Developmental Neuropsychology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hdvn20

The Working Memory Network and Its Association with Working Memory Performance in Survivors of non-CNS Childhood Cancer

Valerie Siegwart, Leonie Steiner, Manuela Pastore-Wapp, Valentin Benzing, Janine Spitzhuttl, Mirko Schmidt, Claus Kiefer, Nedelina Slavova, Michael Grotzer, Claudia Roebers, Maja Steinlin, Kurt Leibundgut & Regula Everts

To cite this article: Valerie Siegwart, Leonie Steiner, Manuela Pastore-Wapp, Valentin Benzing, Janine Spitzhuttl, Mirko Schmidt, Claus Kiefer, Nedelina Slavova, Michael Grotzer, Claudia Roebers, Maja Steinlin, Kurt Leibundgut & Regula Everts (2021) The Working Memory Network and Its Association with Working Memory Performance in Survivors of non-CNS Childhood Cancer, Developmental Neuropsychology, 46:3, 249-264, DOI: 10.1080/87565641.2021.1922410

To link to this article: https://doi.org/10.1080/87565641.2021.1922410

© 2021 The Author(s). Published with license by Taylor & Francis Group, LLC.

Published online: 09 May 2021.

Submit your article to this journal

Article views: 64

View related articles

View Crossmark data

source: https://doi.org/10.48350/156579 | downloaded: 19.4.2024

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=hdvn20

DEVELOPMENTAL NEUROPSYCHOLOGY
2021, VOL. 46, NO. 3, 249–264
https://doi.org/10.1080/87565641.2021.1922410

Routledge
Taylor & Francis Group

OPEN ACCESS Check for updates

The Working Memory Network and Its Association with Working Memory Performance in Survivors of non-CNS Childhood Cancer

Valerie Siegwart[a,b], Leonie Steiner[a], Manuela Pastore-Wapp[c], Valentin Benzing[a,b,d], Janine Spitzhuttl[a,b,e], Mirko Schmidt[d], Claus Kiefer[c], Nedelina Slavova[c], Michael Grotzer[f], Claudia Roebers[e], Maja Steinlin[a], Kurt Leibundgut[b], and Regula Everts[a,b,g]

[a]Division of Neuropediatrics, Development and Rehabilitation, Children's University Hospital, Inselspital, University of Bern, Bern, Switzerland; [b]Department of Pediatric Hematology and Oncology, Children's University Hospital, Inselspital, University of Bern, Bern, Switzerland; [c]Support Center for Advanced Neuroimaging (SCAN), Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [d]Institute of Sport Science, University of Bern, Bern, Switzerland; [e]Department of Psychology, University of Bern, Bern, Switzerland; [f]Department of Pediatric Oncology, University Children's Hospital Zurich, Zurich, Switzerland; [g]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, Bern, Switzerland

ABSTRACT

Childhood cancer and its treatment puts survivors at risk of low working memory capacity. Working memory represents a core cognitive function, which is crucial in daily life and academic tasks. The aim of this functional MRI (fMRI) study was to examine the working memory network of survivors of childhood cancer without central nervous system (CNS) involvement and its relation to cognitive performance. Thirty survivors (aged 7–16 years, ≥ 1 year after cancer treatment) and 30 healthy controls performed a visuospatial working memory task during MRI, including a low- and a high-demand condition. Working memory performance was assessed using standardized tests outside the scanner. When cognitive demands increased, survivors performed worse than controls and showed evidence for slightly atypical working memory-related activation. The survivor group exhibited hyperactivation in the right-hemispheric superior parietal lobe (SPL) in the high- compared to the low-demand working memory condition, while maintaining their performance levels. Hyperactivation in the right SPL coincided with poorer working memory performance outside the scanner in survivors. *Even in survivors of childhood cancer without CNS involvement, we find neural markers pointing toward late effects in the cerebral working memory network.*

ARTICLE HISTORY
Received 28 September 2020
Revised 30 March 2021
Accepted 22 April 2021

Abbreviations

fMRI: Functional magnetic resonance imaging; CNS: Central nervous system; MNI: Montreal Neurological Institute; SES: Socioeconomic status; SPL: Superior parietal lobe

Introduction

The survival rates of children after cancer without the involvement of the CNS reach up to 90% in developed countries (Ward et al., 2019). This encouraging development, however, is accompanied by an increased number of children and adolescents suffering from cognitive late effects, particularly represented among others by low working memory capacity (Ashford et al., 2010; Cheung et al., 2016; Iyer, Balsamo, Bracken, & Kadan-Lottick, 2015; Krull et al., 2013; Robinson et al., 2010; Sleurs et al., 2019; Stefancin et al., 2020). Working memory refers to the ability to hold and manipulate information

CONTACT Regula Everts Regula.Everts@insel.ch Division of Neuropediatrics, Development and Rehabilitation, Children's University Hospital, Inselspital, Bern 3010, Switzerland

© 2021 The Author(s). Published with license by Taylor & Francis Group, LLC.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

in one's mind for a short time (Baddeley, 2012). Hence, working memory is particularly important for the development of reading (Nouwens, Groen, & Verhoeven, 2016) and arithmetic skills (Michel, Molitor, & Schneider, 2020; Raghubar, Barnes, & Hecht, 2010), and for educational achievement overall (Gathercole, Pickering, Knight, & Stegmann, 2004).

Along with reduced working memory capacity, survivors of cancers without CNS involvement have structural and functional brain alterations (Robinson et al., 2010; Sleurs et al., 2018, 2019; Stefancin et al., 2020; Zhou, Zhuang, Lin, Michelson, & Zhang, 2020). These cerebral alterations are likely a consequence of the cytotoxicity of cancer treatments (e.g., chemotherapy, cranial irradiation) (Kesler, Gugel, Huston-Warren, & Watson, 2016). For example, childhood leukemia survivors exhibit decreased structural connectivity (Kesler et al., 2016), alterations in resting-state functional connectivity (Billiet et al., 2018), and reduced white and gray matter volumes (Zhou et al., 2020), whereas survivors of bone and soft tissue sarcoma show microstructural changes (Sleurs et al., 2018) and white matter damage (Sleurs et al., 2019). Furthermore, survivors without CNS involvement demonstrated higher working-memory related activation in prefrontal (Robinson et al., 2010) and in parietal brain areas than healthy controls (Stefancin et al., 2020). Earlier studies also showed that differences in network activation become more pronounced when the complexity of the task performed in a functional magnetic resonance imaging (fMRI) study increases (Arthursson et al., 2017; King, Na, & Mao, 2015; Robinson et al., 2010). These CNS alterations are consistently reported to be related to reduced working memory, poorer attention, and lower intelligence (Sleurs et al., 2018, 2019; Zhou et al., 2020). In survivors of cancer without CNS involvement few fMRI studies have so far been performed using a working memory task and investigating cognitive late effects (Robinson et al., 2010; Stefancin et al., 2020). fMRI is a method closely related to cognitive performance and thus can shed light on the neural underpinnings of low working memory capacity in childhood cancer survivors.

The timing of cancer and its treatment plays an important role in a child's cognitive development (Anderson et al., 2010; Anderson, Spencer-Smith, & Wood, 2011; Krull et al., 2013). Younger age at diagnosis is related to lower cognitive functioning (Jacola et al., 2016; Jones & Pattwell, 2019; Mulhern & Palmer, 2003; Reddick et al., 2014) and to lower activation bilaterally in superior temporal and parietal cortices during an attentional task (Fellah et al., 2019). Brain development continues until young adulthood (Gogtay et al., 2004). Consequently, a young age at diagnosis means that cerebral development is disrupted during the early and hence more vulnerable stages of brain maturation (Anderson et al., 2011; Mulhern & Palmer, 2003).

The present study describes working memory-related neural activation in survivors of non-CNS childhood cancer and healthy controls. We hypothesized that the working memory network differs between survivors and controls and that the working memory-related neural activation is associated with working memory performance. We expected that the differences in neural activation become more pronounced in conditions with high cognitive demands (Arthursson et al., 2017; Chen, Wang, King, & Mao, 2016; King et al., 2015; Robinson et al., 2010). Further, younger age at diagnosis was expected to relate to lower working memory performance and stronger functional alterations.

Methods

This study was based on a subset of data collected within the framework of the Brainfit Study – a multidisciplinary, clinical trial examining the cognitive and neural characteristics of childhood cancer survivors and the efficacy of cognitive and physical training (Benzing et al., 2018, 2020). All data analyzed in the present study come from pre-training assessments, hence no study participant had yet received any form of intervention at the time of assessment. The Brainfit Study received approval from the local ethics committee (KEK) of Bern and Zurich, Switzerland (KEK BE 196/15; KEK ZH 2015–0397; ICTRP NCT02749877) and was conducted between January 2017 and December 2018.

Participants

Childhood cancer survivors

Inclusion criteria for the survivors were as follows: (a) age between 7 and 16 years, (b) diagnosed with cancer without CNS involvement (including secondary tumors, benign, and malignant tumors) within the past 10 years, and (c) termination of cancer treatment at least 12 months ago (i.e., treatment included either chemotherapy or radiation therapy, surgery was no necessity for inclusion). Exclusion criteria were: (a) unstable health status, (b) noncompliance with the study protocol or substance abuse, (c) inability to follow study procedures (e.g. language issues), and (d) braces, metal parts in the body, and pregnancy (making MRI scanning unsafe). Medical information on potentially eligible survivors was made available by the Swiss Childhood Cancer Registry. A total of 30 survivors of childhood cancer without CNS involvement were included in the analyses (for details on the recruitment and study participation process see Figure 1).

Healthy controls

Fifty-seven children and adolescents (age range 7–16 years), comparable to the survivor group in terms of age and sex, and with normal or corrected-to-normal hearing and vision were recruited. Recruitment was via flyers distributed in the neighborhood and posted on the hospital's intranet. The reasons for exclusion were as follows: (a) history of neurological disease or cancer, (b) mental or chronic disorders, (c) developmental or other disorders (e.g., autism, attention deficit/hyperactivity disorder, learning disabilities), (d) noncompliance or substance abuse, (e) inability to follow study procedures, and (f) braces, metal parts in the body, and pregnancy (making MRI scanning unsafe). Data of 30 healthy controls were analyzed (for details see Figure 1).

Study procedure

Childhood cancer survivors and potentially eligible healthy controls received an information booklet by mail. This was followed by a standardized screening interview over the telephone to check that all the inclusion criteria were met. In accordance with the Code of Ethics of the World Medical Association (i.e., Declaration of Helsinki), informed written consent was obtained prior to participation from the legal guardians and from survivors and controls over 14 years of age.

All the participants completed a cognitive assessment outside the scanner in the Division of Neuropediatrics, Development, and Rehabilitation at the Children's University Hospital in Bern and performed a working memory fMRI task inside the scanner at the Department of Diagnostic and Interventional Neuroradiology at the University Hospital of Bern. Trained psychologists administered the assessments. All participants received careful instructions and some extra time to exercise the fMRI task prior to MRI scanning. Instructions and time to exercise lasted until the task was correctly understood and executed. The trained psychologist monitored in real time how the subjects answered on the task during the MRI, All of these endeavors ensured that all participants understood and performed the task correctly. Participants were reimbursed with a gift voucher, worth 20 Swiss francs, 30 Swiss francs, and their travel costs were refunded.

Clinical measures outside the scanner

The socioeconomic status (SES) was measured using the German version of the Family Affluence Scale II (Boudreau & Poulin, 2008); composite scores can range from zero to nine, with higher scores indicating higher SES.

For the current study, the following cognitive measures outside the scanner were used: 1) fluid intelligence – Test of Nonverbal Intelligence, fourth edition (reliability $r = .88$) (Brown, Sherbenou, & Johnsen, 2010, p. 2) visuospatial working memory – block recall test, Working Memory Test Battery for Children (reliability $r = .53$) (Pickering & Gathercole, 2001, p. 3) verbal working memory – subtests

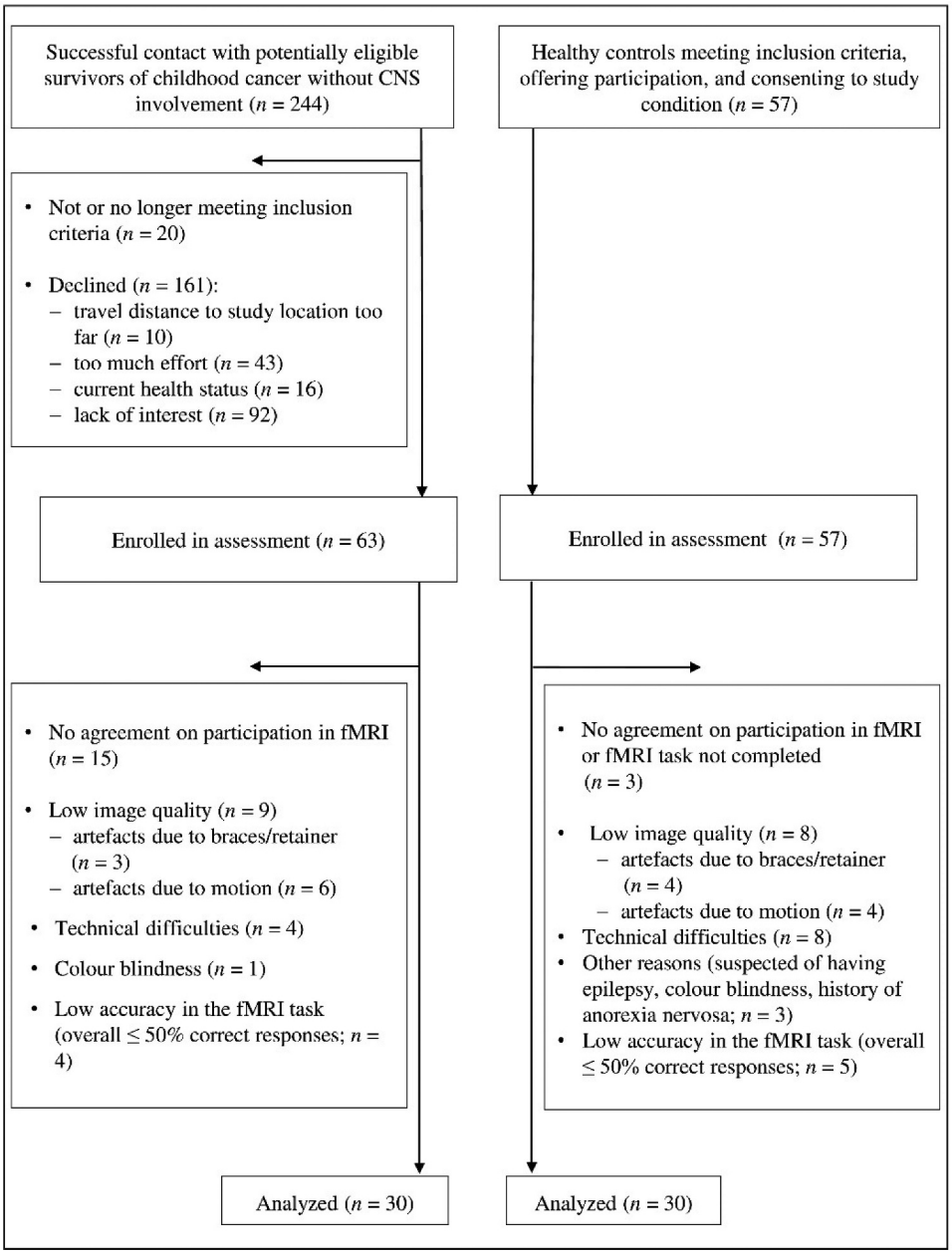

Figure 1. Flowchart of the recruitment and study participation process for the 30 survivors of childhood cancer without CNS involvement and the 30 age- and sex-controlled healthy peers.

number recall and word order, German version of the Kaufman Assessment Battery for Children, second edition (Melchers & Preuss, 2003). Raw scores were converted into age-dependent standard scores (Mean = 100, Standard deviation = 15) based on norms from the relevant test manuals.

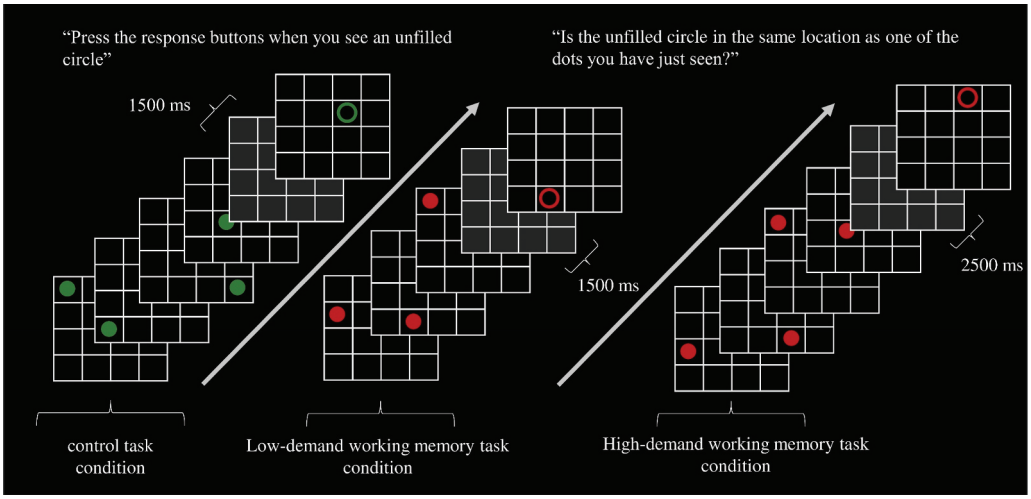

Figure 2. Active and control condition of the visuospatial working memory task inside the scanner. In the low-demand condition a series of three dots and in the high-demand condition a series of four dots were presented. The time lag of the blank delay, presented between the filled dots and the unfilled circle, differed between the low- (1500 ms) and high-demand condition (2500 ms).

Working memory task inside the scanner

All participants performed a dot location task inside the scanner (Figure 2). fMRI was used to study the children's performance in a visuospatial working memory task that was adapted (Klingberg, Forssberg, & Westerberg, 2002) and which has been used in previous studies of children and adolescents (Mürner-Lavanchy et al., 2014; Spencer-Smith et al., 2013). The task was presented in a block-design using E-prime (Psychology Software Tools, PST, Pittsburgh, USA) with five control blocks and four working memory blocks each lasting 33 s and comprising three task sequences. The interval between the task sequences was 1500 ms. In the working memory condition, red dots were presented consecutively in a 4 × 4 grid (each dot displayed for 1500 ms) followed by an unfilled red circle shown on the grid for 2500 ms. Participants were asked to decide within 2500 ms, whether the unfilled circle was at the same location as one of the filled dots displayed beforehand. The response buttons allowed for a "yes" (left hand) or "no" (right hand) answer. The correct response was either one, two, or three dots before the last dot presented. The location of the red dots and unfilled red circles was pseudo-randomized with overall odds of 50:50. The cognitive demand varied within the working memory blocks: the first and second block represented conditions with a low cognitive demand (series of three red dots), the third and fourth block represented conditions with a higher cognitive demand (series of four red dots). In the control condition, four green dots were presented consecutively in each corner of the grid (each dot was displayed for 1500 ms). After a blank delay, an unfilled green circle appeared for 2500 ms indicating that the participants should press both response buttons. The blank delay between the filled dots and unfilled circles was shown for 1500 ms in the low-demand task condition and for 2500 ms in the high-demand task condition.

Statistical analyses of the cognitive and clinical data

Missing values were imputed based on all the variables that were embedded within the dataset using the predictive mean matching algorithm (five datasets) (Sterne et al., 2009). Missing data was evident in two variables: unavailable standardized age norms for 16-year-olds in the visuospatial working memory task used outside the scanner ($n = 1$) and unreturned SES-questionnaires ($n = 4$). The pattern of results remained the same, irrespective of whether the analyses were conducted with or without

imputed data. Hence, the imputed data of 30 survivors and 30 controls were included for all the analyses.

IBM SPSS Statistics software (version 25.0) was used for all the cognitive and clinical data analyses. The significance level was set at $p < .05$, two-tailed tests were conducted, and Cohen's d was reported as effect size.

Independent-samples t-tests were used to examine differences between survivors and controls in continuous demographic (age, SES) and in cognitive variables (fluid intelligence, fMRI task accuracy, visuospatial, and verbal working memory). Pearson's chi-square tests were used to examine group differences in sex and handedness distribution. Paired-sample t-tests, conducted for each group separately (controls, survivors), were performed to examine differences in fMRI task accuracy between the high- and low-demand conditions. Two-tailed Pearson's correlation analysis was applied to examine the relationship between cognitive variables and age at diagnosis or SES.

Neuroimaging

fMRI data acquisition

MRI images were acquired using a 3-Tesla Siemens Magnetom Prisma VE11C Scanner (Siemens, Erlangen, Germany) equipped with a 64-channel head coil. The anatomical imaging was obtained using a sagittal oriented 3-D T1 magnetization-prepared rapid gradient echo (MPRAGE) sequence for acquisition of T1-weighted structural brain imaging (acquisition time, TA = 4:33 min; repetition time, TR = 1950 ms; echo time, TE = 2.19 ms; slices per slap = 176; field of view, FoV = 256 × 256; isovoxel resolution = 1 mm^3). The functional imaging was obtained using a multi-slice single-shot T2-weighted echo planar imaging sequence with 40 interleaved axial oblique slices, positioned in-line with the bicommissural axis (TR = 3000 ms, no delay; TA = 5:35 min; TE = 30 ms; 3 mm resolution, 108 measurements). The sequences were driven in a 3D PACE mode (Siemens, Erlangen, Germany) to enable prospective motion correction. Lumina LP-400 response pads for fMRI (Cedrus, San Pedro, CA, USA) recorded performance during the fMRI task. Inflatable cushions were used to minimize head movement.

fMRI data analysis

Data were analyzed using SPM12 software (Wellcome Trust Center for Neuroimaging, London, UK) running in Matlab R2020a (Mathworks, Natick, MA, USA). The first 12 scans of the functional series (first block of the control condition) were disregarded to ensure the stabilization of longitudinal magnetization. After spatial realignment, the functional images were slice-timed, co-registered, segmented, normalized (Montreal Neurological Institute (MNI) template), and smoothed (Gaussian filter, FWHM = 6 mm). Participants that moved more than one voxel size (3 mm) in any direction were excluded from analyses (for details see Figure 1). The six parameters that describe head movement during MRI were included as confounding variables. All T1-weighted structural brain images were checked for lesions by a neuroradiologist (N.S.), but no survivor included in the analyses had any brain lesions.

Whole-brain first-level analyses were conducted using a General Linear Model (Friston et al., 1995). First-level analyses contrasted the working memory blocks relative to the control blocks of the task. The resulting contrast images of brain activation (low- and high-demand conditions analyzed together) were entered into random-effects second-level analyses. To ensure that our task activated the working memory network and to explore the nature of the working memory-related network in each group separately, one-sample t-tests were conducted on a voxel-by-voxel basis for each group separately. A full factorial design was computed to examine the interaction between cognitive demand (high vs low) and group (survivors vs controls). Post-hoc analyses, including one-sample t-tests, were conducted separately for the two groups (controls, survivors) to examine the differences in working memory-related activation between the two demand conditions (high vs low). Two single-subject

t-contrasts were performed: low-demand > high-demand condition and high-demand > low-demand condition.

Based on guidelines applicable to imaging studies on complex cognitive functions (Lieberman & Cunningham, 2009), all second-level analyses (unless otherwise stated) were thresholded at $p < .001$ and a minimum extent threshold of 10 voxels (uncorrected for family-wise error (FWE)) was reported. Findings surviving FWE correction at the peak- or cluster-level were reported when applicable (Lindquist & Mejia, 2015; Poldrack et al., 2008). All results are reported on whole-brain analyses.

Post-hoc analyses included the extraction of beta values from brain areas with significant clusters surviving FWE correction (i.e., clusters obtained in the one-sample *t*-test examining activation differences between the two demand conditions). Beta estimates were centered on peak voxel activations from spheres (for the right superior parietal lobe (SPL), the left precentral gyrus, and the left SPL, including parts of the left supramarginal gyrus: radius = 10 mm). We determined whether network activation strength in these three brain regions correlated with working memory performance or age at diagnosis, while controlling for age. Partial correlational analyses were conducted separately for the survivor and control group.

Results

Background and clinical data

Survivors and controls were comparable in terms of age, sex, handedness, SES (Table 1), and fluid intelligence (Table 2). Clinical characteristics of the survivor group are presented in the supplementary information (Table S1).

fMRI task accuracy and working memory performance outside the scanner

In the cognitive tests, mean working memory performance was within the normative range in both groups (Table 2). However, small-to-medium effect sizes in verbal and visuospatial working memory outside the scanner indicate worse performance in survivors than controls. During fMRI, task accuracy of survivors was significantly worse than task accuracy of controls in the high-demand fMRI condition. Comparing the task accuracy between the low- and high-demand conditions separately for the control and for the survivor group yielded no significant differences (controls: $t(29) = -1.89$, $p = .07$, Cohen`s $d = .42$; survivors: $t(29) = 0.44$, $p = .66$, Cohen`s $d = .11$). Controls and survivors completed the control fMRI task condition with accuracy rates close to 100%, such as observed by the examiner during the MRI scan. There was no significant relationship between age at assessment and total accuracy of the fMRI task, $r(60) = .141$, $p = .283$, fMRI task accuracy in the low-, $r(60) = .135$, $p = .304$, and in the high-demand condition, $r(60) = .088$, $p = .502$, either in survivors nor in controls.

Table 1. Demographic data.

	Controls ($n = 30$)	Non-CNS survivors ($n = 30$)		
	Mean (*SD*) Range	Mean (*SD*) Range	Test statistic t/χ^2	p
Age	12.50 (2.39) 8.4–16.2	11.44 (2.24) 7.9–15.6	1.79	.079
Sex (female/male)	14/16	13/17	0.07	.795
Handedness R/L/A	27/3/0	29/1/0	1.07	.301
SES	6.61 (1.58) 3–9	6.71 (1.42) 2–9	−0.26	.797

Note. Units of age = *years; SD* = standard deviation; *n* = sample size; SES = socio-economic status: ranging from 0 to 9, with higher scores representing higher SES; *t*= t-value; χ^2 = chi-square; *p* = level of statistical significance.

Table 2. Cognitive performance.

	Controls (n = 30)	Non-CNS survivors (n= 30)			
	Mean (SD) <?h=tRange	Mean (SD) <?h=tRange	Test statistic t/χ^2	p	Effect sizec
Fluid intelligencea	106.87 (13.88) <?h=t88–132	108.33 (10.91) <?h=t86–129	−0.46	.326	0.12
Visuospatial working memorya	110.83 (18.32) <?h=t75–140	103.70 (18.63) <?h=t60–145	1.49	.068	0.39
Verbal working memorya	104.23 (12.70) <?h=t83–125	98.87 (10.57) <?h=t78–119	1.78	.08	0.46
fMRI total task accuracy (% correct)b	87.23 (12.13) <?h=t58.3–100	82.23 (10.43) <?h=t66.7–100	1.71	.092	0.44
Low-demand condition (% correct)	83.89 (18.30) <?h=t50–100	82.78 (14.17) <?h=t50–100	0.26	.793	0.07
High-demand condition (% correct)	90.56 (12.13) <?h=t66.67–100	81.11 (14.99) <?h=t50–100	2.68	.010	0.69

SD = standard deviation; n = sample size; t= t-value; χ^2 = chi-square; p = level of statistical significance.
[a]Standard score (mean 100, SD 15)
[b]Raw scores, max 12
[c]Cohens d

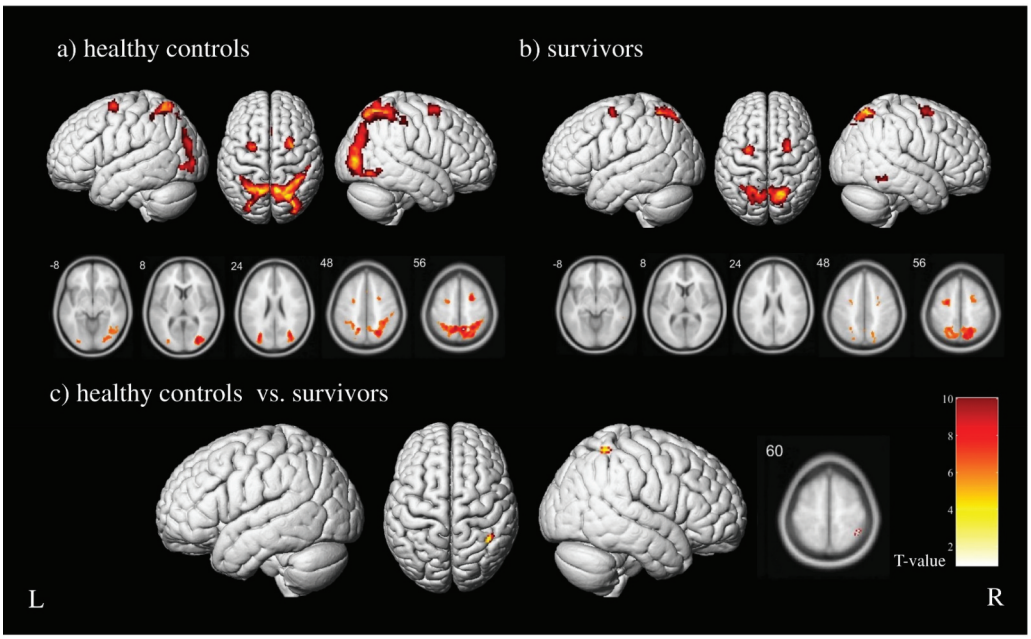

Figure 3. Working memory network in healthy controls and survivors. First-level contrast comparing working memory task blocks vs control task blocks in (a) healthy controls and (b) survivors of childhood cancer without CNS involvement (p < .05, FWE corrected, k > 40). (c) Factorial design contrasting controls and survivors (controls > survivors, p < .001, uncorrected, k > 30). Main activation clusters are presented in render view. L = left, R = right. The reverse contrasts (control task blocks > working memory task blocks, survivors > controls) did not yield any significant suprathreshold clusters.

Working memory network

Brain areas activated during the fMRI task in childhood cancer survivors and controls are presented in Figure 3. Healthy controls and survivors showed the well-known fronto-parietal working memory network (Klingberg, 2006; Thomason et al., 2009). Controls showed neural activation bilaterally in the SPL, precuneus, superior and middle frontal regions, precentral gyri, supplementary motor cortices,

middle cingulate gyri, and in the right anterior cingulate gyrus (Figure 3a). Survivors demonstrated the main activation clusters bilaterally in the superior frontal gyri, in the right SPL, the right middle frontal gyrus, the right precentral gyrus, and the right inferior temporal gyrus (Figure 3b).

The factorial design was employed to explore the potential effects of group (survivors vs controls) and condition (high vs low demand) as well as their interaction on neurophysiological correlates. The low-demand working memory condition showed significantly more neural activation than the control task condition, validating that even in the low-demand working memory condition more effort was needed to solve the task (FWE-corrected, $p < .05$).

Analyses revealed the main effect of group in the right SPL (MNI-coordinate [x y z = 40, −50, 60], k = 33, $F = 18.94$, $Z_E = 4.02$, p uncorr. < .0005, Figure 3c). The main effect of condition was seen in the right supramarginal gyrus, including parts of the right SPL (MNI-coordinate [x y z = 44, −40, 44]), and in the left (MNI-coordinate [x y z = −32, 22, 4]) and right (MNI-coordinate [x y z = 34, 18, 4]) anterior insula (k > 50, $Fs > 13.0$, Z_Es > 3.0, ps uncorr. < .001). The factorial analysis showed a condition by group interaction in the left superior temporal gyrus (MNI-coordinate [x y z = −66, −22, −2] k = 39, $F = 21.89$. $Z_E = 4.32$, p uncorr. < .0005).

Post-hoc analyses in survivors were performed to compare the high- vs low-demand working memory condition. These analyses revealed significantly higher activation during the high- than the low-demand working memory condition in the left SPL with parts of the left supramarginal gyrus (MNI-coordinate [x y z = −30, −50, 52]; FWE corrected on cluster-level: $p < .001$) and in the left precentral gyrus (MNI-coordinate [x y z = −44, −8, 38]; FWE corrected on cluster-level: $p < .05$). Survivors also showed neural hyperactivation during the high- compared to the low-demand condition in the right angular gyrus, including the right SPL (MNI-coordinate [x y z = 42, −48, 52]; FWE corrected on cluster-level: $p < .05$) (k > 150, $Ts > 5.16$, Z_Es > 4.31; see Figure 4a). For survivors, the reverse contrast (low- > high-demand condition) and for controls the comparison between the two conditions (high vs low demand) did not yield any significant suprathreshold clusters. Note that although slight variations in network activation occurred, activation patterns did not substantially differ when comparing the relatively large group of survivors who received chemotherapy only ($n = 17$) with the healthy control group and when comparing the relatively large group of survivors of lymphoid leukemia ($n = 15$) with the healthy control group. The observed slight variations in network activation across groups occurred in clusters where FWE-correction did not yield any suprathreshold activation. Associations between neural activation strength and cognitive outcome or age at diagnosis were not different for survivors receiving chemotherapy only and for survivors of lymphoid leukemia. Background variables and cognitive performance did not differ among subgroups (chemotherapy, lymphoid leukemia and healthy controls). Including a separate group of survivors after radiotherapy or surgery in this comparison was omitted due to small sample sizes.

Associations between working memory-related neural activation and working memory performance

In brain regions where activation differences survived FWE correction (i.e., post-hoc analyses in the survivor group), the strength of neural activation, i.e., the beta values were extracted and their association with working memory performance or age at diagnosis was examined. The post-hoc analyses comparing high- and low-demand working memory conditions in the survivors' group yielded three significant brain clusters (located in the left precentral gyrus, and the right and left SPL) surviving FWE correction (see Figure 4a). For survivors, a significant negative correlation was found between the right-hemispheric SPL activation and verbal working memory ($r(27) = -.416$, $p = .025$) (Figure 4b). In controls, there was no association between working memory performance and working memory-related neural activation (Figure 4c). Age at diagnosis was unrelated to neural activation. Age at assessment did not correlate with activation strength, either in survivors, or in controls. Note that auxiliary analyses on the effect of time elapsed since cancer treatment (≤ 3 years after treatment: $n = 14$; ≥ 4 years after treatment: $n = 16$) did not reveal group differences in working

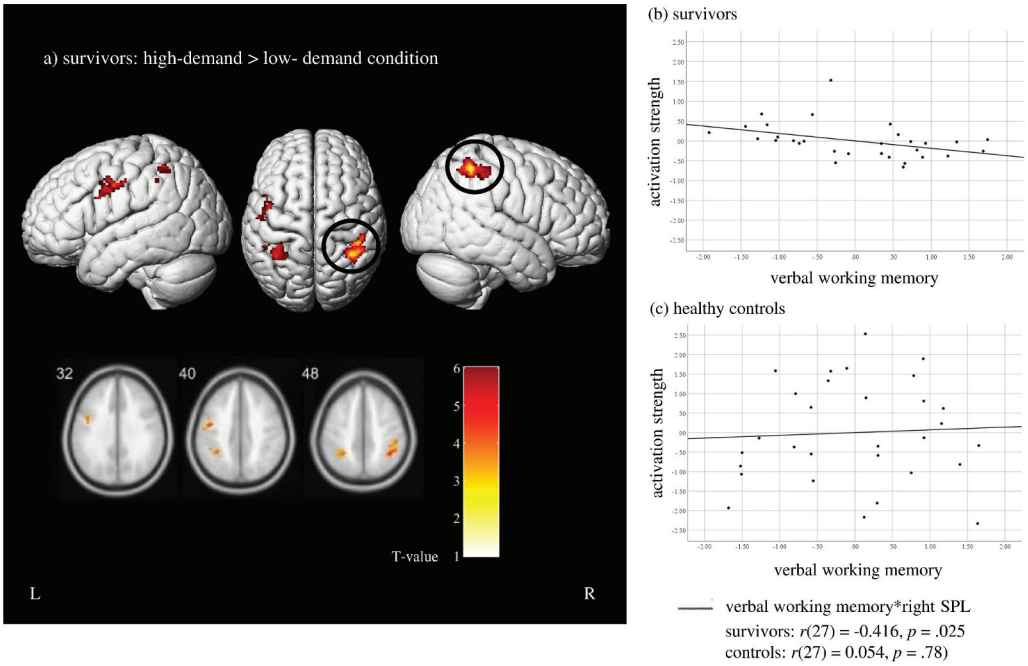

Figure 4. Working memory network, cognitive demand and the relationship between activation strength and working memory performance. One-sample *t*-test contrasting the high- and low-demand condition (a) within the survivor group ($p < .001$, uncorrected, k > 150). Circles indicate where the activation strength significantly correlating with performance scores derives from. L = left, R = right. None of the other contrasts (survivors: low > high-demand, controls: low > high-demand condition and high > low-demand condition) yielded any significant suprathreshold clusters. Activation strength in the right SPL is significantly associated with verbal working memory in survivors (b) but not in controls (c). None of the other extracted cluster activations revealed a significant relationship with working memory performance. Scores were z-standardized.

memory outcome nor group differences in network activation and its relation to cognitive outcome in respect to time since cancer treatment.

Discussion

This study investigated neurophysiological correlates during a working memory task with high vs low demands in children and adolescents who had survived non-CNS cancer. Survivors' task accuracy differed from that of controls only significantly in the high-demand working memory condition with survivors performing more poorly. Small-to-medium effect sizes indicated group differences outside the scanner in verbal and visuospatial working memory. During a working memory task, survivors and controls recruited a fronto-parietal network, which largely confirmed earlier findings (Klingberg, 2006; Klingberg et al., 2002; Thomason et al., 2009). Between-group analyses revealed evidence for slightly atypical activation in the right SPL for survivors compared to controls. High vs low working memory-demand conditions revealed, however, hyperactivation in the right supramarginal gyrus, including parts of the right SPL, and bilaterally in the insula in survivors. In addition, right-hemispheric SPL activation was negatively associated with verbal working memory performance outside the scanner in survivors. Overall, our neurophysiological and cognitive results are consistent with previous findings (Arthursson et al., 2017; King et al., 2015; Robinson et al., 2010) and indicate that, even in survivors without CNS involvement, greater task complexity may lead to poorer working memory performance and to more pronounced activation differences. In more detail, survivors kept up their level of task accuracy when task complexity increased while showing hyperactivation in the right SPL.

Group activation maps (Figure 3b) indicated less pronounced cluster activation in the working memory network of the cancer survivor group. Mürner-Lavanchy et al. (2014) pointed out that less pronounced cluster activation might be the result of high within-group variance, albeit mean beta values might be high.

Group analysis revealed evidence for atypical activation in the right SPL in cancer survivors; however, the evidence for network alterations was relatively weak given that correction for multiple comparisons was not applicable. Nevertheless, this finding extends the existing evidence of altered working memory network activation after non-CNS cancer using a larger sample (Robinson et al. (2010): $n = 8$; Stefancin et al. (2020): $n = 15$). The altered SPL activation and poorer working memory performance observed in our study are in line with the results of Stefancin et al. (2020), however, a direct comparison with our results is not feasible because we used a block task design and Stefancin et al. (2020) used an event-related design. In different pediatric samples (childhood leukemia survivors; Robinson et al., 2010; Stefancin et al., 2020, childhood brain tumor survivors; King et al., 2015, preterm born children; Arthursson et al., 2017) hyperactivation was reported in prefrontal and parietal regions when solving a visuospatial or verbal working memory task. By contrast, our results did not indicate hyperactivation in frontal brain areas, possibly because the fMRI task used in this study was not complex enough (see King et al. (2015)).

Our fMRI tak used one of the traditional measures of working memory (simpel span task) that requires the participant to actively maintain information in working memory ("storage"). However, the present task does not include manipulation of information, such as needed in the often-used complex span tasks or in n-back working memory tasks ("storage and processing"; Redick and Lindsey (2013); Scharinger, Soutschek, Schubert, and Gerjets (2017)) and by this reflects a basic working memory task with additional components. The interaction between attention and working memory is an elementary determinant of broad cognitive ability (Engle & Kane, 2004). Hence, the present task likely has a substantial overlap with neural activations of the attentioal network (Osaka, Komori, Morishita, & Osaka, 2007).

Atypical neural activation is thought to reflect poorer storage capacities for visuospatial information (Edin et al., 2009) and efforts to compensate for a lack of local processing to achieve equal performance levels to those of controls (Arthursson et al., 2017; Edelmann et al., 2013; Krull et al., 2013; Robinson et al., 2010). Atypical neural activation may also indicate the need of auxiliary cognitive control and attentional resources to solve a task (Medaglia et al., 2012). The higher engagement needed for neural mechanisms might drain, however, metabolic resources (Edelmann et al., 2013; Krull et al., 2013). These slight cerebral alterations in non-CNS cancer survivors are likely a consequence of the cytotoxicity of cancer and its treatment (e.g., chemotherapy, cranial irradiation) (Kesler et al., 2016).

Survivors showed hyperactivation within the right SPL in the high- compared to the low-demand fMRI condition, while keeping up their level of performance. However, survivors performed more poorly than controls in the high-demand fMRI condition. This suggests that solving the high-demand visuospatial working memory task may selectively ask for more cognitive control and attentional resources in survivors of non-CNS cancer (compare with Medaglia et al. (2012)). Hence, increased efforts (represented by atypical neural activation) appear insufficient because survivors were not able to attain the controls' level of accuracy during high-demand conditions (Arthursson et al., 2017; Robinson et al., 2010).

In addition, and for survivors only, right-hemispheric SPL hyperactivation was negatively related to verbal working memory performance outside the scanner. Thus, our data indicate that survivors with lower verbal working memory capacities also show right-hemispheric SPL hyperactivation. In contrast, lower SPL activation has previously been linked to poorer performance and younger age, suggesting that lower activation in the right SPL might reflect a less mature network (Lidzba, Ebner, Hauser, & Wilke, 2013).

Lastly, our findings do not provide evidence of a potential influence of age at diagnosis on task-related network activation and cognitive performance (Billiet et al., 2018). Thus, contrary to previous claims (Dennis et al., 2014; Richards & Deary, 2005; Stern, 2009), age at diagnosis did not explain the

variations in functional outcome that have often been reported in survivors of non-CNS childhood cancer (Conklin et al., 2012; Kesler, Tanaka, & Koovakkattu, 2010; Krull et al., 2013). Future research, preferably with a longitudinal study design, should further investigate proxies for neural recovery and the influence of age at diagnosis, as a complex interplay between these factors might uphold cognitive performance until a certain threshold is reached (Stern, 2009).

Limitations

We studied a heterogeneous group of non-CNS cancer survivors in terms of cancer diagnosis, treatment protocols (i.e., treatment modality and intensity), and years elapsed since cancer treatment – factors known to affect brain parameters and cognition differentially (Fellah et al., 2019; Hutchinson, Pfeiffer, & Wilson, 2017; Kim et al., 2015; Krull et al., 2013). To assess the influence of all these clinical factors on neural activation patterns and cognitive performance was not feasible due to small subgroup sizes (see supplementary information Table S1). In addition, the effect of intrathecal therapy needs to be taken into consideration when interpreting study findings on non-CNS cancers.

The study's research design entailed the risk of overrepresentation of survivors with good functional outcomes, families with good resources, and survivors living in urban areas close to the university hospital. Furthermore, the exclusion rate of the fMRI data was rather high (see Figure 1). The generalizability of the findings thus remains limited.

Even though the findings were reported based on imaging guidelines on complex cognitive functions (Lieberman & Cunningham, 2009), results did not survive FWE correction in all analyses. Consequently, there is a risk of false-positive activations and the results should be interpreted with caution (Poldrack et al., 2008).

Survivors and controls with a broad age range were includedreflecting a further limitation because of developmental differences across ages (Jones & Pattwell, 2019). However, age at assessment was not associated with activation strength (i.e., beta values). Moreover, the fMRI task protocol entailed only 12 trials (six low- and six high-demand conditions). This contributes to reduced test power for the fMRI analyses.

Past research suggests that the SES plays a critical role regarding the severity of cognitive impairment in children after cancer (Kesler et al., 2010) and that the SES relates to structural and functional brain characteristics (Hackman & Farah, 2009; Kesler et al., 2010; Yaple & Yu, 2020) and cognition in typically developing children (Hackman, Gallop, Evans, & Farah, 2015). Future studies may investigate whether neural alterations and working memory performance is associated with SES in childhood cancer.

Conclusion

When cognitive complexity increased, survivors performed more poorly than controls and showed evidence for slightly atypical working memory-related activations. Working memory-related neural activation may be altered even in survivors of cancer without CNS involvement, with survivors showing signs of neural hyperactivity located in the right-hemispheric SPL. Additionally, survivor's right-hemispheric SPL hyperactivation was negatively related to working memory performance – an association that was not observed in healthy controls. Overall, these findings highlight the relevance of SPL processing for working memory performance in survivors of non-CNS childhood cancer. Our study provides further confirmation that assessment of neurophysiological correlates with neuroimaging methods, such as fMRI-based tasks, may have the means to shed light on the neural underpinnings of cognitive late effects in survivors.

Acknowledgments

In addition, we would like to thank the team of the Swiss Childhood Cancer Registry for their support, the participating parents, and their children. We are grateful to our postgraduate students and research assistants for their support in performing assessments and to Susan Kaplan for proofreading this manuscript.

Funding

None of the authors have any conflict of interest to disclose. Funding: This work was supported by The Fondation Gaydoul [Churerstrasse 47, 8808 Pfäffikon SZ], the Swiss Cancer Research foundation [KFS-3705-08-2015; KFS-4708-02-2019], the Dietmar Hopp Stiftung GmbH [Walldorf, Germany], the Hans & Annelies Swierstra Stiftung [Meggen, Switzerland], and the Berner Stiftung für krebskranke Kinder und Jugendliche, 3010 Bern; Fondation Gaydoul; the Swiss Cancer Research foundation [KFS-3705-08-2015,KFS-4708-02-2019]; the Berner Stiftung für krebskranke Kinder und Jugendliche; the Hans & Annelies Swierstra Stiftung.

ORCID

Mirko Schmidt http://orcid.org/0000-0003-4859-6547
Regula Everts http://orcid.org/0000-0001-6556-3419

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Anderson, V., Spencer-Smith, M., Coleman, L., Anderson, P., Williams, J., Greenham, M., … Jacobs, R. (2010). Children's executive functions: Are they poorer after very early brain insult. *Neuropsychologia*, *48*(7), 2041–2050. doi:10.1016/j.neuropsychologia.2010.03.025

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*, *134*(8), 2197–2221. doi:10.1093/brain/awr103

Arthursson, P. S. H., Thompson, D. K., Spencer-Smith, M., Chen, J., Silk, T., Doyle, L. W., & Anderson, P. J. (2017). Atypical neuronal activation during a spatial working memory task in 13-year-old very preterm children. *Hum Brain Mapp*, *38*(12), 6172–6184. doi:10.1002/hbm.23820

Ashford, J., Schoffstall, C., Reddick, W. E., Leone, C., Langingham, F. H., Glass, J. O., … Conklin, H. M. (2010). Attention and working memory abilities in children treated for acute lymphoblastic leukemia. *Cancer*, *116*(19), 4638–4645. doi:10.1002/cncr.25343

Baddeley, A. (2012). Working memory: Theories, models, and controversies. *Annual Review of Psychology*, *63*(1), 1–29. doi:10.1146/annurev-psych-120710-100422

Benzing, V., Eggenberger, N., Spitzhuettl, J., Siegwart, V., Pastore-Wapp, M., Kiefer, C., … Leibundgut, K. (2018). The Brainfit study: Efficacy of cognitive training and exergaming in pediatric cancer survivors – A randomized controlled trial. *BMC Cancer*, *18*(18). doi:10.7892/boris.109130

Benzing, V., Spitzhüttl, J., Siegwart, V., Schmid, J., Grotzer, M., Heinks, T., … Everts, R. (2020). Effects of cognitive training and exergaming in pediatric cancer survivors–A randomized clinical trial. *Medicine & Science in Sports & Exercise*, *52*(11), 2293–2302. in press. doi:10.1249/MSS.0000000000002386

Billiet, T., Elens, I., Sleurs, C., Uyttebroeck, A., D'Hooge, R., Lemiere, J., & Deprez, S. (2018). Brain connectivity and cognitive flexibility in nonirradiated adult survivors of childhood leukemia. *JNCI: Journal of the National Cancer Institute*, *110*(8), 905–913. doi:10.1093/jnci/djy009

Boudreau, B., & Poulin, C. (2008). An examination of the validity of the Family Affluence Scale II (FAS II) in a general adolescent population of Canada. *Social Indicators Research*, *94*(1), 29–42. doi:10.1007/s11205-008-9334-4

Brown, L., Sherbenou, R. J., & Johnsen, S. K. (2010). *Test of Nonverbal Intelligence: TONI-4*. Austin, TX: Pro-ed. doi:10.1177/0734282911400400

Chen, H., Wang, L., King, T. Z., & Mao, H. (2016). Increased frontal functional networks in adult survivors of childhood brain tumors. *NeuroImage: Clinical*, *11*, 339–346. doi:10.1016/j.nicl.2016.02.010

Cheung, Y. T., Sabin, N. D., Reddick, W. E., Bhojwani, D., Liu, W., Brinkman, T. M., … Krull, K. R. (2016). Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: A longitudinal analysis. *The Lancet Haematology*, *3*(10), e456–e466. doi:10.1016/s2352-3026(16)30110-7

Conklin, H. M., Krull, K. R., Reddick, W. E., Pei, D., Cheng, C., & Pui, C. H. (2012). Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. *J Natl Cancer Inst*, *104*(18), 1386–1395. doi:10.1093/jnci/djs344

Dennis, M., Spiegler, B. J., Simic, N., Sinopoli, K. J., Wilkinson, A., Yeates, K. O., … Fletcher, J. M. (2014). Functional plasticity in childhood brain disorders: When, what, how, and whom to assess. *Neuropsychol Rev*, *24*(4), 389–408. doi:10.1007/s11065-014-9261-x

Edelmann, M. N., Ogg, R. J., Scoggins, M. A., Brinkman, T. M., Sabin, N. D., Pui, C. H., … Krull, K. R. (2013). Dexamethasone exposure and memory function in adult survivors of childhood acute lymphoblastic leukemia: A report from the SJLIFE cohort. *Pediatric Blood & Cancer*, *60*(11), 1778–1784. doi:10.1002/pbc.24644

Edin, F., Klingberg, T., Johansson, P., McNab, F., Tegner, J., & Compte, A. (2009). Mechanism for top-down control of working memory capacity. *Proceedings of the National Academy of Sciences*, *106*(16), 6802–6807. doi:10.1073/pnas.0901894106

Engle, R. W., & Kane, M. J. (2004). Executive attention, working memory capacity, and a two-factor theory of cognitive control.

Fellah, S., Cheung, Y. T., Scoggins, M. A., Zou, P., Sabin, N. D., Pui, C. H., … Krull, K. R. (2019). Brain activity associated with attention deficits following chemotherapy for childhood acute lymphoblastic leukemia. *JNCI: Journal of the National Cancer Institute*, *111*(2), 201–209. doi:10.1093/jnci/djy089

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-P., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*(4), 189–210. doi:10.1002/hbm.460020402

Gathercole, S., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology*, *18*(1), 1–16. doi:10.1002/acp.934

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., … Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, *101*(21), 8174–8179. doi:10.1073/pnas.0402680101

Hackman, D. A., & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Trends in Cognitive Sciences*, *13*(2), 65–73. doi:10.1016/j.tics.2008.11.003

Hackman, D. A., Gallop, R., Evans, G. W., & Farah, M. J. (2015). Socioeconomic status and executive function: Developmental trajectories and mediation. *Developmental Science*, *18*(5), 686–702. doi:10.1111/desc.12246

Hutchinson, A. D., Pfeiffer, S. M., & Wilson, C. (2017). Cancer-related cognitive impairment in children. *Current Opinion in Supportive & Palliative Care*, *11*(1), 70–75. doi:10.1097/SPC.0000000000000258

Iyer, N. S., Balsamo, L. M., Bracken, M. B., & Kadan-Lottick, N. S. (2015). Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: A review and meta-analysis. *Blood*, *126*(3), 346–353. doi:10.1182/blood-2015-02-627414

Jacola, L. M., Krull, K. R., Pui, C. H., Pei, D., Cheng, C., Reddick, W. E., & Conklin, H. M. (2016). Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. *Journal of Clinical Oncology*, *34*(11), 1239–1247. doi:10.1200/JCO.2015.64.3205

Jones, R. M., & Pattwell, S. S. (2019). Future considerations for pediatric cancer survivorship: Translational perspectives from developmental neuroscience. *Developmental Cognitive Neuroscience*, *38*, 100657. doi:10.1016/j.dcn.2019.100657

Kesler, S. R., Gugel, M., Huston-Warren, E., & Watson, C. (2016). Atypical structural connectome organization and cognitive impairment in young survivors of acute lymphoblastic leukemia. *Brain Connectivity*, *6*(4), 273–282. doi:10.1089/brain.2015.0409

Kesler, S. R., Tanaka, H., & Koovakkattu, D. (2010). Cognitive reserve and brain volumes in pediatric acute lymphoblastic leukemia. *Brain Imaging and Behavior*, *4*(3–4), 256–269. doi:10.1007/s11682-010-9104-1

Kim, S. J., Park, M. H., Lee, J. W., Chung, N. G., Cho, B., Lee, I. G., & Chung, S. Y. (2015). Neurocognitive outcome in survivors of childhood acute lymphoblastic leukemia: Experience at a tertiary care hospital in Korea. *Journal of Korean Medical Science*, *30*(4), 463–469. doi:10.3346/jkms.2015.30.4.463

King, T. Z., Na, S., & Mao, H. (2015). Neural underpinnings of working memory in adult survivors of childhood brain tumors. *Journal of the International Neuropsychological Society*, *21*(7), 494–505. doi:10.1017/S135561771500051X

Klingberg, T. (2006). Development of a superior frontal-intraparietal network for visuo-spatial working memory. *Neuropsychologia*, *44*(11), 2171–2177. doi:10.1016/j.neuropsychologia.2005.11.019

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *Journal of Cognitive Neuroscience*, *14*(1), 1–10. doi:10.1162/089892902317205276

Krull, K. R., Brinkman, T. M., Li, C., Armstrong, G. T., Ness, K. K., Srivastava, D. K., … Hudson, M. M. (2013). Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St Jude lifetime cohort study. *Journal of Clinical Oncology*, *31*(35), 4407–4415. doi:10.1200/JCO.2012.48.2315

Lidzba, K., Ebner, K., Hauser, T. K., & Wilke, M. (2013). Complex visual search in children and adolescents: Effects of age and performance on fMRI activation. *PLoS One*, *8*(12), e85168. doi:10.1371/journal.pone.0085168

Lieberman, M. D., & Cunningham, W. A. (2009). Type I and Type II error concerns in fMRI research: Re-balancing the scale. *Social Cognitive and Affective Neuroscience*, *4*(4), 423–428. doi:10.1093/scan/nsp052

Lindquist, M. A., & Mejia, A. (2015). Zen and the art of multiple comparisons. *Psychosomatic Medicine*, *77*(2), 114–125. doi:10.1097/PSY.0000000000000148

Medaglia, J. D., Chiou, K. S., Slocomb, J., Fitzpatrick, N. M., Wardecker, B. M., Ramanathan, D., . . . Hillary, F. G. (2012). The less BOLD, the wiser: Support for the latent resource hypothesis after traumatic brain injury. *Human Brain Mapping*, *33*(4), 979–993. doi:10.1002/hbm.21264

Melchers, P., & Preuss, U. (2003). *K-ABC: Kaufman assessment battery for children, German version*. Bern: Hogrefe & Huber.

Michel, E., Molitor, S., & Schneider, W. (2020). Executive functions and fine motor skills in kindergarten as predictors of arithmetic skills in elementary school. *Dev Neuropsychol*, 1–13. doi:10.1080/87565641.2020.1821033

Mulhern, R. K., & Palmer, S. L. (2003). Neurocognitive late effects in pediatric cancer. *Current Problems in Cancer*, *27*(4), 177–197. doi:10.1016/S0147-0272(03)00026-6

Mürner-Lavanchy, I., Ritter, B. C., Spencer-Smith, M. M., Perrig, W. J., Schroth, G., Steinlin, M., & Everts, R. (2014). Visuospatial working memory in very preterm and term born children–impact of age and performance. *Developmental Cognitive Neuroscience*, *9*, 106–116. doi:10.1016/j.dcn.2014.02.004

Nouwens, S., Groen, M. A., & Verhoeven, L. (2016). How working memory relates to children's reading comprehension: The importance of domain-specificity in storage and processing. *Reading and Writing*, *30*(1), 105–120. doi:10.1007/s11145-016-9665-5

Osaka, M., Komori, M., Morishita, M., & Osaka, N. (2007). Neural bases of focusing attention in working memory: An fMRI study based on group differences. *Cognitive, Affective, & Behavioral Neuroscience*, *7*(2), 130–139. doi:10.3758/cabn.7.2.130

Pickering, S., & Gathercole, S. (2001). *Working memory test battery for children (WMTB-C)*. San Antonio: Psychological Corporation.

Poldrack, R. A., Fletcher, P. C., Henson, R. N., Worsley, K. J., Brett, M., & Nichols, T. E. (2008). Guidelines for reporting an fMRI study. *Neuroimage*, *40*(2), 409–414. doi:10.1016/j.neuroimage.2007.11.048

Raghubar, K. P., Barnes, M. A., & Hecht, S. A. (2010). Working memory and mathematics: A review of developmental, individual difference, and cognitive approaches. *Learning and Individual Differences, 20*, *20*(2), 110–122. doi:10.1016/j.lindif.2009.10.005

Reddick, W. E., Taghipour, D. J., Glass, J. O., Ashford, J., Xiong, X., Wu, S., . . . Conklin, H. M. (2014). 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*, *61*(6), 1074–1079. doi:10.1002/pbc.24947

Redick, T. S., & Lindsey, D. R. (2013). Complex span and n-back measures of working memory: A meta-analysis. *Psychonomic Bulletin & Review*, *20*(6), 1102–1113. doi:10.3758/s13423-013-0453-9

Richards, M., & Deary, I. J. (2005). A life course approach to cognitive reserve: A model for cognitive aging and development? *Annals of Neurology*, *58*(4), 617–622. doi:10.1002/ana.20637

Robinson, K. E., Livesay, K. L., Campbell, L. K., Scaduto, M., Cannistraci, C. J., Anderson, A. W., . . . Compas, B. E. (2010). Working memory in survivors of childhood acute lymphocytic leukemia: Functional neuroimaging analyses. *Pediatric Blood & Cancer*, *54*(4), 585–590. doi:10.1002/pbc.22362

Scharinger, C., Soutschek, A., Schubert, T., & Gerjets, P. (2017). Comparison of the working memory load in N-Back and working memory span tasks by means of EEG frequency band power and P300 amplitude. *Frontiers in Human Neuroscience*, *11*, 6. doi:10.3389/fnhum.2017.00006

Sleurs, C., Lemiere, J., Christiaens, D., Billiet, T., Peeters, R., Sunaert, S., . . . Deprez, S. (2018). Advanced MR diffusion imaging and chemotherapy-related changes in cerebral white matter microstructure of survivors of childhood bone and soft tissue sarcoma? *Hum Brain Mapp*, *39*(8), 3375–3387. doi:10.1002/hbm.24082

Sleurs, C., Lemiere, J., Radwan, A., Verly, M., Elens, I., Renard, M., . . . Uyttebroeck, A. (2019). Long-term leukoencephalopathy and neurocognitive functioning in childhood sarcoma patients treated with high-dose intravenous chemotherapy. *Pediatric Blood & Cancer*, *66*(10), e27893. doi:10.1002/pbc.27893

Spencer-Smith, M., Ritter, B. C., Murner-Lavanchy, I., El-Koussy, M., Steinlin, M., & Everts, R. (2013). Age, sex, and performance influence the visuospatial working memory network in childhood. *Developmental Neuropsychology*, *38*(4), 236–255. doi:10.1080/87565641.2013.784321

Stefancin, P., Cahaney, C., Parker, R. I., Preston, T., Coulehan, K., Hogan, L., & Duong, T. Q. (2020). Neural correlates of working memory function in pediatric cancer survivors treated with chemotherapy: An fMRI study. *NMR in Biomedicine*, *33*(6), e4296. doi:10.1002/nbm.4296

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. doi:10.1016/j.neuropsychologia.2009.03.004

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., . . . Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *Bmj*, *338*, b2393. doi:10.1136/bmj.b2393

Thomason, M. E., Race, E., Burrows, B., Whitfield-Gabrieli, S., Glover, G. H., & Gabrieli, J. D. (2009). Development of spatial and verbal working memory capacity in the human brain. *Journal of Cognitive Neuroscience*, *21*(2), 316–332. doi:10.1162/jocn.2008.21028

Ward, Z. J., Yeh, J. M., Bhakta, N., Frazier, A. L., Girardi, F., & Atun, R. (2019). Global childhood cancer survival estimates and priority-setting: A simulation-based analysis. *Lancet Oncol*, *20*. doi:10.1016/S1470-2045(19)30273-6

Yaple, Z. A., & Yu, R. (2020). Functional and structural brain correlates of socioeconomic status. *Cerebral Cortex*, *30*(1), 181–196. doi:10.1093/cercor/bhz080

Zhou, C., Zhuang, Y., Lin, X., Michelson, A. D., & Zhang, A. (2020). Changes in neurocognitive function and central nervous system structure in childhood acute lymphoblastic leukaemia survivors after treatment: A meta-analysis. *British Journal of Haematology*, *188*(6), 945–961. doi:10.1111/bjh.16279