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The Impact of Attention on Social Functioning in Survivors of Pediatric Acute Lymphoblastic Leukemia and Brain Tumors

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Abstract

Background—The cognitive late effects experienced by many survivors of pediatric acute lymphoblastic leukemia (ALL) and brain tumors are well-established. The most commonly reported deficit is difficulty with attention. Problems with social functioning have also been identified, but their relationship with cognitive functioning is not well understood. This multi-site, cross-sectional study aimed to examine the impact of attention on social functioning.

Procedure—469 survivors of ALL and brain tumors (55% ALL; 57% male) completed study procedures, including parent- and teacher-report measures of attention (Conners' Rating Scales, Revised) and parent-report of social functioning (Social Skills Rating System) as part of their screening evaluation for a large clinical trial. Survivors were 12.1 years of age and 4.9 years from the end of treatment at the time of study.

Results—Results revealed that survivors' parent-reported attention problems were uniquely associated with their social functioning, relative to known demographic- and treatment-related risk factors. Teacher-reported attention problems, in contrast, were not, despite a significant correlation between the two. Deficits in intelligence and female gender were also significantly associated with poor social functioning.

Conclusions—Attention problems uniquely impact difficulties with social functioning in survivors of pediatric cancer. Future studies will need to further examine the relationship between attention and social functioning in survivors, particularly when assessed by teacher report.

Keywords

childhood cancer survivors; attention problems; social functioning; late effects

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Note: Methods of this study are based on a study first reported in Mulhern et al., 2004.

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Deficits in attention are a significant consequence of the diagnosis and treatment of childhood cancer that affects the central nervous system (CNS) [1, 2]. While risk factors (e.g., diagnosis, treatment intensity, time since treatment) may be associated with increased severity of attention deficits [3–5], the majority of survivors of pediatric brain tumors and acute lymphoblastic leukemia (ALL) will evidence some degree of impairment [6–8]. Given the prevalence of these deficits, recent research has sought to describe the effect of attention problems on daily functioning and quality of life. The objective of the current paper is to examine the impact of attention on one aspect of quality of life – social functioning (the ability to competently interact with others across settings [9]) – in a large sample of survivors.

Survivors who receive CNS-directed treatment may experience a constellation of late effects that includes both cognitive problems such as inattention and psychosocial difficulties such as internalizing psychopathology, withdrawal, and social problems [10, 11]. Attention dysfunction has been previously associated with social problems in this population [12, 13], and has been suggested as a contributing factor to inadequate processing of social stimuli [14]. These findings are consistent with recent integrative models of social functioning in children with brain injury which suggest that cognitive and affective functions are interrelated [15]. Specifically, social functioning is theorized to depend on individual developmental and personal characteristics and on interactions between the child and his/her social world. Cognitive and affective functioning may then be influenced by brain insult-related risk and resiliency factors, and ultimately impact how a child understands and responds to social information [15]. Consistent with this model, social difficulties such as difficulty coping with or engaging in social interactions [16–18], appear to be specific to those survivors who underwent CNS-directed treatment [13]. Over time, the relatively poor cognitive and social functioning experienced by these survivors is associated with disruptions in their achievement of developmental milestones, including maintaining both stable employment and romantic relationships [11, 19–22].

Given this long term impact on quality of life, it is important to understand whether survivors of pediatric cancer are experiencing functional problems as a result of changes in attention. Such knowledge will be particularly important for the development of clinical interventions and the determination of relevant outcomes. Although the literature suggests that inattention is correlated with social problems [12, 17, 23], it is unknown whether attention offers a unique contribution to the characterization of social dysfunction relative to known medical and demographic risk factors. To address this gap in the literature, the relationship between attention and social functioning was examined in survivors of ALL and brain tumors. We hypothesized that: (a) a significant proportion of survivors would have clinically elevated attention deficits relative to the measure's normative group and that known demographic and treatment variables would predict these deficits; (b) key demographic and treatment variables would be associated with difficulties in social functioning; and (c) parent- and teacher-rated attention problems would be uniquely associated with social functioning, over and above the influence of demographic and treatment variables.

Method

Participants

Survivors of pediatric ALL or brain tumors between the ages of 6 and 18, at least one year post-treatment, and who spoke English as a primary language were eligible for this multi-site, cross-sectional study. Participants included all individuals screened for participation in a methylphenidate efficacy study [24–26]. Survivors were recruited from three medical centers and were treated with CNS-directed therapy with no evidence of recurrent disease at

the time of evaluation. Individuals with a diagnosis of ADHD predating cancer diagnosis (determined by parent report or notation in the medical record) or who met criteria that could contraindicate a later pharmacological intervention (e.g., glaucoma, current psychotropic medication, recent history of uncontrolled seizures, uncorrected hypothyroidism) were not eligible for this study.

The final sample included 469 survivors of pediatric brain tumors and ALL (57% male; 55% ALL). On average, survivors were 12.1 (SD=3.36) years of age and 4.9 (SD=3.05) years from the end of treatment at the time of study. The vast majority ($n=197$; 93.4%) of survivors of brain tumors were treated with cranial radiation therapy (CRT), as well as 16.3% ($n=42$) of survivors of ALL. The most common brain tumor diagnoses included medulloblastoma, ependymoma and astrocytoma. See Table I for all demographic and clinical information.

Procedures

Following Institutional Review Board (IRB) approval at each site, initial eligibility was established by medical chart review and verified through either a letter or telephone call with the parent. Survivors were approached by study personnel during routine medical appointments. All survivors of ALL and brain tumors at least one year post-treatment and medically stable were eligible for participation; there was no requirement for attention problems as this was determined during screening procedures. Greater than 90% of those approached consented to participate in the screening evaluation. Following consent and assent procedures, participants and parents completed questionnaire measures of attention and social functioning. Schools were contacted via telephone and teacher measures of attention were sent for completion and returned via facsimile. Please see original reports of the trial [26, 28] for additional procedural information.

Measures

Conners' Rating Scales – Revised, Short Version [27]—The Conners' Rating Scales are a measure of the observed frequency of behaviors associated with ADHD in children 3–17 years of age. The Parent (CPRS; $n=455$) and Teacher (CTRS; $n=363$) versions were used in this study, with the CPRS primarily completed by mothers (76.1%). The measure consists of four scales: Oppositional-Defiant, Cognitive Problems/Inattention, Hyperactivity, and ADHD, and a factor analysis confirmed the validity of this structure with a subsample of this study group [28]. The Cognitive Problems/Inattention scale was used as a primary outcome as prior research [29] has suggested survivors do not typically exhibit hyperactive or oppositional behavior. Scales are reported with T-scores separately normed by age and gender and, as suggested by the manual [27], T-scores greater than 60 represent atypical functioning.

Social Skills Rating System [SSRS; 30]—The SSRS is a measure of social behavior in children. Using a Likert format, parents rate the frequency of their child's behavior on 38 items, and include evaluation of prosocial behavior (e.g., helps with household tasks), social adjustment (e.g., getting along with others), social cognition (e.g., responds appropriately to teasing from peers), social competence (e.g., participates in organized activities), social interactions (e.g., avoids situations likely to result in trouble), and social skills (e.g., follows rules when playing games). The SSRS Total Score is reported as a standard score that is normed by child's gender and grade [Elementary (K-6) or Secondary (7-12)]. The median internal consistency reliability (coefficient alpha) for the SSRS-P Social Skills Total score across forms and levels is .90 [30].

Wechsler Intelligence Scales—The age-appropriate Wechsler scale was used to measure intellectual functioning (Wechsler Intelligence Scale for Children, Third Edition [WISC-III; 31] or the Wechsler Adult Intelligence Scale, Third Edition [WAIS-III; 32]). Estimated intellectual functioning (EIQ) was calculated using a formula provided by Sattler [33] based on the Information, Similarities, and Block Design subtests, which is highly correlated with the Full Scale IQ derived from full test administration ($r=.93$ for the WISC-III and $r=.92$ for the WAIS-III).

Demographic and Clinical Variables—Demographic and treatment information was abstracted from medical records. Variables of interest included: diagnosis (brain tumor or ALL), age at diagnosis, tumor location (infratentorial, supratentorial, or both), treatment intensity, time since treatment, and age at screening (see Table I).

Statistical Considerations

Descriptive statistics for demographic, clinical, and psychometric data were calculated. A T-score > 60 on the Cognitive Problems/Inattention scale [27] was selected to indicate clinically significant attention problems for all analyses. To investigate the first hypothesis that a significant proportion of survivors would have clinically elevated attention deficits, ratings of attention were compared with the normative mean using one-sample t -tests. To further characterize our sample, we completed linear regression models to identify medical and cognitive predictors of attention problems. To investigate the second hypothesis that key demographic and treatment variables would be associated with difficulties with social functioning, a series of univariate analyses were performed. To assess the third hypothesis that parent- and teacher-rated attention problems would be uniquely associated with social functioning, two hierarchical regression analyses (parent and teacher ratings were analyzed separately) were performed. The order of entry for the hierarchical regression was determined by the results of the univariate analyses used to investigate the second hypothesis, with attention ratings entered in the final step.

Results

Rate of Clinically Significant Attention Difficulties

To test the first hypothesis, analyses were conducted to determine the rate of clinically significant attention difficulties in this sample. Intra-class correlations revealed only fair agreement between parent and teacher ratings (Intra Class Coefficient = $.21$, $p<.001$); hence, subsequent analyses were conducted separately. Both parent and teacher ratings of attention problems significantly deviated from normative means (Table II). A higher than expected proportion of clinically significant attention problems ($T>60$) were identified by parents (33.6%) and teachers (36.4%) in comparison to the measure's normative sample (16%; $p<.001$). Overall, attention dysfunction was identified by at least one rater in 49.9% of the participants.

Predictors of Attention Deficits—Analyses were then conducted to identify demographic and medical predictors of parent-and teacher-reported attention problems using linear regression models. The set of predictors included common risk factors for cognitive deficits [3–6] (e.g., diagnosis, age at diagnosis, gender, time since treatment, and EIQ) and accounted for a significant proportion of the variance in attention problems: 15% on the CPRS and 24% on the CTRS. Furthermore, several individual predictors reached significance. Specifically, female survivors ($t=3.95$, $p<.001$), survivors closer to treatment's end ($t=-2.63$, $p<.01$) and survivors with lower EIQs ($t=-6.49$, $p<.001$) demonstrated greater parent-rated attention problems. Similarly, teachers rated survivors of pediatric brain tumors

($t=2.07$, $p<.05$) and survivors with lower EIQs ($t=-9.88$, $p<.001$) as having greater attention problems.

Association between Attention Problems and Social Functioning—Pearson correlation coefficients revealed a moderate inverse relationship between parent-rated social functioning (SSRS Total Score) and parent attention ratings (CPRS; $r=-.46$, $p<.001$), indicating that more attention problems are associated with poorer social functioning. A significant but modest relationship in the expected direction ($r=-.23$, $p<.001$) was found between teacher-rated attention problems (CTRS) and parent-reported social functioning (SSRS Total Score).

Predictors of Social Functioning

To assess the second hypothesis, analyses were conducted to identify demographic and treatment-related predictors of social functioning. To this end, female gender and lower EIQ were identified in univariate models as associated with lower social functioning (Table III). Diagnosis, treatment intensity, age at diagnosis, and years off-treatment were unrelated to social functioning.

It was hypothesized that attention deficits would contribute uniquely to social dysfunction. To assess the variance explained by these factors and the incremental contribution of attention ratings to social functioning, hierarchical regression analyses were performed. Order of variable entry in the regression model was empirically determined by the analyses conducted above. As such, EIQ was revealed to have greatest significance in the univariate model, and was entered in step one. Gender was entered in step two and attention ratings (Cognitive Problems/Inattention scale from the CPRS or CTRS) were entered in step three. Separate regressions were performed for parent and teacher attention ratings with parent-rated SSRS Total Score as the dependent variable (Tables IV and V).

In the model using parent attention ratings, only individuals with EIQ, parent ratings of attention (CPRS), and SSRS Total Score were included in the analysis ($n=455$; Table IV). In step one, EIQ accounted for significant variance (R^2 $p<.001$) in social functioning. In step two, gender was added to the model and accounted for significant additional variance (R^2 change $p=.04$). In step three, the CPRS was a significant predictor ($p<.001$), and the model accounted for significant additional variance (R^2 change $p<.001$).

In the model using teacher attention ratings, only individuals with EIQ, teacher ratings of attention (CTRS), and SSRS Total Score were included in the analysis ($n=363$). In step one, EIQ accounted for significant variance in parent-rated social functioning (R^2 change $p<.001$). With the addition of gender in step two, the additional variance accounted for by the model was not significant ($p=.22$). In step three, the CTRS was not significant ($p=.19$), nor was the overall model (Table V).

Exploratory Analyses

Given the demonstrated relationship between attention problems and social functioning, a series of exploratory analyses were completed to probe this association. Specifically, questions were raised regarding the social functioning of survivors who had attention problems in multiple domains (e.g., home and school), a criteria required for diagnosis of ADHD in the DSM-IV [34]. A smaller proportion of survivors ($n=363$) had Conners' ratings from both parents and teachers and 57 survivors (15.7%) had attention deficits above the cut-off ($T>60$) as indicated by both raters. Analyses were then completed between those 57 survivors and survivors who had T-scores below the cut-off as rated by both parents and teachers ($n=177$; 48.8%). Of note, the remaining 129 survivors had T-scores above the

clinical cut-off as rated by either parent ($n=53$, 14.6%) or teacher ($n=76$, 20.9%) and were not included in additional analyses.

Preliminary analyses revealed that children with attention problems across settings had lower EIQs ($t=7.62$, $p<.001$). An analysis of covariance (ANCOVA) was completed to assess differences in social functioning (SSRS Total Score) between groups with and without attention problems after accounting for IQ. Analyses revealed that survivors with clinically significant attention problems, as indicated by multiple raters, demonstrated significantly greater difficulties with social functioning [$F(1, 231) = 18.18$, $p<.001$] as reported by their parents.

Of interest, groups did not differ based on common risk factors for cognitive late effects, including gender, age at diagnosis, diagnosis or treatment intensity. However, there was a significant difference between groups for time since treatment, such that survivors with attention problems across settings were approximately one year closer to treatment's end ($t=2.22$, $p<.05$) and significantly younger at evaluation ($t=2.80$, $p<.01$).

Discussion

The objective of the current study was to investigate the relationship between attention and social functioning in survivors of pediatric ALL and brain tumors, relative to the contribution of known demographic and clinical risk factors. Through the use of a large sample of survivors, as well as ratings of attention across multiple settings, this study was able to extend previous work [12, 23, 35] and to provide new information regarding the relationship between attention and social functioning. Analyses demonstrated that female survivors and those with lower estimated IQs evidenced greater difficulties with social functioning. Additionally, as hypothesized, parent-reported attention problems accounted for an additional significant proportion of the variance in parent-rated social functioning. In contrast, teacher-reported attention problems did not explain additional variance in the model, despite a correlational relationship between teacher-rated attention problems and parent-rated social functioning. Such findings highlight the potential impact of attention on survivors' social outcomes, as well as the need for assessment by multiple raters, and provide a direction for future research.

Of interest, beyond female gender and IQ, no other known demographic or clinical risk factors for cognitive deficits (e.g., age at diagnosis, time off-treatment, or brain tumor diagnosis [3–5, 36]), were similarly predictive of deficits in social functioning. While female gender has long been associated with increased risk for cognitive deficits [37–40], it has only recently received notice as a potential risk factor for social deficits as well [41, 42]. Future studies should further examine the interaction between gender, neurocognitive skills, and social functioning.

In contrast to expectations, teacher attention ratings were not uniquely associated with social functioning as measured by parent-report. It is certainly possible this finding is due to method variance such that ratings by the same person (i.e., parent) were related, while ratings by different raters (i.e., parent vs. teacher) were not. Prior research has indicated there may be poorer agreement across settings for cognitive symptoms as compared to externalized behaviors [29, 43]. It is also possible that differences between parents and teachers in what behaviors are observed [43, 44] and the setting in which observations are made [44, 45] impact agreement between raters and thus influenced this finding. Specifically, teachers may be more likely than parents to compare the survivor to a group of typically developing peers [43, 45] and thus provide a less biased view of a child's behavior.

These differences emphasize the importance of obtaining ratings across raters and settings to obtain a more comprehensive evaluation of behavioral skills.

To probe the association between parent and teacher ratings of attention, survivors identified as experiencing problems in multiple settings were further examined. As expected, the sample of survivors exhibiting difficulties at home and school experienced significantly greater difficulties with social functioning than survivors without attention problems in either domain. This difference remained after controlling for significant group differences in EIQ. While the two groups did not differ on several key factors, including gender, age at diagnosis, diagnosis, or treatment intensity, they did, however, differ regarding age at evaluation and time since treatment. Specifically, survivors with attention problems were younger at evaluation and approximately one year closer to the end of treatment. This is in contrast to the extant literature, which has typically identified *greater* time since treatment as a significant risk factor for increased cognitive late effects [3, 5]. Given that agreement between parents and teachers was a primary inclusion criterion for these analyses, it may be that agreement is stronger at younger ages when parents and teachers have a greater presence in a child's life. Indeed, prior research has demonstrated that teachers and parents become less accurate raters of children's functioning, particularly social functioning, as children age [46, 47]. Alternatively, it is possible these children had not yet been identified as having cognitive or academic concerns and therefore were not receiving services in the classroom. As such, their parents and teachers may be particularly attuned to behavioral difficulties as they may be causing more problems in the classroom than survivors who are already receiving services. Certainly this finding will require additional study and replication.

While the current study has provided important information regarding the impact of attention on social functioning in survivors, the findings should be considered in light of limitations. First, this study relied on a single measure of social functioning completed by parents. While the *Social Skills Rating System* is widely used [48], the psychometric properties and validity of this measure has been questioned [49, 50]. Furthermore, it should be noted that the mean score for the SSRS for this sample was in the Average range, suggesting that parents did not, as a whole, observe difficulties with social functioning in this sample, at least as measured by the SSRS. Future work would be enhanced by inclusion of additional measures of social functioning, including parent and teacher assessment, as well as self and/or peer report. Further, this study relied on proxy ratings to measure attention problems and social functioning. Future studies would benefit from the inclusion of direct measures of survivors' social and attentional behavior. To contribute to a more comprehensive understanding of social effects, the measures could characterize aspects of social functioning predicted by recent models [15]. Specifically, measures to evaluate individual characteristics, the effectiveness of interactions between children and their social environment, and social adjustment may be included. Finally, it must be acknowledged that this study used a sample of survivors that were recruited for an intervention trial targeting attention problems. While the current study used participants who participated in the screening phase and thus did not exclude survivors who did not have attention problems, it is certainly possible that the sample was biased with regards to survivors whose parents believed they may be aided by the use of a stimulant medication. Future studies will wish to ensure that measures are taken to confirm an unbiased recruitment procedure that may prevent this potential bias.

In summary, this study provided support for the relationship between attention problems and social functioning in survivors of pediatric cancer. Results highlight the need for continued monitoring of both attention problems and difficulties with social functioning in survivors of CNS-impacting pediatric cancer, with particular attention paid to the interplay between the

two. Moreover, the design of interventions seeking to optimize either social outcomes or attention problems may be strengthened by inclusion of components targeting both.

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Table I**Demographic and Clinical Information**

	Mean $\pm$ SD	Range	N (%)
Age at screening (years)	12.1 $\pm$ 3.36	6.1 – 19.0	
Age at diagnosis (years)	5.4 $\pm$ 3.28	0.1 – 15.5	
Years off-treatment	4.9 $\pm$ 3.05	1.0 – 14.7	
Gender			
Male			265 (56.5)
Female			204 (43.5)
Race/Ethnicity			
Caucasian			400 (85.3)
African-American			60 (12.8)
Hispanic			4 (0.9)
Other			5 (1.0)
Diagnosis			
ALL			258 (55.0)
Brain Tumor			211 (45.0)
CNS Treatment Intensity			
Mild			230 (49.0)
Moderate			40 (8.6)
High			199 (42.4)
Brain Tumor Location			
Supratentorial			75 (35.5)
Infratentorial			118 (55.9)
Both			7 (3.3)
Unknown			11 (5.2)

Note: ALL, acute lymphoblastic leukemia; CNS, central nervous system

Treatment intensity: Mild: systemic and/or intrathecal chemotherapy only; Moderate: 24 Gy cranial radiation therapy (CRT) with or without systemic and/or intrathecal chemotherapy; High: >24 Gy CRT with or without systemic and/or intrathecal chemotherapy

Table II

Descriptive information for study measures

	Mean $\pm$ SD	Range	t^1	Effect Size ²
Conners' Rating Scale – Parent (CPRS) ^a	56.1 $\pm$ 12.77	41 – 90	10.17 ^{**}	0.53
Conners' Rating Scale – Teacher (CTRS) ^a	56.7 $\pm$ 12.13	36 – 90	10.56 ^{**}	0.60
Social Skills Rating System Total Score ^b	100.4 $\pm$ 18.22	52 – 130	0.50	0.024
Estimated IQ ^b	94.5 $\pm$ 17.92	46 – 140	–6.57 ^{**}	0.33

^{**}
 $p < .001$;

¹ one-sample t -test comparing survivors to normative means;

² Cohen's d ;

^a Mean = 50, SD = 10; higher scores are indicative of difficulties with attention;

^b Mean = 100, SD = 15; lower scores are indicative of poor social functioning

Table III

Demographic and medical predictors of parent-rated social functioning (SSRS Total Score)

	<i>n</i>	<i>Std β</i>	<i>SE</i>	<i>p</i> - <i>value</i>
Female Gender [*]	461	−0.12	1.70	0.01
Age at diagnosis	460	0.057	0.26	0.22
Years off- treatment	461	0.009	0.28	0.84
Brain tumor diagnosis	461	0.044	1.71	0.34
High treatment intensity	461	0.039	1.78	0.42
Estimated IQ [*]	458	0.33	0.04	< .001

^{*} significant predictor of social functioning and included in subsequent hierarchical regression model

Table IV
Individual Predictors of Social Functioning – Parent Attention Rating (CPRS; *n* = 455)

	<i>Std β^a</i>	<i>SE</i>	<i>t</i>	<i>F change</i>	<i>ΔR²</i>
Block 1				54.55**	0.11
Estimated IQ	.33	0.04	7.39**		
Block 2				4.38*	0.01
Female Gender	-.09	1.62	-2.09*		
Block 3				80.01**	0.13
CPRS	-.39	0.06	-8.94**		

^aRegression weights at entry into the model.

* *p* < .05;

** *p* < .001

Table V
Individual Predictors of Social Functioning – Teacher Attention Rating (CTRS; *n* = 363)

	<i>Std β^a</i>	<i>SE</i>	<i>t</i>	<i>F change</i>	<i>ΔR²</i>
Block 1				52.48**	0.12
Estimated IQ	.36	0.05	7.24**		
Block 2				1.52	0.00
Female Gender	-.06	1.77	-1.23		
Block 3				1.76	0.00
CTRS	-.07	0.08	-1.33		

^aRegression weights at entry into the model.

* *p* < .05

** *p* < .001