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Cortical Surface Area and Thickness in Adult Survivors of Pediatric Acute Lymphoblastic Leukemia

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Background. Advances in the treatment of acute lymphoblastic leukemia (ALL) have led to great improvements in survival rates and outcomes, but there is concern about cognitive late effects. We aimed to determine whether ALL survivors have smaller cortical surface area and/or thickness, and test whether this is related to disease and treatment variables and self-reported executive functioning in everyday life. ***Procedure.*** Magnetic resonance imaging (MRI) scans from 130 adult long-term survivors of childhood ALL (age: 18–46 years; age at diagnosis: 0–16 years; years since diagnosis: 7–40) and 130 healthy controls were assessed to estimate and compare regional cortical surface area and thickness. Information on disease and treatment factors were obtained from patients' records, and executive functioning in survivors was measured using a validated questionnaire (BRIEF-A). ***Results.*** Smaller cortical surface area was observed in several regions in both cerebral hemispheres in ALL survivors. In these regions, mean surface area was 4.1–5.5% smaller in ALL survivors compared to healthy controls. In contrast, only one region showed lower cortical thickness in ALL survivors. There were no significant associations between cortical surface area/thickness in these regions and disease or treatment variables. In ALL survivors, smaller surface area in prefrontal regions, encompassing parts of the superior frontal gyri and the left anterior cingulate cortex, was associated with problems in executive functioning, specifically with emotional control and self-monitoring. ***Conclusions.*** ALL survivors had smaller surface area in several cortical regions and smaller surface area in prefrontal regions was associated with reported problems in executive functioning. Pediatr Blood Cancer 2015;62:1027–1034. © 2015 The Authors. *Pediatric Blood & Cancer* published by Wiley Periodicals, Inc.

Key words: cancer; cerebral cortex; chemotherapy; executive function; late effects; MRI

INTRODUCTION

Advances in the treatment of pediatric acute lymphoblastic leukemia (ALL) over the last decades have dramatically increased survival rates and outcomes [1,2]. Treatment protocols have included CNS-directed chemotherapy and/or cranial irradiation. Therefore, there is concern about cognitive late effects, even in ALL survivors treated with lower doses of irradiation, or those treated with chemotherapy agents only [3–6]. A large study of adult survivors documented increased impairment rates across cognitive domains, with the highest rates for executive function and processing speed. Cognitive impairments were also found to have adverse impact on educational attainment and employment [7].

The anatomical and physiological base of these cognitive impairments is largely unknown. An increasing number of studies using various imaging techniques have attempted to shed light on the biological underpinnings of these late effects. Quantitative magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) studies have identified lower white matter volumes and white matter microstructural alterations in ALL survivors [8–16] (Table I). Less attention has been focused on the cortical regions subserved by white matter fibers and the potential impact of cortical abnormalities on cognition and behavior. In addition to smaller white matter volume, we recently found lower volume of several subcortical structures and total cerebral cortex in long-term survivors of childhood ALL [17].

Importantly, cortical volume is determined by both surface area and thickness. These distinct components are influenced by different evolutionary [18], genetic [19] and cellular [20] processes, and follow unique developmental trajectories [21,22], and thus may show different vulnerability to ALL therapy. Further, different cortical regions support distinct cognitive functions, and it is therefore important to investigate regional deviations to be able to map these to cognitive functions. We, therefore, examined regional cortical surface area and thickness in adult survivors of childhood ALL and the relationships to disease and treatment variables and self-reported executive functioning.

METHODS

Sample

The study included 130 adult long-term survivors of pediatric ALL and 130 healthy controls. Whole-brain volumetric results from

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TABLE I. Overview of Selected Quantitative MRI and DTI Follow-up Studies of Survivors of Pediatric ALL

Study	N	Age	Age at diagnosis	Follow-up time	Treatment	Healthy controls	Analysis	Group differences
Aukema et al. (2009)	17[a]	9–17	2–13	3–14	CT/CRT & CT	17 volunteers	ROIs: Manually outlined	Lower FA: mean WM, right inferior fronto-occipital fasciculus, genu of corpus callosum
Carey et al. (2008)	9	8–26	1–9	3–17	CT	14 siblings/volunteers	VBM	Smaller WM volume: right frontal
Dellani et al. (2008)	13	17–37	2–16	16–28	CRT & CT	14 volunteers	ROIs: Manually placed	Smaller WM volume: total Lower FA: Temporal WM, hippocampus, thalamus
Edelmann et al. (2014)	75	24.9/26.7[b]	10.0/2.8[b]	15.0/23.9[b]	CT/CRT & CT	23 volunteers	Automated segmentation	Smaller WM volume in both groups: frontal and temporal lobes Higher FA in both groups: Left superior fronto-occipital fasciculus and internal capsule
Genschaft et al. (2013)	27	15–22	1–10	6–18	CT	27 siblings/volunteers	VBM and ROIs	Smaller GM volume: Hippocampus, left calcarine gyrus, lingual gyri, left precuneus
Kesler et al. (2010)	26	5–19	NaN	NaN	CT	29 volunteers	VBM	Smaller WM volume: total, caudate, corpus callosum, fornix, anterior thalamic radiation, superior fronto-occipital fasciculus
Porto et al. (2008)	20	18–28	2–14	NaN	CT/CRT & CT	21 volunteers	VBM	Smaller GM and WM volume: distributed regions Lower FA in irradiated group: WM bordering the caudate
Reddick et al. (2006)	112	9.8/11.1[b]	4.5/3.1[b]	5.3/8.0[b]	CT/CRT & CT	33 siblings	ROI: Transverse volume	Smaller WM volume: CRT & CT < CT < healthy siblings
Reddick et al. (2014)	199	6–18	4.7 ± 2.7[c]	5.4 ± 3.0[c]	CT/CRT & CT	67 siblings	ROI: Transverse volume	Smaller WM volume: total
Schuitema et al. (2013)	93	18–43	5.3/5.7[b]	21.4/25.4[b]	CT/CRT & CT	49 volunteers	Voxel-based analysis	Lower FA in CRT group: frontal, parietal and temporal WM
Zeller et al. (2013)	130	18–46	0–16	7–40	CT/CRT & CT	130 volunteers	Whole-brain automated segmentation	Smaller volume: total WM, total cortex, amygdala, caudate, hippocampus and thalamus

NaN, Not a number; CT, Chemotherapy; CRT, Cranial radiation therapy; VBM, Voxel-based morphometry; ROIs, regions of interest; GM, Gray matter; WM, White matter; TBV, Total brain volume; FA, Fractional anisotropy. [a]11 ALL and 6 medulloblastoma survivors. [b]Mean for CT / CRT & CT group. [c]Mean ± SD.

these 260 participants have been previously reported [17], whereas in this manuscript we report on detailed analyses of two distinct facets of cortical structure: surface area and thickness. The Regional Committee for Medical and Health Research Ethics approved the projects and written informed consent was obtained from all participants. The recruitment, eligibility criteria, screening and final samples are described in detail elsewhere [17].

Survivors were identified by the Cancer Registry of Norway (April 2009). Out of 210 eligible survivors (age ≤ 16 years when diagnosed with ALL at Oslo University Hospital in the period 1970–2002, age ≥ 18 years at investigation, ≥ 5 years since completed therapy) 160 were willing to participate, and 135 underwent MRI. Data sets from two survivors were lost due to technical difficulties and three subjects were excluded because of major central nervous system pathology (one with pineal cyst and hydrocephalus, one with cerebellar atrophy, one with sequelae following brain surgery). Thus, the final ALL survivors sample included 130 subjects. Among these, two had self-reported neurological conditions (epilepsy and history of cerebral contusion, respectively) and 14 replied yes to whether they had mental health problems (mainly affective symptoms/fatigue). Information on cancer disease and treatment was obtained by review of patients' records (Table II, also see Supplemental Table I for an overview of treatment characteristics by cohort). Only 18 survivors had received cranial irradiation.

An equal number of healthy controls (n = 130), matched as closely as possible to the ALL survivors on sex and age, were drawn from two ongoing research projects [23,24]. The controls were recruited through newspaper advertisements and from local workplaces and schools. Standardized health screening interviews were conducted, and controls were required to be right handed, fluent Norwegian speakers, have normal or corrected to normal vision and hearing, and not to have self-reported neurological or psychiatric conditions. Additionally, all scans were examined by a specialist in neuroradiology and required to be deemed free of significant anomalies.

There were no significant group differences between the ALL survivors and the healthy controls on age, sex, height, length of education or estimated intelligence, as assessed by the Wechsler Abbreviated Scale of Intelligence [25] (Table II). However, due to different inclusion criteria, all controls were right handed, whereas 18 of the survivors were left handed.

Image Acquisition

MRI was performed using a 12-channel head coil on a 1.5-T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The sequence used for cortical surface analyses was two repeated 3D T1-weighted MP-RAGE sequences with the following parameters: repetition time (TR) = 2,400 ms, echo time (TE) = 3.61 ms, inversion time (TI) = 1,000 ms, flip angle = 8°, bandwidth = 180 Hz/pixel, field of view (FOV) = 240 mm, matrix = 192 × 192 × 160, 1.25 × 1.25 × 1.2 mm voxels, sagittally acquired. The two runs were averaged to increase the signal-to-noise ratio. The protocol also included a 25-slice coronal T2-weighted FLAIR (TR = 7,000–9,000 msec, TE = 109 msec) sequence to aid the neuroradiological examination.

Image Analysis

All data sets were automatically processed and analyzed using Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu), which is documented and freely available for download online, and described in depth elsewhere [26–29]. The cortical surface was reconstructed for each subject to measure surface area and thickness at each surface location or vertex. Individual surfaces were inspected for accuracy, and corrected if judged inaccurate. Minor manual edits were

TABLE II. Demographic and Clinical Characteristics of ALL Survivors and Healthy Controls

			Difference[a]	
	ALL survivors (n = 130)	Healthy controls (n = 130)	*t*	*P*
Age, years mean (SD, range)	29.3 (7.3, 18.6–46.5)	28.9 (8.8, 16.9–48.5)	0.40	0.692
Females, n (%)	65 (50.0)	66 (50.8)	−0.12	0.902
Right handed, n (%)	112 (91.1)	130 (100.0)	−3.46	0.001
Height, cm mean (SD, range)	173.8 (10.5,153–202)	174.9 (8.7, 151–193)	−0.89	0.374
Education, years mean (SD, range)	13.7 (2.7, 10–18)	14.3 (2.5, 10–18)	−1.65	0.101
Estimated intelligence, mean (SD, range)[b]	114.0 (9.4, 91–135)	111.9 (9.6, 86–139)	1.74	0.083
Age at diagnosis, years mean (SD, range)	6.2 (4.0, 0.3–16.0)			
White blood cell count at diagnosis, median (range)	10.3 (0.5–409.0)			
Relapsed disease, n (%)	19 (14.6)			
Follow-up, years mean (SD, range)	23.0 (7.7, 7.4–40.0)			
Cranial radiation, n (%)	18 (13.8)			
Cranial radiation dose (n = 18), Gy mean (SD, range)	20.0 (3.2, 12–25)			
Stem-cell transplantation, n (%)	3 (2.3)			
Vincristine, mg/m^2 median (range)	22 (8–102)			
Methotrexate intravenous, mg/m^2 median (range)	21000 (0–75000)			
Methotrexate intrathecal injections, median (range)	13 (0–36)			
Antracyclines, mg/m^2 median (range)	120 (0–510)			
Oral steroids, mg/m^2 median (range)[c]	4380 (1860–17250)			

Notes: Information missing for handedness: 7 survivors, height: 15 controls, education: 1 control, estimated intelligence: 9 survivors, white blood cell count: 15 survivors, and cumulative chemotherapy doses: 2 survivors. [a]Group differences tested with independent samples t-tests. [b]Wechsler Abbreviated Scale of Intelligence (WASI) two-subtest form. [c]Prednisolone plus dexamethasone; steroid dose (mg) = prednisolone dose (mg) + dexamethasone dose (mg) × 6.5.

performed on most subjects, usually restricted to the removal of non-brain tissue. Before statistical analyses, maps were smoothed with a Gaussian kernel of full-width at half maximum of 15 mm.

Self-Reported Executive Functioning

To measure aspects of executive function that are important for everyday life, ALL survivors completed the Behavior Rating Inventory of Executive Functioning — Adult Version (BRIEF-A) (n = 125, data missing for five survivors) [30]. The BRIEF-A is a standardized self-report questionnaire comprising 75 items that are rated on a 3-point scale, yielding a Global Executive Composite which is an overarching summary score of nine nonoverlapping subscales. The Global Executive Composite is split into two summary indexes. The Behavioral Regulation Index measures the ability to maintain appropriate regulatory control of one's own behavior and emotional responses, and includes the following four subscales: Inhibit, Shift, Emotional Control and Self-Monitor. The Metacognition Index measures cognitive aspects of executive functioning, and includes five subscales: Initiate, Working Memory, Plan/Organize, Task Monitor and Organization of Materials. Raw scores were transformed to T-scores, which were used in the analyses. Higher scores reflect more reported problems.

Statistical Analysis

Surface-based cortical analyses were performed on a vertex-wise (point-by-point) level using general linear models (GLMs), as implemented in FreeSurfer. Main effects of group were tested by contrasting the ALL survivors and healthy controls while controlling for sex, age and the interaction of sex and age. Separate analyses were performed for cortical surface area and thickness maps. The data were tested against an empirical null distribution of maximum cluster size across 10,000 iterations using Z Monte Carlo simulations as implemented in FreeSurfer [31,32] synthesized with a cluster-forming threshold of $P < 0.05$ (two-sided), yielding clusters fully corrected for multiple comparisons across the surfaces. Clusterwise corrected $P < 0.05$ (two-sided) was regarded significant. Mean vertex-wise cortical surface area or thickness values were then extracted from each significant cluster, as well as from all hemisphere vertices.

To further examine the observed group differences, we first performed one-way between-group analyses of covariance (ANCOVAs) with mean surface area or thickness in each cluster as dependent variable, group as a fixed factor, and sex and age as covariates. Next, the same analyses were repeated with global cortical surface area or thickness (average values across all vertices in the respective hemisphere) as an additional covariate. Finally, the initial ANCOVAs were repeated after excluding: (1) the 18 survivors who had received cranial irradiation; (2) the 19 survivors with relapsed disease; and (3) the three survivors with stem-cell transplantation. Note that the effect sizes in these analyses are inflated because they are based on already-identified significant clusters.

To test whether observed differences at the group level were related to other variables of interest within the group of ALL survivors, we performed Spearman's rank order correlations (two-sided), controlling for sex and age, between cortical surface area/thickness in each cluster and (1) disease (age and white blood cell count at diagnosis) and treatment characteristics (cranial irradiation and cumulative chemotherapy doses) and (2) self-reported executive functioning (BRIEF-A). Spearman's rank order correlations were used as most of the disease, treatment and self-report variables were not normally distributed. The associations with executive functioning were tested in a hierarchical fashion, starting with the Global Executive Composite and continuing with follow-up analyses first on the two summary indexes and finally on the subscales only if significant ($P < 0.05$) relationships were found for the higher order scales.

RESULTS

Cortical Surface Area

Group differences in cortical surface area between ALL survivors and healthy controls were tested with GLMs, controlling for the effects of sex and age and their interaction. The results revealed four clusters in the left hemisphere and three clusters in the right hemisphere where ALL survivors showed significantly smaller surface area (Fig. 1). First, effects were observed bilaterally

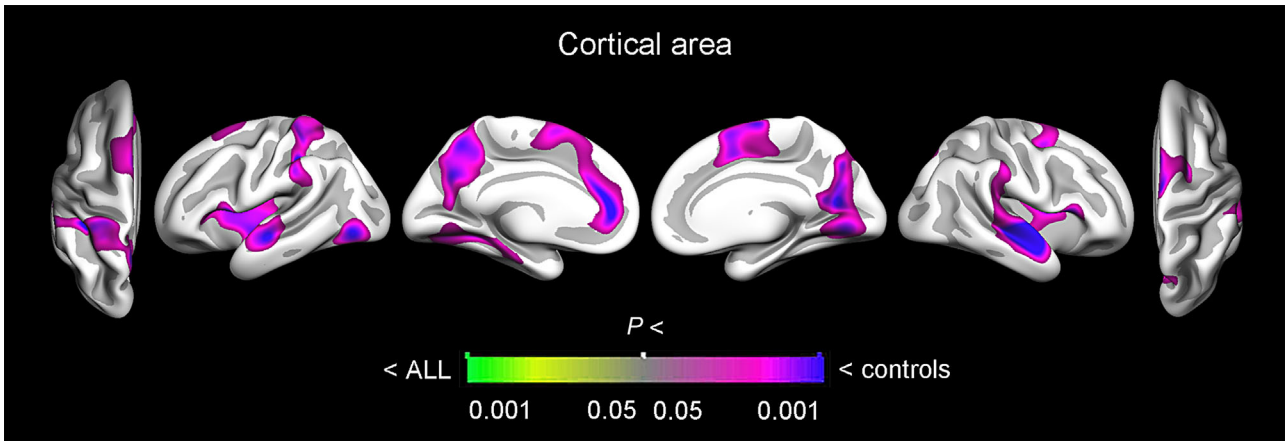

Fig. 1. Cortical surface area in ALL survivors vs. healthy controls. GLMs were used to test the main effects of group while controlling for sex and age. The results were corrected for multiple comparisons using cluster size inference. Uncorrected p values within the corrected significant clusters are shown. Four cluster in the left hemisphere and three clusters in the right hemisphere showed negative effects, indicating smaller cortical surface area in ALL survivors. No effects were seen in the opposite direction.

in prefrontal clusters covering posterior portions of the superior frontal gyri and also the left anterior cingulate cortex (LH: 2,943 mm^2, clusterwise $P = 0.002$, RH: 2,277 mm^2, clusterwise $P = 0.014$). Second, effects were seen in clusters comprising large parts of the superior temporal gyri and parts of the insula bilaterally and in the right hemisphere extending into the supramarginal gyrus (LH: 4,410 mm^2, RH: 5,505 mm^2, clusterwise $P < 0.001$). Third, clusters were found in precuneus, extending over to the postcentral and supramarginal gyri in the left hemisphere and inferiorly into the lingual gyrus in the right hemisphere (LH: 5,481 mm^2, RH: 4,542 mm^2, clusterwise $P < 0.001$). Additionally, a cluster was observed in the left hemisphere in the parahippocampal gyrus and parts of lingual and fusiform gyri and the lateral occipital cortex (3,585 mm^2, clusterwise $P < 0.001$). No cortical regions had significantly larger surface area in ALL survivors than in controls.

Mean cortical surface area within these clusters was 4.1–5.5% smaller in ALL survivors compared to the healthy controls. ANCOVAs with mean surface area in each cluster as dependent variable, group as a fixed factor, and sex, age and additionally average surface area across all hemisphere vertices as covariates showed that the effects remained significant (all P-values < 0.05) when controlling for global surface area differences. Next, ANCOVAs were performed after excluding the 18 ALL survivors who had received cranial irradiation and the effects remained significant (all P-values < 0.01) (Table III). Finally, the same analyses were performed after excluding either the 19 survivors with relapsed disease or the three survivors with stem-cell transplantation and the effects remained significant (all P-values < 0.001) (Supplemental Table II).

Cortical Thickness

Group differences in cortical thickness between ALL survivors and healthy controls were tested with GLMs, controlling for sex and age and their interaction. The results showed only one significant cluster that covered superior portions of the precentral gyrus in the right hemisphere (1,721 mm^2, clusterwise $P = 0.010$) (Fig. 2). Mean cortical thickness within this cluster was 3.5% lower in ALL survivors. The group difference remained significant ($P < 0.001$) after controlling for average thickness across all hemisphere vertices, and after excluding participants who had either received cranial irradiation (n = 18; Table III), who had experienced relapse (n = 19), or individuals who had received stem-cell transplants (n = 3; Supplemental Table II).

Relationships with Disease and Treatment Characteristics

Within the ALL survivors group, there were no significant associations between either disease (age at diagnosis, white blood cell count at diagnosis) or treatment variables (cranial irradiation, cumulative chemotherapy doses) and cortical surface area/thickness in the above described clusters (all P-values > 0.05).

Relationships with Self-Reported Executive Functioning

ALL survivors reported significantly more problems in executive functioning, as reflected by higher scores on the Global Executive Composite, than expected based on the norms (mean = 54.7, SD = 10.9, $t = 4.78$, $P < 0.001$). Among the survivors, 16% reported problems above cut-off defined as more than 1.5 SD above the norm mean (T > 65). More difficulties in executive functioning were associated with smaller surface area in both the left ($r_s = -0.20$, $P = 0.028$) and the right prefrontal cluster ($r_s = -0.19$, $P = 0.031$). In both prefrontal clusters, associations were also seen between the Behavioral Regulation Index and surface area (LH: $r_s = -0.21$, $P = 0.020$, RH: $r_s = -0.18$, $P = 0.046$). Finally, we tested the relationships between the subscales of the Behavioral

TABLE III. Group Differences in Cortical Surface Area and Thickness Between ALL Survivors and Healthy Controls

		Difference	ANCOVA[a]			ANCOVA[b]			ANCOVA[c]		
Cluster	Anatomic regions	%	F	*P*	Partial eta^2	F	*P*	Partial eta^2	F	*P*	Partial eta^2
Area: left prefrontal	Superior frontal, anterior cingulate	−4.3	13.87	<0.001	0.051	6.95	0.009	0.027	11.96	<0.001	0.048
Area: right prefrontal	Superior frontal, paracentral	−5.0	11.44	<0.001	0.043	4.39	0.037	0.017	9.43	0.002	0.038
Area: left lateral temporal	Superior temporal, insula	−4.1	15.89	<0.001	0.058	8.87	0.003	0.034	14.40	<0.001	0.057
Area: right lateral temporal	Superior temporal, insula, supramarginal	−4.7	19.41	<0.001	0.070	13.43	<0.001	0.050	18.77	<0.001	0.073
Area: left parietal	Precuneus, cuneus, postcentral, supramarginal	−5.5	21.87	<0.001	0.079	15.72	<0.001	0.058	19.66	<0.001	0.076
Area: right parietal	Precuneus, cuneus, lingual	−4.2	14.51	<0.001	0.054	7.35	0.007	0.028	11.15	<0.001	0.045
Area: left medial temporal	Parahippocampal, lingual, fusiform, lateral occipital	−4.3	14.78	<0.001	0.055	7.38	0.007	0.028	12.28	<0.001	0.049
Thickness: right frontal	Precentral	−3.5	12.93	<0.001	0.048	12.62	<0.001	0.047	14.95	<0.001	0.059

[a]ANCOVAs, with sex and age as covariates. [b]ANCOVAs, with sex, age and average surface area or thickness within hemisphere as covariates. [c]ANCOVAs after excluding 18 ALL survivors who had received cranial irradiation, with sex and age as covariates.

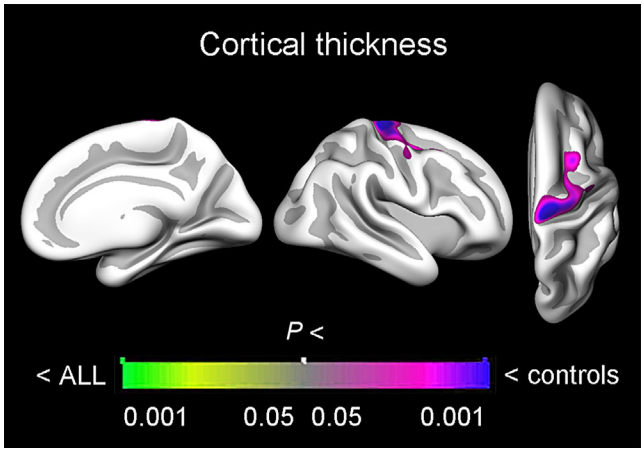

Fig. 2. Cortical thickness in ALL survivors vs. healthy controls. GLMs were used to test the main effects of group while controlling for sex and age. The results were corrected for multiple comparisons using cluster size inference. Uncorrected *P* values within the corrected significant cluster are shown. One cluster in the right hemisphere showed a negative effect, indicating thinner cortex in ALL survivors. No effects were seen in the left hemisphere or in the opposite direction.

Regulation Index and surface area in these clusters and found that Emotional Control was associated with surface area of the left prefrontal cluster ($r_s = -0.20$, $P = 0.025$), while Self-Monitor was associated with surface area of the right prefrontal cluster ($r_s = -0.18$, $P = 0.046$).

DISCUSSION

The present study reports an analysis of cortical structure in long-term survivors of pediatric ALL. Compared to healthy controls, ALL survivors on average showed smaller cortical surface area in several regions in both cerebral hemispheres, while limited differences were observed in cortical thickness. No relationships were found between cortical structure in these regions and age when ALL was diagnosed, white blood cell count at diagnosis or treatment intensity. Smaller surface area in prefrontal cortical regions was associated with more self-reported problems in executive functioning in ALL survivors.

Previous MRI and diffusion tensor imaging (DTI) studies have documented lower volumes [9–13,15–17] and microstructural alterations [8,10,12,14] in white matter in survivors of childhood ALL. Effects of chemotherapy on white matter have also been shown by two recent studies comparing the same patients before and after treatment [33,34]. Only a few studies, mostly with relatively small samples, have examined long-term effects of childhood ALL and treatment on cortical or subcortical structure, with mixed results [9,11,12,16,35]. Our previous study of this large cohort showed smaller caudate, amygdala, hippocampus and thalamus volumes in ALL survivors compared to healthy controls, and also lower total volume of the cerebral cortex [17]. In the present study, we investigated cortical structure in ALL survivors in detail by differentiating between surface area and thickness [18–21] and by performing analyses sensitive to regional effects. The results revealed smaller cortical surface area in distributed regions, including parts of the superior frontal, left anterior cingulate, superior temporal, insular, precuneus, lingual and left parahippocampal cortices. In contrast, only a restricted region in the right precentral cortex showed lower cortical thickness in ALL survivors.

The present study indicated that ALL survivors experience more problems in executive functioning as compared to normative data. Further, our results showed that smaller cortical surface area in prefrontal regions covering posterior portions of the superior frontal gyri and the left anterior cingulate cortex was associated with more reported problems. Follow-up analyses revealed that these relationships were primarily driven by reported difficulties with emotional control and self-monitoring. Impaired performance on various neuropsychological tests among ALL survivors have previously been found to be associated with smaller white [9,13,16] and gray [17,35,36] matter volumes, as well as lower white matter fractional anisotropy [8,14,37] and functional hypoconnectivity [38]. For instance, memory impairments in adult survivors treated with cranial radiation therapy have been associated with smaller temporal lobe volumes and thinner fronto-parietal cortices [39]. The results from the current study add to the existing evidence that differences in brain structure may partly account for impairments in cognitive functions that affect normal day to day functioning in a sizable portion of ALL survivors.

Studies using animal models have demonstrated evidence for a wide variety of candidate mechanisms for the neurocognitive effects of chemotherapeutic agents [40–42]. However, many questions with regard to the pathogenesis of long-term neurocognitive dysfunctions among ALL survivors remain to be clarified, including the neurobiological events underlying the observed differential effects on cortical surface area and thickness in the present study, and how these unfold over time. Three broad, nonmutually exclusive, perspectives are available. First, the phase shift hypothesis posits that aspects of the disease, treatment and/or associated factors such as malnutrition, stress or repeated general anesthesia could have a direct and stable negative impact on neurocognitive systems [43]. Second, the disrupted development hypothesis predicts that cancer and/or treatment factors may interfere with developmental processes resulting in larger impairments that become increasingly apparent with age if occurring in periods of rapid development. Third, the accelerated aging hypothesis states that cancer and/or its therapy may accelerate cognitive decline and brain structure changes associated with normal aging [43]. The cross-sectional design of the current study does not enable direct testing of any of these hypotheses. We did not find any relationships between age at diagnosis and cortical structure as one would expect from the disrupted development hypothesis given that the most dramatic brain changes take place early in life [44]. However, cortical surface area shows prolonged developmental increase relative to thickness [21,45], and ALL survivors did show smaller surface area in various regions compared to healthy controls and there were limited differences in cortical thickness. While this pattern is consistent with the disrupted development hypothesis, it is the opposite of what one would predict from the accelerated aging hypothesis, since cortical thickness generally show more pronounced reductions in aging [46]. To gain more insights regarding which of these perspectives may best account for late effects in ALL survivors, we need large-scale longitudinal studies, also including older survivors. This is especially important when studying wide age ranges of survivors, since

differences in treatment and other cohort effects can cause age-related differences in cross-sectional studies.

The present study had limitations. First, this study used a cross-sectional design, making it difficult to rule out the potential impact of cohort effects. In particular, investigations of the impact of demographic, disease and treatment variables are complicated by the fact that these typically are confounded due to the initial risk stratification [47], and by changing treatment protocols over time. The ALL survivors in the current study were diagnosed during a period of more than 30 years and management was, therefore, highly variable (Supplemental Table I). Longitudinal studies can account for these cohort effects and are also critically needed to assess how neurocognitive dysfunctions among ALL survivors unfold over the lifespan of individuals (see [48] for a review of methods and considerations for longitudinal structural MRI). Second, the BRIEF-A was only administered to the ALL survivors and not the healthy controls, thus preventing direct group comparisons regarding executive functioning. Third, the study was limited to self-report assessment of executive functioning. Rates of executive dysfunction in ALL survivors have previously been found to be higher for performance-based tests than for self-report measures, which is though to reflect long-term adaptation, lack of insight or differential sensitivity [7]. Different tests and questionnaires tap into different aspects of behavior (see [49]), therefore future studies on the relationships between cortical structure and executive functioning could benefit from including multimethod cognitive assessment.

While the clinical implications of our findings remain uncertain, they do add to a growing body of evidence suggesting that cancer therapies may have a considerable long-term impact on the developing brain. As long as we do not know the underlying mechanisms, ongoing efforts, wherever possible, to minimize treatment load, especially of CNS directed therapy, may be a way to reduce neurocognitive late effects.

In conclusion, we found that adult long-term survivors of childhood ALL on average had smaller cortical surface area in several brain regions compared to healthy controls, but showed only limited differences with respect to cortical thickness. Smaller surface area in prefrontal cortical regions was related to more self-reported problems describing emotional and behavioral aspects of executive functioning. Longitudinal studies are needed to avoid potential cohort effects and to delineate how brain structure and cognitive functions within the heterogeneous ALL survivor group change over the lifespan.

REFERENCES

1. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the children's oncology group. J Clin Oncol 2012:30:1663–1669.
2. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 2006:354:166–178.
3. Campbell LK, Scaduto M, Sharp W, Dufton L, Van Slyke D, Whitlock JA, Compas B. A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. Pediatr Blood Cancer 2007:49:65–73.
4. Peterson CC, Johnson CE, Ramirez LY, Huestis S, Pai AL, Demaree HA, Drotar D. A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2008:51:99–104.
5. Buizer AI, de Sonneville LM, Veerman AJ. Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: A critical review of the literature. Pediatr Blood Cancer 2009:52:447–454.
6. Anderson FS, Kunin-Batson AS. Neurocognitive late effects of chemotherapy in children: The past 10 years of research on brain structure and function. Pediatr Blood Cancer 2009:52:159–164.
7. Krull KR, Brinkman TM, Li C, Armstrong GT, Ness KK, Srivastava DK, Gurney JG, Kimberg C, Krasin MJ, Pui CH, Robison LL, Hudson MM. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St Jude Lifetime Cohort Study. J Clin Oncol 2013:31:4407–4415.
8. Aukema EJ, Caan MW, Oudhuis N, Majoie CB, Vos FM, Reneman L, Last BF, Grootenhuis MA, Schouten-van Meeteren. White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. Int J Radiat Oncol Biol Phys 2009:74:837–843.
9. Carey ME, Haut MW, Reminger SL, Hutter JJ, Theilmann R, Kaemingk KL. Reduced frontal white matter volume in long-term childhood leukemia survivors: A voxel-based morphometry study. AJNR Am J Neuroradiol 2008:29:792–797.
10. Dellani PR, Eder S, Gawehn J, Vucurevic G, Fellgiebel A, Muller MJ, Schmidberger H, Stoeter P, Gutjahr P. Late structural alterations of cerebral white matter in long-term survivors of childhood leukemia. J Magn Reson Imaging 2008:27:1250–1255.
11. Kesler SR, Tanaka H, Koovakkattu D. Cognitive reserve and brain volumes in pediatric acute lymphoblastic leukemia. Brain Imaging Behav 2010:4:256–269.
12. Porto L, Preibisch C, Hattingen E, Bartels M, Lehrnbecher T, Dewitz R, Zanella F, Good C, Lanfermann H, DuMesnil R, Kieslich M. Voxel-based morphometry and diffusion-tensor MR imaging of the brain in long-term survivors of childhood leukemia. Eur Radiol 2008:18:2691–2700.
13. Reddick WE, Shan ZY, Glass JO, Helton S, Xiong X, Wu S, Bonner MJ, Howard SC, Christensen R, Khan RB, Pui CH, Mulhern RK. Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. Cancer 2006:106:941–949.
14. Schuitema I, Deprez S, Van Hecke W, Daams M, Uyttebroeck A, Sunaert S, Barkhof F, van Dulmen-den Broeder, van der Pal E, van den Bos HJ, Veerman C, de Sonneville AJ. Accelerated aging, decreased white matter integrity, and associated neuropsychological dysfunction 25 years after pediatric lymphoid malignancies. J Clin Oncol 2013:31:3378–3388.
15. Edelmann MN, Krull KR, Liu W, Glass JO, Ji Q, Ogg RJ, Sabin ND, Srivastava DK, Robinson LL, Hudson MM, Reddick WE. Diffusion tensor imaging and neurocognition in survivors of childhood acute lymphoblastic leukemia. Brain 2014:137:2973–2983.
16. Reddick WE, Taghipour DJ, Glass JO, Ashford J, Xiong X, Wu S, Bonner M, Khan RB, Conklin HM. Prognostic factors that increase the risk for reduced white matter volumes and deficits in attention and learning for survivors of childhood cancers. Pediatr Blood Cancer 2014:61:1074–1079.
17. Zeller B, Tamnes CK, Kanellopoulos A, Amlien IK, Andersson S, Due-Tønnessen P, Fjell AM, Walhovd KB, Westlye LT, Ruud E. Reduced neuroanatomic volumes in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 2013:31:2078–2085.
18. Geschwind DH, Rakic P. Cortical evolution: Judge the brain by its cover. Neuron 2013:80:633–647.
19. Kremen WS, Fennema-Notestine C, Eyler LT, Panizzon MS, Chen CH, Franz CE, Lyons MJ, Thompson WK, Dale AM. Genetics of brain structure: Contributions from the Vietnam Era Twin Study of Aging. Am J Med Genet Part B 2013:162B:751–761.
20. Chenn A, Walsh CA. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. Science 2002:297:365–369.
21. Wierenga LM, Langen M, Oranje B, Durston S. Unique developmental trajectories of cortical thickness and surface area. Neuroimage 2014:87:120–126.
22. Lyall AE, Shi F, Geng X, Woolson S, Li G, Wang L, Hamer RM, Shen D, Gilmore JH. Dynamic development of regional cortical thickness and surface area in early childhood. Cereb Cortex 2014; doi: 10.1093/cercor/bhu027.
23. Tamnes CK, Østby Y, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB. Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb Cortex 2010:20:534–548.
24. Westlye LT, Walhovd KB, Dale AM, Bjørnerud A, Due-Tønnessen P, Engvig A, Grydeland H, Tamnes CK, Østby Y, Fjell AM. Differentiating maturational and aging-related changes of the cerebral cortex by use of thickness and signal intensity. Neuroimage 2010:52:172–185.
25. Wechsler D, Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX The Psychological Corporation, 1999.
26. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I Segmentation and surface reconstruction. Neuroimage 1999:9:179–194.
27. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999:9:195–207.
28. Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp 1999:8:272–284.
29. Fischl B. FreeSurfer. Neuroimage 2012:62:774–781.
30. Roth RM, Isquith PK, Gioia GA. Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A). Lutz, FL: Psychological Assessment Resources, 2005.
31. Hagler DJ, Jr., Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. Neuroimage 2006:33:1093–1103.
32. Hayasaka S, Nichols TE. Validating cluster size inference: Random field and permutation methods. Neuroimage 2003:20:2343–2356.
33. Reddick WE, Glass JO, Johnson DP, Laningham FH, Pui CH. Voxel-based analysis of T2 hyperintensities in white matter during treatment of childhood leukemia. AJNR Am J Neuroradiol 2009:30:1947–1954.
34. Morioka S, Morimoto M, Yamada K, Hasegawa T, Morita T, Moroto M, Isoda K, Chiyonobu T, Imamura T, Nishimura A, Morimoto A, Hosoi H. Effects of chemotherapy on the brain in childhood: Diffusion tensor imaging of subtle white matter damage. Neuroradiology 2013:55:1251–1257.
35. Genschaft M, Huebner T, Plessow F, Ikonomidou VN, Abolmaali N, Krone F, Hoffmann A, Holfeld E, Vorwerk P, Kramm C, Gruhn B, Koustenis E, Hernaiz-Driever P, Mandal R, Suttorp M, Hummel T, Ikonomidou C, Kirschbaum C, Smolka MN. Impact of chemotherapy for childhood leukemia on brain morphology and function. PLoS One 2013:8: e 78599.
36. Monje M, Thomason ME, Rigolo L, Wang Y, Waber DP, Sallan SE, Golby AJ. Functional and structural differences in the hippocampus associated with memory deficits in adult survivors of acute lymphoblastic leukemia. Pediatr Blood Cancer 2013:60:293–300.
37. Khong PL, Leung LH, Fung AS, Fong DY, Qiu D, Kwong DL, Ooi GC, McAlonan G, Cao G, Chan GC. White matter anisotropy in post-treatment childhood cancer survivors: Preliminary evidence of association with neurocognitive function. J Clin Oncol 2006:24:884–890.
38. Kesler SR, Gugel M, Pritchard-Berman M, Lee C, Kutner E, Hosseini SM, Dahl G, Lacayo N. Altered resting state functional connectivity in young survivors of acute lymphoblastic leukemia. Pediatr Blood Cancer 2014:61:1295–1299.
39. Armstrong GT, Reddick WE, Petersen RC, Santucci A, Zhang N, Srivastava D, Ogg RJ, Hillenbrand CM, Sabin N, Krasin MJ, Kun L, Pui CH, Hudson MM, Robison LL, Krull KR. Evaluation of memory impairment in aging adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiotherapy. J Natl Cancer Inst 2013:105:899–907.
40. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 2007:7:192–201.
41. Kaiser J, Bledowski C, Dietrich J. Neural correlates of chemotherapy-related cognitive impairment. Cortex 2014:54C:33–50.
42. Seigers R, Fardell JE. Neurobiological basis of chemotherapy-induced cognitive impairment: A review of rodent research. Neurosci Biobehav Rev 2011:35:729–741.
43. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: An update on the state of the science. J Clin Oncol 2012:30:3675–3686.

44. Li G, Nie J, Wang L, Shi F, Lin W, Gilmore JH, Shen D. Mapping region-specific longitudinal cortical surface expansion from birth to 2 years of age. Cereb Cortex 2013:23:2724–2733.
45. Brown TT, Jernigan TL. Brain development during the preschool years. Neuropsychology Review 2012:22:313–333.
46. Storsve AB, Fjell AM, Tamnes CK, Westlye LT, Overbye K, Aasland HW, Walhovd KB. Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: Regions of accelerating and decelerating change. J Neurosci 2014:34:8488–8498.
47. Janzen LA, Spiegler BJ. Neurodevelopmental sequelae of pediatric acute lymphoblastic leukemia and its treatment. Dev Disabil Res Rev 2008:14:185–195.
48. Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. Dev Cogn Neurosci 2014:9:172–190.
49. Sølsnes AE, Skranes J, Brubakk AM, Løhaugen GC. Executive functions in very-low-birth-weight young adults: A comparison between self-report and neuropsychological test results. J Int Neuropsychol Soc 2014:20:506–515.