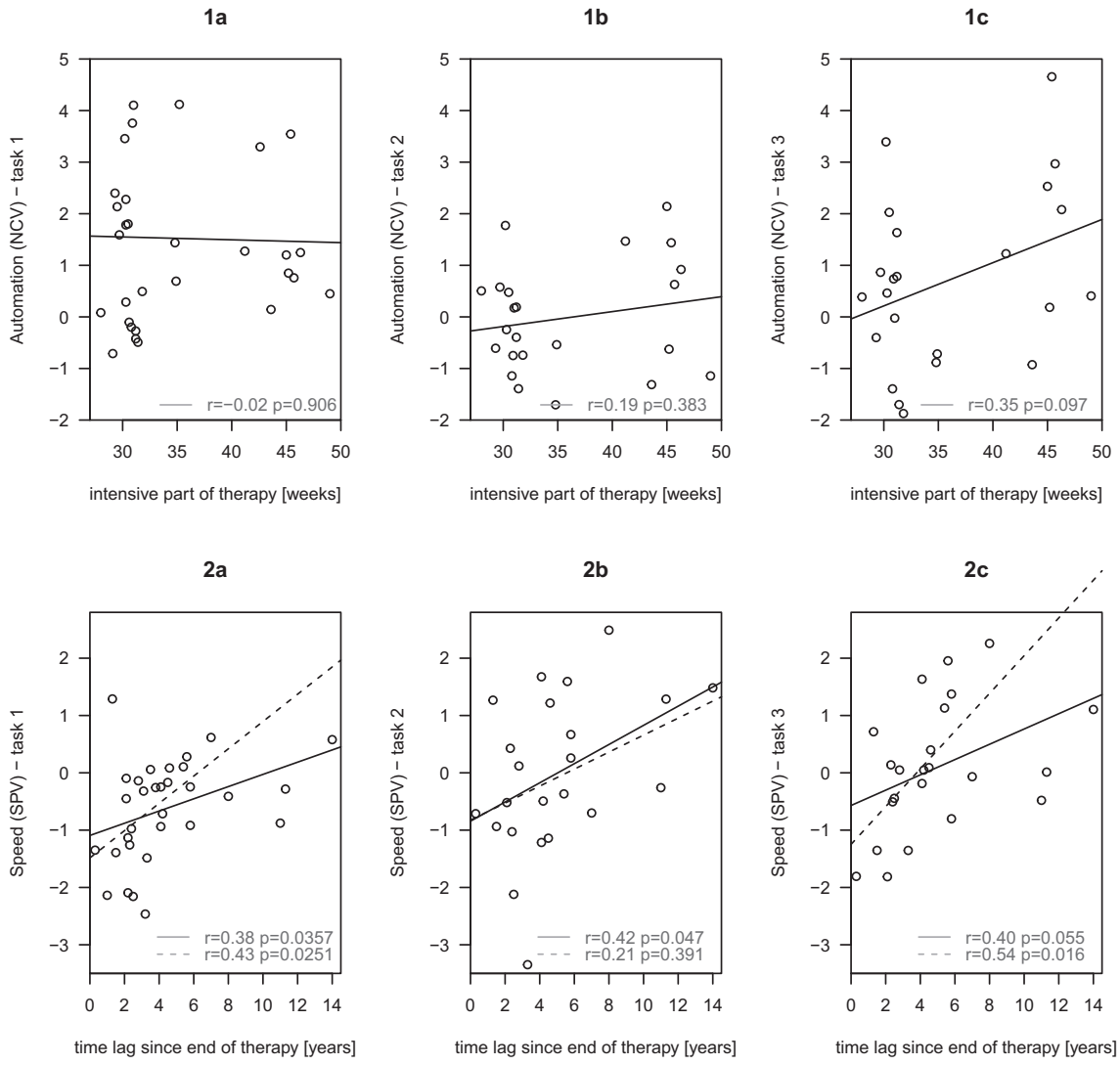

Fig. 2 – Correlation of kinematic parameters (*DT*) with duration of intensive part of therapy and time lag since end of therapy. 1a-c: Continuous regression line: correlation for the entire time-period of intensive part of chemotherapy, i.e. start of induction to end of re-induction therapy. 2a-c Continuous regression line: correlation for the entire time-period after therapy; Broken regression line: estimated correlation for the first 8 years after end of therapy.

These findings are partially in accordance with results from Reinders-Messelink et al., who found that drawing pressure in non-irradiated ALL survivors increased from the time of diagnosis to 46 weeks later, whereas impaired speed and pause duration recovered after end of VCR-therapy.[60] At least 2 years after therapy, Reinders-Messelink et al. only found prolonged pause duration in the younger ALL survivors.[59] The differences between our studies may be explained in part by a different experimental design, different kind of kinematic parameters, and the low number of participants in the study of Reinders-Messelink et al., which would limit the discriminatory power for detection of subtle changes in fine-motor function.

Other cross-sectional studies that examined childhood ALL survivors' fine-motor skills with the *Movement Assessment Battery for Children* (*movement ABC*) or *Perdue Pegboard* (*PP*) corroborate our findings of fine-motor impairment in non-irradiated ALL patients during and up to 10 years after therapy.[30,33,37,38,58,59] Two longitudinal studies of childhood ALL survivors with the *PP* revealed improving but still significantly impaired fine-motor performance over all time-points between 8 weeks and 2–5 years after diagnosis.[29,50] Syrjala et al. found impairment of motor dexterity with the *Grooved Pegboard* in adult cancer survivors, who had received hematopoietic stem cell transplantation (HSCT) after previous chemotherapy with or without irradiation at 1–5 years after HSCT. Interestingly, almost 40% of cancer survivors never showed impaired motor skills, ≈30% were impaired initially but recovered, and another ≈30% remained impaired 5 years after HSCT.[67]

Taken together, we cannot exclude that we might have had detected a lesser degree of fine-motor pathology in our cohort if examined after a longer time lag since end of therapy. It remains unsolved what the underlying pathomechanisms of impaired handwriting capacity of ALL survivors 3.5 years after therapy might be. The impaired motor function may either

reflect neuronal damage caused by the ALL itself, neurotoxicity of anti-leukemic treatment, or neurodegeneration after therapy with progression over time. Still, it is an important finding, as impaired fine-motor function may reduce self-confidence, participation in daily social activities, and academic ambitions and may be the cause for worries about their future.[12,65] Manual dexterity was strongly associated with intellectual and scholarly achievement.[3,20,40]

4.2. *Risk factors for impaired fine-motor function*

We found a tendency towards normal speed (SPV) with longer time lag since end of therapy in all three tasks. This correlation was especially high and significant in tasks 1 and 3 for the first 8 years after end of therapy. This is in line with other studies describing improvement of impaired motor-performance secondary to disease and therapy over time after end of neurotoxic chemotherapy.[29,50,60] Therefore, we assume that neuronal plasticity after therapy allows improvement of kinematic deficits. Whether the rate of recovery is higher in the first years after therapy and slows down or stops after a certain time period warrants further prospective longitudinal studies.

The survivor group who had received prednisone instead of dexamethasone during induction therapy performed tasks 1 and 2 with more pressure. As these two subgroups differed significantly with respect to the time lag since end of therapy (prednisolone-group median 4.5 years, dexamethasone-group median 3.25, $p = 0.039$), we cannot exclude interaction-bias. In contrast, two other studies revealed more CNS deficits or myopathic effects in survivors of ALL having received dexamethasone instead of prednisolone.[5,51]

We did not find any significant difference of kinematic parameters between female and male survivors of ALL. Sex as a risk factor for developing fine-motor impairment has been studied insufficiently and reports are controversial. Two studies found female survivors to have better fine-motor function than males if tested with the *Movement ABC* or *PP*,[33,58] whereas two other studies showed that female sex was a risk factor for impaired visuomotor control and fine motor function after chemotherapy.[8,10] So far, most studies investigating ALL patients or survivors on the *DT*, *PP*, *Movement ABC*, or *Beery Developmental Test of Visual-Motor Integration* did not report any significant differences for sex.[29,37,38,50,67]

As several studies found a significant correlation between younger age and more severe impairment of motor performance and visuomotor control,[10,16,58,59] we expected age at diagnosis to be a robust predictor for impaired motor function after end of therapy. However, we did not find any correlation between younger age and impaired motor performance. Conversely, we found that older age at diagnosis was associated with higher variability in the more complex task 3. Neither Jansen et al. nor Kingma et al. found a correlation between age and fine-motor performance if tested with the *PP*.[33,37,38]

We had hypothesized that extra-curricular motor practice would positively influence handwriting and -drawing skills. There might be an interdependence of dexterity and choice of leisure activity in accordance with personal interests, motivation, and physical capabilities. Thus, somebody who disposes of high dexterity may increase this advantage by his choice of leisure activity. However, we were unable to statistically verify a positive influence of leisure activity. This may be explained in part as reduced motor abilities in our cohort may have led to selection of easier activities thereby weakening the effect of extra-curricular motor practice. Motor-practice in our setting did not reflect any approved training program. As several studies have shown positive effects of *specific* training programs on dexterity and handwriting skills of children with poor handwriting abilities, developmental coordination disorders, or visual impairment[2,19,49,57] we suggest that also patients or survivors of ALL with impaired motor function may benefit from such guided interventions to improve upper limb dexterity, which in turn should be evaluated in a prospective setting.

In summary, we did not find any significant correlation between impaired fine-motor performance and other putative clinical risk factors. Further longitudinal studies of non-irradiated ALL survivors are required to identify risk factors for fine-motor deficits after therapy.

4.3. *Handedness in pediatric ALL survivors*

We found more left-handed survivors of ALL 3.5 years after therapy than expected. Although this finding was significant with a medium effect size (Hedges' g 0.5) and a trend for fewer right-handers, it is most probable a random result due to our comparatively small sample size. However, shift of handedness has been described after early brain damage such as left temporal lobe epilepsy or bacterial meningitis.[14,42,55] A very speculative explanation for our findings might be that leukemia and its treatment may have led to a shift of handedness as result of a cerebral adaptation or re-organization after neurotoxic damage. We did not find other studies examining handedness in patients or survivors of ALL. From our perspective, handedness or the change thereof is worth being investigated in future prospective studies.

4.4. *Pediatric ALL survivors do not present ataxia*

In our cohort of non-irradiated ALL survivors none had cerebellar ataxia nor impairment of balance, coordination, speech, or oculomotor function if examined with the *ICARS*. This is in accordance with a study of Buizer et al. who neither found ataxia on clinical examination of motor function in non-irradiated ALL survivors more than one year after therapy.[10] In general, ataxia in non-irradiated ALL survivors might be rare, as we found only few reported cases of ataxia in ALL patients during intensive chemotherapy and no reports using standardized ataxia tests.[11,46,71] Götte et al. support our findings revealing no significant upper limb coordination impairment in their cohort of mostly non-irradiated childhood cancer survivors.[23] Contrary to our results, Wright et al. found impaired balance in ALL survivors if tested with the *Bruininks-Oseretsky Test of Motor Proficiency* 3.3 years after therapy.[73] This discrepancy may be explained as the majority of their cohort (29 out of $n = 36$) had received cranial irradiation. In another study, 7.5% of non-irradiated ALL survivors reported in a questionnaire to experience coordination deficits even 20 years after diagnosis.[22] While in

irradiated ALL survivors ataxia appears to be a common adverse effect,[36,52] it seems to be rare after chemotherapy-only or might in some survivors only develop with a long time lag after end of therapy.

4.5. *Tremor is not detectable in pediatric ALL survivors*

In our study, ALL survivors did neither show isometric tremor nor impaired hand-eye coordination if examined with the *NHST*. Corroborating our findings, Buizer et al. did not find tremor in non-irradiated ALL survivors more than one year after therapy,[10] whereas in a study by van Brussel et al. 4 out of 13 ALL survivors showed hand-eye coordination below the 5th percentile with the *Movement ABC* 5 years after chemotherapy-only.[9] In a mixed group of 47 pediatric oncologic survivors, Götte et al. found that at the end of intensive therapy hand-eye coordination of 87% of patients was below average if tested with the *Test for Motor Performance in Pediatric Oncology*.[23] Thus, after chemotherapy-only, impaired hand-eye coordination may be a late adverse event. Further studies are necessary to clarify the exact incidence and time-point of occurrence.

4.6. *Pathophysiological explanations for fine-motor impairment*

The impaired motor performance of our cohort may be explained by toxicity to several structures of the nervous system: the muscle compartment, the peripheral and the central nervous system.

Our results could be explained by direct muscle fiber damage related either to the anti-leukemic therapy or to a more sedentary lifestyle, resulting in decreased muscle strength described for other pediatric patients with chronic disease.[18,72] Several studies reported reversible corticosteroid induced myopathy and reduced limb-muscle strength in survivors of ALL during and 3.3 years after therapy.[1,5,73] Still, as our cohort did not significantly differ from healthy peers concerning extra-curricular gross-motor activity, general muscle weakness seems a less probable explanation for their impaired fine-motor function.

Motor impairment in our cohort particularly the increased drawing-pressure in the low-demanding task may be secondary to chemotherapy-induced polyneuropathy (CIPN). Despite a high incidence of CIPN in pediatric ALL patients during treatment it is well known to recover with increasing lag time after end of therapy. Still, 16–68% of ALL survivors are reported to suffer from CIPN 2–3 years after end of therapy.[21,32,41,56,68] Axonal damage and demyelination of the peripheral nervous system (PNS) has been described in electrophysiological studies in irradiated and non-irradiated ALL survivors up to 5 years after therapy.[24,39] Harila et al. revealed an inverse correlation of conduction delay of magnetic-evoked potentials between the brachial plexus and hand with recovery time after therapy.[26] In accordance with this report, we found a significant correlation between lag time after end of therapy and the normalization of speed in our cohort.

Fine-motor function in terms of drawing and handwriting abilities do not only depend on intact peripheral nerves and muscles but also on hand-eye coordination, visuomotor integration, visual- and motor-perception, and higher cognitive function, i.e. motor planning, reaction time, performance IQ, motor-coordination and sustained attention.[13,17,20,45,64,70] While some studies showed that global intelligence may not be affected in non-irradiated survivors of pediatric ALL,[30,31,35,37,38] others reported specific cognitive functions to be impaired up to 20 years after therapy, i.e. visuomotor integration,[10,33,38,48] executive functions,[35] processing speed, working memory,[4,30,31,35] visuomotor and sustained attention,[4,30,31] and verbal and reading comprehension.[4,30,31] The absence of tremor, impaired hand-eye coordination when examined with the NHST, and ataxia (ICARS) in our cohort allows us to suggest that fine-motor deficits in ALL survivors are rather related to PNS damage than to whole CNS damage or cerebellar functional impairment. The highest number of survivors (19%) to perform below the 5th percentile on the DT was found for the low-complexity but speed dependent task 1 (drawing circles). This was also the task where we found most of kinematic parameters to be significantly impaired. In this task higher cognitive functions do play a lesser role than in the high-complexity tasks.[61,63] Nevertheless, at this point we cannot exclude that survivors' lower performance on the DT, especially in the high-complexity tasks, may also have been modulated by impaired cognitive function.

4.7. *Limitations of our study*

We are aware of limitations of our study: **(i)** ALL survivors were significantly younger (2.2 years) than healthy subjects examined with the *NHST*. Although, z-scores are age-adapted, we cannot completely exclude a subsequent bias in our findings concerning results for parameters of *NHST*. **(ii)** Due to the small sample size of 31 ALL survivors, smaller effects or less frequent symptoms such as isometric tremor, impaired hand-eye coordination, or ataxia may not have been detected by our methods. As only 22% of eligible patients eventually participated in our study, while 46% rejected our request, we cannot exclude a certain selection bias when interpreting our results. **(iii)** The cross-sectional design of our study limits conclusions about the temporal dynamics of fine-motor impairment. **(iv)** ALL survivors and healthy peers were not examined by the same investigators. Despite the fact that all tools were standardized, we cannot fully exclude limited inter-observer reliability. **(v)** We did not examine survivors for cognitive function or learning abilities. Since motor function is also influenced by higher cognitive processes, we cannot exclude that cognitive impairment to some extent may have contributed to fine-motor deficits observed in our cohort.

5. Conclusion

ALL survivors treated with chemotherapy-only exhibit relevant deficits of fine-motor function. The underpinnings of this neurotoxicity are not yet fully understood and seem to be most probably caused by PNS damage.[21,24,26,32,39,56,59,68] An important question will be to which extent fine-motor deficits correlate with the dynamics of CIPN.[26,68] Many factors such as the course of the disease, iatrogenic factors (e.g. medication), and damage to other organs as well as predisposing factors

may have a modulating influence on the observed motor deficits. Most importantly, the biologic and genetic underpinnings are still unknown. Future studies should start at the date of diagnosis and prospectively follow patients for manual dexterity, general motor as well as for cognitive function, adaptive behavior together with electrophysiological assessment of peripheral nerve function.

Specific interventions may ameliorate these deficits in patients or survivors of pediatric ALL, such as physio- and occupational therapy, plain physical activity, or even cognitive intervention as some authors have suggested.[2,6,23,74]

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Conflict of interest

All authors report no conflict of interest.

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Appendix A. Supplementary data

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