Neurodevelopmental Functioning in Very Young Children Undergoing Treatment for Non-CNS Cancers

Marc H. Bornstein,[1] PhD, Sara Scrimin,[2] PhD, Diane L. Putnick,[1] PhD, Fabia Capello,[2] O. Maurice Haynes,[1] PhD, Simona de Falco,[3] PhD, Modesto Carli,[4] MD, and Marta Pillon,[4] MD

[1]*Eunice Kennedy Shriver National Institute of Child Health and Human Development,* [2]*Department of Developmental and Social Psychology, University of Padova,* [3]*Department of Cognitive Science and Education, University of Trento, and* [4]*Pediatric Hematology Oncology, Department of Pediatrics, University of Padova*

All correspondence concerning this article should be addressed to Dr Marc H. Bornstein, Child and Family Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Suite 8030, 6705 Rockledge Drive, Bethesda, MD, 20892-7971, USA. E-mail: Marc_H_Bornstein@nih.gov

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Objective We initiated a prospective study of very young children with cancer, in comparison with matched healthy children, to investigate neurodevelopmental consequences of non-CNS cancers and treatment. **Methods** A total of 61 children (≤42 months) with non-CNS cancers and 61 matched controls underwent an identical age-appropriate neuropsychological test battery. **Results** Children with cancer manifested deficits compared to healthy controls in motor, mental, and language development, but were similar to controls in cognitive representational abilities and emotional relationships in interaction with their mothers. Better physician-rated health status at diagnosis and mother-rated behavioral status 1 month prior to assessment were associated with better motor and mental performance in the cancer group. **Conclusions** This study identifies deficits as well as spared functions in children with non-CNS cancers; the results suggest ways parents and healthcare professionals may plan specific remediations to enhance quality of life in young cancer survivors.

Key words childhood cancer; cognitive behavior; growth and development; pediatric psychology; social behavior.

Introduction

Two epidemiological trends characterize trajectories of modern pediatric oncology: increasing incidence and decreasing mortality (Gurney, Smith, & Ross, 1999). The combined incidence of all pediatric cancers slowly but steadily increased between 1975 and 2008 (Howlader et al., 2011). In terms of mortality, in the United States between 2001 and 2007, 82% of children diagnosed with any cancer type in the first 4 years of life became 5-year survivors (range = 46.9% for gliomas to 95.9% for Hodgkin lymphoma; Howlader et al., 2011). These simultaneously startling and reassuring numbers prompt questions about well-being and quality of life in the youngest cancer survivors (Dickerman, 2007; Hewitt, Weiner, & Simone, 2003; Oeffinger et al., 2006).

Most studies of childhood cancer have been conducted later in development and have been retrospective in design. Retrospective reports of child survivors suggest that young age at diagnosis is a risk factor for poorer neurocognitive development (Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Kadan-Lottick et al., 2009a; von der Weid, Mosimann, & Hirt, 2003; Waber et al., 2000). The study reported here is prospective and begins in infancy, and it circumscribed initial

recruitment to the first years of life and testing to the first cycles of therapy. The paucity of data on very young children with cancer is striking because the first years of life constitute a crucial developmental period when the brain grows in size and capacity (Stiles, 2008) as the young child rapidly acquires new competencies and skills (Casey, Giedd, & Thomas, 2000; Paus et al., 2001; Pfefferbaum et al., 1994). Adverse early biological and environmental experiences are known to exert dramatic influences over the emergence and ontogeny of brain structure and function (Belsky & de Haan, 2011).

Moreover, most extant studies in this literature have targeted a single developmental outcome; this study adopted a multivariate design in the same sample. Contemporary developmental science and human neuropsychology cast cognition as a constellation of multiple specialized abilities that develop for particular performance situations (Cosmides & Tooby, 1994; Durston et al., 2006; Oliver Johnson, Karmiloff-Smith, & Pennington, 2000). These abilities are relatively independent in the sense that the level of performance achieved by one is not necessarily related to the level achieved by others. In turn, human activity is believed to reflect the integrated functioning of these many cognitive abilities as they work in concert.

Based on this prevailing domain-specific framework, and guided by the extant literature, we hypothesized that childhood cancer patients would manifest diminished functioning compared to children without a chronic health condition and to test-normative standards in some, but not necessarily all, domains of neurodevelopment. In this study, we therefore applied a battery of multiple, specific, developmentally significant, and age-appropriate competencies that spanned motor skills, cognitive performance, and language acquisition. We also assessed exploratory and symbolic representational capacities and emotional relationships in children and their mothers. As no relevant literature exists on the latter topics, we consider their inclusion exploratory. The design and value of such a multimodal approach are based on our goal to identify non-CNS cancers' possible differential effects on an array of specific domains of early neurodevelopmental functioning. Thus, the main aim of this study was to test modular specificity of non-CNS cancers in a prospective design of very young children with these cancers in comparison with sociodemographically matched children without a chronic health condition.

Our study had a secondary aim. Among children with cancer, we further examined how neurodevelopmental outcomes might relate to specific aspects of disease, treatment, and ecology to identify possible sources of neurodevelopmental deficits. Even non-CNS cancers have the potential to compromise healthy development because cancer cells and healthy cells compete for critical resources. As cancer progresses through the body, it could instigate a cascade of effects that compromise child development and functioning. In terms of treatment, questions persist regarding possible long-term effects of conventional chemotherapeutic agents on neurocognitive function; those agents include the mitotic inhibitor vincristine (VCR) (Duffner, 2004; Jansen et al., 2008), the anti-inflammatory corticosteroids prednisone (PDN) and dexamethasone (DEXA) (Kadan-Lottick et al., 2009a; Kaleita, 2002; Waber et al., 2000), and high-dose or intrathecal methotrextate (IT MTX), an inhibitor of DNA synthesis (Buizer et al., 2005; Duffner, 2004; Kadan-Lottick et al., 2009b; Moleski, 2000; Oeffinger & Hudson, 2004). Neuropsychological assessments following chemotherapy point to cognitive impairments of verbal IQ, attention, information processing, executive function, memory, and learning (Anderson & Kunin-Batson, 2009; Brown et al., 1996; Çetingül et al., 1999; Hill, Ciesielski, Sethre-Hofstad, Duncan, & Lorenzi, 1997; Kadan-Lottick et al., 2009a; Moleski, 2000), reductions in specific nonverbal functions (Brown et al., 1998), and increases in behavioral problems (Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2006). A third possibility is that being chronically ill and interrupting a child's normal developmental routines have their own untoward effects. Parents of children with cancer are likely to be anxious which can be communicated to a child who is too young to understand the full implications of cancer. Children with cancer also spend more time in hospitals and away from playgrounds, other children and adults, and educational settings. We explore aspects of cancer, treatment, and ecology in an attempt to better understand the performance of children with cancer.

In overview, most published studies of childhood cancer sequelae are retrospective in design and begin late in development. Few longitudinal (Anderson, Godber, Smibert, Weiskop, & Ekert, 2000) or prospective (Brown et al., 1996; Espy et al., 2001) studies after infancy with non-CNS cancers treated with chemotherapy exist, and no prospective studies of the development of children diagnosed with non-CNS cancers in the first years of life have been published. Most investigations have focused on one or a limited number of developmental outcomes, few have compared children with cancer to healthy controls, and fewer still have instituted appropriate covariates. The identification of specific deficits in very young childhood cancer survivors would be instructive and would, in turn, raise questions about the sources of deficits. Here we report

findings from the first assessment wave of a covariate-controlled prospective longitudinal multimodal study of children with non-CNS cancers in comparison with healthy controls.

Methods

Participants

Sixty-one children with cancer and 61 age- and gender-matched children without a chronic health condition comprised the samples. From January 2004 through June 2008, 66 consecutive young patients from the Pediatric Onco-hematologic Clinic of the University of Padua, Italy, became eligible for the study. Eligibility criteria were: newly diagnosed children with all types of non-CNS cancers (except tumors requiring immediate surgery or limited chemotherapy before surgery), age $\leq$42 months, Italian-speaking, and no preexisting CNS involvement, radiation, developmental disorders, or low birth weight. During recruitment, three parents declined participation, and two children passed immediately after diagnosis. Informed consent was obtained in accordance with the Declaration of Helsinki and standards approved by the Department of Pediatrics, University of Padua, which also approved the protocol.

Table I shows sociodemographic and diagnostic characteristics of patients, their parents, and controls. Acute lymphoblastic leukemia (ALL) was the most common malignancy. Children ranged from 4 to 42 months of age at the assessment. Mothers' education and anxiety were included as covariates in analyses because they differed between groups and had the potential to affect child functioning.

Children with cancer were 18.99 months on average ($SD = 11.19$; range = 0.16 – 39.16) when diagnosed. Children with leukemia were assessed before the first cycle of the consolidation phase of chemotherapy, and children with solid tumors between cycle V and VIII of chemotherapy before surgery. We chose this timing so that children with different types of cancer would have experienced similar amounts and types of treatment. All children had central venous catheter (CVC), and the majority of the therapies were delivered via CVC. Treatment drugs related to individual children's therapy protocol and were specific to diagnosis. Patients were tested in a quiet clinic room with mothers present on a day when they were unimpeded by medical interventions (e.g., peripheral IVs) and evaluated by pediatricians as able to engage in normal activity (Karnofsky $\geq$ 80; Mor, Laliberte, Morris, & Wiemann, 1984). Furthermore, mothers rated the cancer and control children similarly on a measure of behavioral status at the assessment, indicating that the children with cancer had similar levels of pain, restlessness, and anxiety to control children, $F(1, 114) = 1.38$, *ns*, $\eta_p^2 = .01$.

Control children were recruited and assessed at local childcare centers on a first-contacted first-recruited basis

Table I. *Demographic Characteristics of the Children and Parents in the Cancer and Control Proups*

	Cancer *M (SD)*	Control *M (SD)*	*F*(1,120)
Child			
Age at assessment (months)	22.23 (10.91)	22.13 (10.89)	.003
Gender (% female)	52.5	52.5	
Diagnosis (%)			
ALL	55.74	–	–
AML	9.84	–	–
Neuroblastoma	19.67	–	–
Hepatoblastoma	4.92	–	–
Retinoblastoma	4.92	–	–
Rhabdomyosarcoma	3.28	–	–
Yolk sac tumor	1.64	–	–
Parent			
Age at assessment (years)	33.97 (5.40)	33.16 (3.35)	.97
Education (school years)	13.38 (3.72)	15.43 (2.81)	11.79***
State anxiety	46.16 (12.83)	33.57 (7.03)	45.17***
Trait anxiety	38.56 (9.60)	32.00 (8.59)	15.80***

Note. $n = 61$ for both the cancer and control groups. Descriptive statistics are presented in variables' original metrics. –, not applicable; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia.
***$p < .001$.

and matched by age and gender with oncology children (participation > 90%).

Procedures

Each participant underwent the same half-day neuropsychological battery that included age-appropriate standardized tests of motor and cognitive performance, a naturalistic mother–child play session, and questionnaires. The battery was administered in a standard order by trained, reliable, qualified child neuropsychologists who were familiar to pediatric patients and had several years of experience working in the pediatric clinic.

Neuropsychological Assessments

Motor and Mental Function

The *Bayley Scales of Infant Development—Second Edition* (BSID-II; Bayley, 1993) is an individually administered examination that assesses general developmental functioning. The Motor Scale assesses control of gross movements and fine manipulation, and the Mental Scale assesses memory, problem solving, and numeracy. The published Italian version of the BSID-II was administered, but no Italian norms are available for the full age range. Because there was no reason to believe that Italian and U.S. children would develop mental and motor skills differently, we used U.S. norms. The BSID-II correlates with other cognitive instruments and is sensitive to performance differences between children in normative samples and samples of children with various medical and psychological conditions that place them at risk for delayed development (Bayley, 1993). Internal consistency was .84 for the Motor Scale and .88 for the Mental Scale, and test-retest reliability was .78 for the Motor Scale and .87 for the Mental Scale (Bayley, 1993).

Language

The BSID-II Mental Scale contains items that assess pre-verbal (gesture, babbling), receptive, and expressive language. These items were used to evaluate children's language development directly. Scores were computed as a ratio of the number of questions the child correctly answered divided by the number of questions he/she was expected to answer given his/her age. Scores <1 indicate below-average performance, $=1$ indicate average performance, and >1 indicate above-average performance. The Italian adaptation of the *MacArthur Communicative Development Inventory* (MCDI; Caselli & Casadio, 1995) is a maternal report of child communicative abilities. The MCDI is composed of two separate forms: the infant ''Words and Gestures'' Form and the toddler ''Words and Phrases'' Form. As our sample varied in age, we used both forms as age appropriate. To have a comparable index of communicative development across the two forms, we used children's proportion of word production as an index.

Exploratory and Symbolic Representation

Mothers and children played collaboratively for 10 min with a set of standard, age-appropriate toys that allow simple exploration to symbolic representation. Child exploratory and symbolic play and maternal exploratory and symbolic demonstrations (showing the child how to play) and solicitations (verbally or physically eliciting play behavior from the child) of play were coded from video records in accordance with a mutually exclusive and exhaustive category system that included eight levels and a default (no play) category; these play levels were derived from previous research on the progressive nature of play across the early years of life (Bornstein, Haynes, O'Reilly, & Painter, 1996). Scores for levels 1–4 of play were summed to form measures of the frequency and duration of exploratory play, and scores for levels 5–8 were summed to form measures of the frequency and duration of symbolic play. For child collaborative play and maternal demonstrations of play, four indices of exploratory and symbolic play, respectively, were standardized and averaged: the count of play bouts that were exploratory or symbolic, the proportion of play bouts that were exploratory or symbolic, the total duration of exploratory or symbolic play, and the proportion of play duration that was exploratory or symbolic. For maternal solicitations of play, two indices were standardized and averaged: the count of play bouts that were exploratory or symbolic and the proportion of play bouts that were exploratory or symbolic. Coder reliabilities (kappa; κ) for child play and mother play were based on second-by-second agreement for the 600 s in each play session. Coders trained to high reliability ($\kappa > .80$) on consensus coding.

Emotional Relationships

Dyads were evaluated independently on the basis of videorecords using the *Emotional Availability Scales* (EA Scales 4th ed.; Biringen, 2008). These scales operationalize the construct of emotional availability between parent and child and are considered global indices of the emotional quality of parent–child interaction. For the child, the *Responsiveness* scale focused on the age- and context-appropriate balance between the child's interest in exploring the environment and in responding to the mother's bids (i.e., the balance between relatedness and autonomy) as well as the child's enjoyment of interaction with the mother. The *Involvement of Mother* scale assessed the

child's ability, willingness, and success in engaging the mother. For the mother, the *Sensitivity* scale assessed acceptance, flexibility, affect regulation, conflict resolution, and the variety and creativity of interactions. The *Structuring* scale assessed the degree to which the mother appropriately facilitated, scaffolded, and organized child play, exploration, and routine by providing rules, regulations, and a supportive framework for interaction without compromising the child's autonomy. The *Nonintrusiveness* scale assessed the degree to which the mother supported the child's play, exploration, and routine by waiting for optimal breaks before initiating interactions and by not being overdirective, overstimulating, overprotective, or interfering. The *Nonhostility* scale assessed the degree to which the mother was generally patient, pleasant, and harmonious and not abrasive, antagonistic, or rejecting.

All EA Scales were rated on a 7-point Likert-type format in half-points. Coders were trained to reliability with one of the authors of the EA Scales and with each other. Coders were blind to the hypotheses and purposes of the study. Reliability was assessed using average absolute agreement intraclass correlation coefficients (*ICC*) in a two-way random-effects model (McGraw & Wong, 1996). *ICC*s were computed on 23% of the interactions and ranged from .85 to .91 (except for Nonhostility which was .56 due to restricted range; all mothers in the reliability sample scored between 5 and 7 on the scale).

Medical Variables for Children with Cancer

Oncologists used the *Karnofsky Performance Scale* (KPS; Mor et al., 1984) to rate children's level of functioning when first hospitalized. The scale ranges from 0 (Dead) to 100 (Normal; no evidence of disease). Scores > 80 indicate the ability to carry on normal activity. Oncologists also rated children's risk status (high vs. low risk of death) at the time of diagnosis and illness status (complete vs. partial vs. no remission) and the presence or absence of neuropathy at the time of the assessment. The risk groups were assigned at diagnosis to inform parents and other lay people of the severity of the illness. Oncologists used ≥80% chance of survival as a guideline for low-risk and ≤40% chance of survival as high risk. The number of days of hospitalization (range = 9–108) and whether (1) or not (0) PDN, DEXA, VCR, and IT MTX had been administered to children were gathered by oncologists independently from medical charts. We did not use total dosages of drugs because children were administered drugs according to standard protocols for their particular diagnosis, and therefore drug treatments did not vary within cancer types. Furthermore, dosages were administered based on the child's age and/or weight, rendering comparisons across children difficult. Mothers rated (scale = 1–5) the degree to which their children were in pain, restless and stressed, and nervous or crying at the assessment and 1 week and 1 month prior to the assessment (α's = .71, .83, and .86; cumulative status, α = .79). We developed this measure to evaluate the mother's perception of her child's behavioral status over the course of the month preceding the assessment. This measure was given to mothers of children with and without cancer.

Covariates

The *State-Trait Anxiety Inventory* (STAI; Spielberger, Gorsuch, & Lushene, 1970) differentiates between transient ''state anxiety'' and long-standing ''trait anxiety'' (αs = .95 and .90) in mothers. The *Social Desirability Scale* (SDS; Crowne & Marlowe, 1960) assesses mothers' tendency to answer questions in a socially desirable way and was used as a control on maternal reports. The SDS has significant test-retest reliability (r = .89) and high internal consistency (α = .88; Crowne & Marlowe, 1960).

Results

Statistical and Preliminary Analyses

Data were analyzed with PASW (SPSS) Statistics 18 with two-tailed tests and α = .05. Partial eta-squared (η^2_p) indicates effect size (percentage of variance accounted for by the target variable, controlling for other predictors where $\eta_p^2 \approx .01$ is interpreted as a small effect, $\eta_p^2 \approx .06$ as a medium effect, and $\eta_p^2 \approx .14$ as a large effect; Cohen, 1988). For child motor and mental performance, language, exploratory and symbolic representation, mother exploratory and symbolic representation, and child-mother emotional relationships, Group by Gender MANCOVAs were performed, controlling for covariates that were significantly correlated with neuropsychological outcomes. Next, we explored the correspondence of mother and child exploratory and symbolic representation, and correlations between various medical variables and performance within the cancer group. We considered child age, mothers' age, education (as a proxy for SES; Bornstein, Hahn, Suwalsky, & Haynes, 2003), state and trait anxiety, and social desirability bias in responding as potential covariates for all analyses. With group *N*s = 61, there was adequate power in MANCOVAs and correlations to detect medium (78% and 92% power) or large (99% power for both) effects. Preliminary analyses of differences in motor, mental, language, representation, and emotional relationships by cancer type (leukemia vs. solid tumor) were all nonsignificant ($p > .05$). Because they were not of primary interest, any main effects of child gender are not reported, but we included gender in the

models because it is possible that the effects of cancer are different in boys and girls (an interaction between Group and Gender), and including gender in the model effectively controls for any systematic gender differences.

Descriptive Statistics of Neuropsychological and Medical Variables

On the BSID-II Motor and Mental Scales, children with cancer scored ½–1 *SD* below test norms, $t(57) = -5.74$, $p < .001$, and $t(57) = -3.13$, $p < .01$, respectively, and children without a chronic health condition scored significantly above test norms, $t(60) = 4.83$, $p < .001$, and $t(60) = 5.58$, $p < .001$, respectively (Table II). Neuropsychological variables shared only 0–16% of their variance. The first two columns of Table III display descriptive statistics of medical variables for children with cancer.

Comparisons of Children With Cancer and Children Without a Chronic Health Condition

Statistical results for comparisons of children with and without cancer, controlling for child and maternal ages at assessment, maternal education, anxiety, and social desirability bias (as needed), are presented in Table II.

Child Motor and Mental Performance

The multivariate main effect of group was significant. At the univariate level, the main effects of group were significant for Motor and Mental Scales. Children with cancer scored lower than healthy controls overall on the BSID-II and on its Motor and Mental Scales. In a follow-up test to ensure that language items were not accounting for the results for the Mental Scale (see below), the group difference on the Mental Scale remained significant

Table II. *Descriptive Statistics for the Neuropsychological Measures, and Test Results for Gender by Group Interaction and Main Effects of Group*

	Cancer		Control		Gender × Group		Group	
	n	*M (SD)*	*n*	*M(SD)*	*F*	η^2_p	*F*	η^2_p
Multivariate BSID-II[a]	58	–	61	–	1.73	.03	16.27***	.23
Motor[a,b]	58	85.91 (18.03)	61	105.25 (8.93)	3.14	.03	29.41***	.21
Mental[a,b]	58	93.43 (14.55)	61	106.82 (9.69)	1.89	.02	18.00***	.14
Multivariate language[c]	40	–	48	–	0.96	.02	10.66***	.21
BSID-II language[c,d]	40	0.82 (0.15)	48	0.97 (0.16)	0.58	.01	17.67***	.18
MCDI production[c,e]	40	0.36 (0.37)	48	0.35 (0.36)	1.86	.02	0.10	.00
Total child representation[f,g]	53	0.01 (0.21)	53	−0.01 (0.26)	0.27	.01	0.60	.01
Exploratory[f,g]	53	0.08 (0.75)	53	−0.08 (0.90)	0.17	.00	1.21	.01
Symbolic[f,g]	53	−0.07 (0.94)	53	0.07 (0.90)	0.00	.00	0.92	.01
Multivariate mother representation[f]	53	–	53	–	1.90	.04	4.92**	.09
Total demonstrations[f,g]	53	0.10 (0.37)	53	−0.10 (0.26)	0.54	.01	9.94**	.09
Exploratory demonstrations[f,g]	53	0.07 (0.83)	53	−0.07 (0.76)	0.00	.00	0.97	.01
Symbolic demonstrations[f,g]	53	0.13 (0.92)	53	−0.13 (0.75)	0.30	.00	2.37	.02
Total solicitations[f,g]	53	0.02 (0.55)	53	−0.02 (0.33)	2.60	.03	0.44	.00
Exploratory solicitations[f,g]	53	0.10 (1.05)	53	−0.10 (0.67)	1.36	.01	0.79	.01
Symbolic solicitations[f,g]	53	−0.05 (0.85)	53	0.05 (0.74)	0.37	.00	0.42	.00
Emotional relationships[h]	52	–	50	–	1.25	.08	0.61	.04
Responsiveness[h,i]	52	5.01 (0.91)	50	5.37 (0.97)	0.53	.01	1.28	.01
Involvement[h,i]	52	4.78 (1.00)	50	5.12 (1.10)	1.32	.01	0.80	.01
Sensitivity[h,i]	52	5.25 (1.07)	50	5.48 (1.13)	4.14*	.04	0.15	.00
Structuring[h,i]	52	5.06 (1.15)	50	5.40 (1.08)	1.61	.02	0.77	.01
Nonintrusiveness[h,i]	52	5.57 (1.03)	50	5.91 (0.95)	0.65	.01	1.41	.01
Nonhostility[h,i]	52	6.16 (0.88)	50	6.31 (0.77)	0.28	.00	0.61	.01

Note. Descriptive statistics are presented in variables' original metrics. *N*s vary due to missing or uncodable data (e.g., poor quality videorecord).

[a]Controlling child age at assessment, maternal age at assessment, education, state, and trait anxiety.

[b]Standard score ($M = 100$, $SD = 15$).

[c]Controlling child age at assessment, and maternal state anxiety.

[d]Scores were computed as a ratio of the number of questions the child correctly answered divided by the number of questions he/she was expected to answer given his/her age. Scores < 1 indicate below-average performance, = 1 indicates average performance, and > 1 indicate above-average performance.

[e]Proportion of words on the form that the child produced.

[f]Controlling child age at assessment.

[g]Average of standard scores ($M = 0$, $SD = 1$).

[h]Controlling maternal education.

[i]Range = 1–7.

*$p < .05$; **$p < .01$; ***$p < .001$.

Table III. *Descriptive Statistics and Relations of Medical Variables with the BSID-II in Children with Cancer*

		r	
	M (SD)	BSID-II Motor	BSID-II Mental
Age at diagnosis	18.99 (11.19)	.13	.14
Karnofsky at diagnosis[a]	68.39 (14.11)	.42**	.30*
Risk (% high risk) at diagnosis[b]	59%	−.06	.13
Illness status (% partial/no remission) at the assessment[b]	33%	.15	.10
Days of hospitalization	46.92 (25.87)	−.10	.10
Presence of neuropathy[b]	37%	−.02	.11
Child status at the assessment[c]	1.52 (0.60)	−.26	−.24
Child status 1 week before assessment[c]	2.07 (1.03)	−.22	−.21
Child status 1 month before assessment[c]	2.20 (0.95)	−.41**	−.30*
Child status, cumulative over last month[c]	1.92 (0.58)	−.45***	−.41**
Treatment drugs			
PDN[b,d]	51%	−.14	−.20
DEXA[b,d]	14%	−.22	−.13
VCR[b,d]	69%	−.20	−.25
IT MTX[b,d]	56%	−.09	−.24

Note. *ns* = 53–57. All correlations controlled for child age at assessment, and child status also controlled for mother social desirability bias.
[a]Range = 0 (Dead)–100 (Normal; no evidence of disease); A score ≥ 80 indicates the ability to carry on normal activity.
[b]r_{pb}.
[c]Range = 1–5.
[d]Percent of children who were administered the drug.
*$p < .05$. **$p < .01$. ***$p < .001$.

when language items were removed from the Scale, $F(1, 111) = 8.64$, $p < .01$, $\eta_p^2 = .07$.

Child Language

The multivariate main effect of group was significant. At the univariate level, the main effect of group was significant for BSID-II language items, but not the MCDI. Children with cancer were less verbal on the BSID-II than healthy controls.

Child Exploratory and Symbolic Representation

No differences between cancer and control groups emerged.

Mother Exploratory and Symbolic Representation

At the univariate level, the main effect of group was significant for maternal demonstrations, but not solicitations. Mothers of children with cancer demonstrated more play overall than mothers of healthy controls.

Emotional Relationships

The multivariate and univariate effects of group were nonsignificant. However, the means in Table II show that children with cancer and their mothers scored (nonsignificantly) lower in every emotional relationships scale than did children without a chronic health condition and their mothers. A small Gender by Group interaction was significant for maternal Sensitivity. Mothers were more sensitive to girls than boys in the control group, $F(1, 47) = 9.81$, $p = .003$, $\eta^2_p = .17$, but not in the cancer group, $F(1, 49) = .04$, *ns*, $\eta^2_p = .00$.

Correspondence of Mother and Child Exploratory and Symbolic Representation in Families With and Without Cancer

Child and mother exploratory and symbolic representation were concordant in each group. However, a notable trend emerged of weaker agreement of maternal exploratory and symbolic demonstrations with child exploratory and symbolic representation in the cancer group (r's = .20–.27, *ns*) than in the control group (r's = .48–.53, p's < .001), indicating that concordance in representation between mothers and children with cancer was somewhat weaker than concordance in mothers and children without cancer.

Relations Between Medical Variables and Neuropsychological Outcomes in Children with Cancer

For outcomes that differed by group, we explored relations between medical variables and neurodevelopmental functioning within the cancer group, controlling for child age at assessment (Table III). Better scores on the KPS at diagnosis and the mother's assessment of the child's behavioral status 1 month prior to the assessment and cumulative status over the previous month were associated with

better BSID-II Motor and Mental performance. [The child's behavioral status was not associated with BSID-II performance in the control group, r's(56) = .02– .18, *ns*.] No significant relations emerged between medical variables and child language.

Discussion

Very young children with non-CNS cancers undergoing chemotherapy-only treatments performed worse on motor and mental assessments, including language, than comparable children without a chronic health condition. Scores of children with cancer also fell below mean normative standards in a general developmental assessment. Moreover, pediatricians and mothers independently rated children with cancer who scored more poorly as less able to perform regular activities and more restless, stressed, and nervous in the time before they were assessed (but not at the assessment itself). Studies like ours that include direct comparisons of children with cancer and children without a chronic health condition are infrequent in pediatric oncology, and non-CNS cancer patient samples undergoing chemotherapy-only protocols typically have been small. Moreover, ours were conservative assessments, as they controlled multiple important covariates. We also studied several neuropsychological functions that shared a maximum of 16% of their common variance. This result confirms that performance on the different tasks reflected abilities from different domains and enhances credibility of a plurality of child competencies. These abilities presumably engage different operations or processes, and are mediated by different structures in the brain.

Some Relative Deficits in Childhood Cancer Survivors

The deficit in motor skills we found in the pediatric patient sample accords with reported deficiencies in motor timing (Mahone, Prahme, Ruble, Mostofsky, & Schwartz, 2007), spatial problem solving (Brown et al., 1998), and performance IQ in older survivors of ALL treated with chemotherapy only (Çetingül et al, 1999; von der Weid et al., 2003).

We also identified specific cognitive and verbal deficits in this group. The deficit in verbal skills was only observed on the BSID-II and not on the MCDI. There are several possible reasons for this difference, including the fact that language assessed via the BSID-II is a direct measure of the child made by a trained tester vs. language assessed via the MCDI which is an indirect measure of the child dependent on an unskilled rater. Furthermore, the MCDI only covers vocabulary production, whereas the BSID-II covers attention to verbal cues, communicative gestures, verbal comprehension, vocal imitation, and vocabulary. Perhaps the deficit in verbal skills is not evident in productive vocabulary, but is in other aspects of adaptive communication.

The identification of cognitive and language deficits in this study also match those from older children and adolescents who had cancer treated with chemotherapy who are reported to score lower than matched healthy controls on total IQ, verbal IQ, and verbal comprehension (Çetingül et al, 1999; Hill et al., 1997; Lofstad, Reinfjell, Hestad, & Diseth, 2009; Peterson et al., 2008; Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000). Children who are in or have completed treatment for cancer with chemotherapy are known (by retrospective report) to process information (Buizer et al., 2005; Kadan-Lottick et al., 2009a; Mennes et al., 2005) and perform in school (Brown et al., 1996, 1998; Buizer et al., 2006; Peterson et al., 2008) more poorly, especially when diagnosed at a young age and receiving more intense treatments. Young ALL patients receiving chemotherapy run a higher risk of neurocognitive impairments (Harila-Saari et al., 2007; Jansen, Kingma, & Schuitema, 2006; Kadan-Lottick et al., 2009a; von der Weid et al., 2003), and studies enlisting sibling controls (Brown et al., 1992; Buizer et al., 2006; Giralt et al., 1992; Jansen et al., 2006; Lansky, Cairns, & Zwarjies, 1984; Schlieper, Esseltine, & Tarshis, 1989) have reported relative deficits in neuropsychological, intellectual, or academic achievement. However, no previous studies have investigated motor and cognitive skills so early in life in the same children with cancer during treatment or undertaken so broad an array of neuropsychological assessments as here.

The present data support the hypothesis that early childhood non-CNS cancers treated in chemotherapy-only protocols are accompanied by specific neurodevelopmental sequelae. Considered together, the data indicate that these children suffered specific deficits that are not confounded by a global (cognitive) deficiency. Further conclusions about the effects of function-specific deficits call for more precise neuropsychological tests (targeting, e.g., procedural versus declarative memory, different components of language, higher-order concept formation).

Relatively Spared Functions in Childhood Cancer Survivors

Children with non-CNS cancers differed from children without a chronic health condition in certain ways (indicated above) but did not differ in their exploratory and symbolic representation or in emotional relationships

with their mothers during normal social interactions. Apparently, some features of early development in cancer survivors are spared or may be remediated (see below), and even perturbations as dramatic as cancer are insufficient to deflect their development from following a species-general ontogenetic course. It could be that functions such as representational ability and emotional attachments are universal and are well-ingrained in the species evolutionally (Bornstein et al., 1999, 2008), or it could be that, despite individual cognitive deficits, the social interactions that surround the play and emotional exchanges between child and mother adequately scaffold child function (Vygotsky, 1978). We return to important implications of this interpretation below.

Why Does Childhood Cancer Have Neurodevelopmental Sequelae?

Cancer in infancy appears to impact some salient child neuropsychological functions. Why? Are deficits reflective of cancer as a disease, cancer treatment, or cancer's local and larger social contexts? Our study begins to address this vexing question. Consider social context first. Cancer's social context includes macro-level issues (such as social class) as well as micro-level ones (such as anxiety and lost opportunity). On the one hand, differences in children's motor and mental performance was explained by group membership, separate and apart from exogenous factors like maternal education (SES) and anxiety. Furthermore, mothers of cancer patients interacted largely the same as mothers of healthy children. Despite such a preoccupying diagnosis, mothers appeared to be sensitive to their children's signals and able to scaffold their children's exploration and engage in emotional interactions without becoming intrusive. In our study, the number of days of hospitalization was unrelated to children's test performance; children with cancer and control children were rated by mothers to have similar levels of functioning at the assessment; children were only assessed when unimpeded by medical interventions (like peripheral IVs); children with cancer knew the testers prior to assessment; and children's general functioning at the assessment was not related to their performance. Taken together, these findings suggest that a severe illness occurring in the first years of life poses unique and specific risks in child development that may stand apart from broad factors of family ecology or specific ones like parental behavior or child status.

On the other hand, children with cancer scored the same as healthy controls in domains of competence that tapped interactions with their mothers (and mothers of children with cancer demonstrated more play), indicating that some aspects of social context remain unaffected. Moreover, we did not assess all aspects of the child's daily life (e.g., the breadth of children's interactions with other people, in multiple contexts, and during other activities), and other unmeasured ecological factors may influence the performance of children with cancer. Hospitalized young cancer patients are likely limited in their motor activities, and their compromised health status could well circumscribe the scope of children's everyday experiences. Cancer diagnosis is also confounded with chronic illness, loss of normal routine, and dearth of stimulation generally. Raymond-Speden et al. (2000) found that children with ALL treated with CNS chemotherapy (IT MTX) had full, performance, and verbal IQs and verbal comprehension scores averaging 10.1–13 points below chronic asthma controls. These differences of $\geq$½ *SD*, and consistent differences in the two groups in a battery of achievement and academic scores, were not statistically significant (possibly because of insufficient power of small sample comparisons). However, this pattern suggests that not all of the deficits in CNS-chemotherapy children may be attributable to chronic illness. Clearly, future research needs to include a broader spectrum of family and environmental factors (e.g., breadth of experiences with people, places, and activities) and also assess how depression, anxiety, and motivation might affect test performance in young children with cancer.

Cancer chemotherapy could affect child quality of life. Opinions here are also mixed. On the one hand, Espy et al. (2001) and Kaleita, Reaman, MacLean, Sather, and Whitt (1999) reported that infants and children treated for ALL with IT MTX with and without systemic MTX performed within normal levels on a wide variety of neuropsychological tests. Our data also indicated that PDN, DEXA, VCR, and IT MTX had small, non-significant associations with performance on the multiple measures we took in children with cancer. However, we were not able to consider the dosage of drugs, and of course, our findings of no effect do not mean there are no effects to be found. Small effects of different explanatory variables could combine or compound to produce the differences we report.

On the other hand, neonates randomized to DEXA versus a placebo (for lung disease associated with prematurity) have worse visual motor integration and lower IQ (Yeh et al., 2004), and PDN at younger ages at diagnosis is associated with diminished functioning (Kadan-Lottick et al., 2009a). In a review, Anderson and Kunin-Batson (2009) noted late effects of chemotherapy on attention, executive functions, visual processing, and visual-motor

functions. This review suggests that our assessments may be too early to identify the effects of chemotherapy that compound over time. There exists a possible mechanism of these effects. Structural brain changes evidenced by abnormal MRIs, such as reduced density of white matter and leukoencephalopathy, cerebral calcifications, and dilation of ventricular or subarachnoid spaces, have been reported in children treated by chemotherapy only for ALL. Both transient and long-term correlations of such structural changes with neurocognitive measures have been observed, especially in very young children (Anderson & Kunin-Batson, 2009; Duffner, 2004; Friedman & Meadows, 2002; Iuvone et al., 2002; Lesnik, Ciesielski, Hart, Benzel, & Sanders, 1998; Pääkkö et al., 2000; Reddick et al., 2006). Here, too, future research needs to attempt to disentangle ecology and therapy treatments as causative factors in the deficient neurodevelopmental performance of very young children with non-CNS cancers.

Finally, the etiology of observed group differences may also lie in early onset cancer and associated biological effects in very young children. It is possible that the special developmental status of the CNS in infancy renders infants and young children susceptible to some invasive effects of cancer per se. Cancer effects on one part of the developing organism may cascade to other organ systems and so compromise normal development. This provocative hypothesis of cancer *qua* disease on motor, cognitive, and language functions may merit additional attention now that stress and other experiential factors have been shown to compromise the developing CNS. Retrospective reports indicate that young age at diagnosis is an important prognostic factor in intellectual outcomes of children with cancer (von der Weid et al., 2003). Generally, early illnesses (premature birth, low birth weight, or surgeries) are acknowledged risk factors in child development. Our data demonstrate this case for early pediatric cancers. Deficits in specific functions may be associated with disruptions during critical periods of brain development as functions that are emerging tend to be more vulnerable to concurrent insult (Belsky & de Haan, 2011; Stiles, 2008). If tenable, this conclusion would be troubling on several counts. One is that of the possible general causes of deficits, cancer per se is the one we can do least about (except of course in terms of prevention). A second is that patients in this study showed neuropsychological deficits although they were stricken with non-CNS cancers. A third is that more than 60% of the sample with cancer was already in remission at assessment (although children were still undergoing therapy).

Future Directions and Conclusions

The next generation of studies of neuropsychological outcomes in pediatric cancer could advance from this effort in several additional productive ways. First, they might be designed to distinguish more precisely among different possible causes of specific deficits. This first-wave report perforce recounts cross-sectional results, so causality between disease and neurodevelopmental outcome cannot be known with certainty, but can be strongly inferred. We were also somewhat limited by our recruitment of control children from childcare settings. None of the children under 12 months with cancer had been in childcare prior to diagnosis. Mothers with higher education may be more likely to return to work sooner which could explain why the mothers in the control group had higher education than mothers of children with cancer (a difference controlled in the analyses). Better matched comparisons are in order. Moreover, the differences we observed may be transient or long-lasting, and other potential long-term effects might not yet be apparent (Copeland, Moore, Francis, Jaffee, & Culbert, 1996). To address these additional methodological and conceptual questions, longitudinal methods are required and desirable; and this is our design. In future waves of this prospective study, we will follow the development of these children with more refined assessments (such as of memory) to understand which specific domains of cognition and language continue to be affected and therefore constitute candidates for remediation, and to discern which factors predict which enduring child neuropsychological outcomes and therefore constitute candidates for prevention or intervention.

In overview, the low correlations among scores for different neuropsychological tasks indicate that the functions we assessed are largely independent, and the lower scores obtained by children with cancer for select motor, mental, and verbal functions therefore begin to identify specific neurodevelopmental domains affected by cancer, chemotherapy, or the ecology surrounding cancer. These early-appearing deficits may have long-term implications. A young child's neurocognitive profile might be carried across many situations, and experiences in one domain will likely have an impact on others (Masten & Cicchetti, 2010). If not addressed adequately, the effects of early problems can spread, affecting many aspects of children's development in significant ways. For example, experiences of failure and frustration in cognition that repeat can lead to disengagement from academics, with further fallout for psychosocial and adaptive development. Children can become discouraged as their self-efficacy is undermined, with significant consequences for their adjustment.

In this connection, we note that child exploratory and symbolic representation and emotional relationships emerged as strengths that could be reinforced and exploited to aid recovery and enhance wholesome child development. On this basis, it might be possible to plan effective interventions for parents and child health care professionals to improve the quality of life in very young children diagnosed with and surviving cancer.

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