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ORIGINAL ARTICLE

Cognitive functioning of pediatric patients with brain tumor: an investigation of the role of gender

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Abstract

Purpose The female gender has been considered a risk factor for cognitive impairment in pediatric brain tumor survivors. However, it is still unknown which specific cognitive domains are at greater risk of impairment in females. The aim of this study was to explore differences between male and female children in distinct domains of cognitive functioning, in order to deepen knowledge on the topic.

Methods The cognitive performance of 100 males and 71 females aged 6–16 years was assessed by Wechsler Intelligence Scales for Children-Third Edition (WISC-III). Differences between males and females were tested not only on intellectual quotients, but also on WISC-III subtests, which allow the evaluation of different cognitive domains. Analyses were performed in the whole sample and dividing children based on the supratentorial vs. infratentorial location of the tumor.

Results Gender was the only predictor of VIQ in the whole group and in children with supratentorial tumor. Female children with supratentorial tumor performed significantly worse than males in four out of six verbal subtests. However, even among children with infratentorial tumor, females performed worse than males on two verbal subtests.

Conclusions Overall, findings of this study suggest that females may have more difficulties than males at manipulating verbal oral material. A possible explanation of these findings could be that females present a greater vulnerability to white matter damage due to the illness and post-adjuvant therapies, in line with reports of the literature on female children with lymphoblastic leukemia.

Keywords Neuropsychological functioning · Sex · Pediatric oncology · Rehabilitation

Introduction

Children with brain tumor often present with impairments in specific cognitive domains and global intellectual functioning [1–3]. Moreover, they may exhibit deficits in literacy, numeracy, and acquisition of foreign languages [4–6]. Several risk factors related to the tumor, post-surgical primary adjuvant therapies, and demographic characteristics have been associated to such neurocognitive difficulties. The most consistently reported risk factors are tumor location, radiation therapy, specific chemotherapy agents, young age at diagnosis, longer time since diagnosis, presence of neurological complications associated with the illness, and female gender [7–12].

Concerning gender, female children suffering from cancer affecting the central nervous system (CNS) have been found to exhibit a lower neurocognitive performance than males. This

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neurocognitive risk has been reported for survivors of both brain tumor [13–15] and lymphoblastic leukemia [16–18]. Previous studies suggested that such risk could be the consequence of the higher vulnerability of females to treatments affecting the CNS [16–18], in particular radiotherapy [19]. It has been hypothesized that radiotherapy mostly affects white matter, which is usually less represented in female than male brain [20], with the consequence that the diminished availability of intact white matter after adjuvant therapies in females could be associated with greater cognitive impairment.

To date, it still has to be determined which specific neurocognitive abilities are at greater risk of impairment in female brain tumor survivors. Previous studies reported a negative effect of female gender on Estimate Intellectual Quotient (EIQ) [14] and Verbal Intellectual Quotient (VIQ) [15], but no further indication on impairments in specific cognitive functions was provided. In contrast, more detailed findings were provided for patients with lymphocytic leukemia, for whom previous studies reported not only lower EIQ scores in females [18] than males, but also a lower performance on WISC-III Arithmetic and Digit Span subtests and in arithmetic achievement [17].

Our study aimed at providing an investigation of the differences between male and female pediatric brain tumor survivors on specific cognitive domains, by examining the performance of children not only on intellectual indices but also on subtests of WISC-III. Previous research showed that these subtests may provide important information on the nature of specific cognitive difficulties [21, 22]. The main risk factors for cognitive impairment, such as age at diagnosis, age at evaluation, time since diagnosis, and post-surgical primary adjuvant therapies, have been taken into account for the comparisons between males and females. Moreover, as the supratentorial and infratentorial tumor locations have been found to be associated with different neurocognitive performance levels by some previous studies [22–24], the investigation of gender differences was performed not only in the whole sample but also in the supratentorial and infratentorial groups separately.

Our study was retrospective and observational; thus, it depicts an ecological overview of the cognitive functioning of the population of pediatric brain tumor survivors referring to a rehabilitation Institute.

Materials and methods

Participants' selection and study procedure

Participants of this study were children with a previous diagnosis of brain tumor, who were referred to the Neuro-oncological and Neuropsychological Rehabilitation Unit of Scientific Institute, IRCCS E. Medea, Bosisio Parini, Italy, to receive a cognitive evaluation. Children were involved in the study if they received a cognitive evaluation between 2006 and 2012. As since 2012 the Italian version of the WISC-III [25, 26] was progressively replaced by the newer WISC-IV [27, 28], children who received a cognitive evaluation by WISC-IV were excluded from this study. Indeed, WISC-III and WISC-IV present significant construct differences (e.g., [29, 30]); thus, the intellectual indices of the two instruments are not properly comparable. For patients who had more than one evaluation in the selected time frame, we took into account the last evaluation for this study, as it was considered more indicative of the long-term sequelae.

For children with tumors requiring surgery, chemotherapy, and/or radiotherapy, cognitive evaluations were conducted at least 6 months after the end of oncological treatments, as required by the institute's evaluation protocol. No selection was made regarding tumor histology, since the study aimed at assessing the neurocognitive risk associated with gender with respect to the broad diagnosis of brain tumor.

Patients were included in the study if their age was 6 to 16 years; Italian was their mother tongue; they had no active disease at the moment of the evaluation; they had no ongoing oncological treatment; and they had not received any neuropsychological rehabilitative intervention in the last 6 months.

Children were excluded if they presented premorbid neurocognitive disabilities or psychological difficulties (as reported in the clinical records by the referring physician), as they could confound results; had no diagnosis of primary or secondary epilepsy; and had no severe hearing deficits, visual impairments, ataxia, or hemiparesis (as reported in the clinical records filled out by the neurologist).

Out of a pool of 216 patients, 171 fulfilled the research criteria and were thus considered eligible for study inclusion. Among the excluded patients, 28 were males and 17 females.

Measures

Neurocognitive abilities were assessed by WISC-III intellectual quotients (IQs) and subtests [21, 25, 26]. The mean score (M) of IQs is set at 100 (SD = 15). WISC-III subtest scaled scores range from 1 to 19 (M = 10, SD = 3) (Table 1).

For clinical reasons associated with organizational timelines, not all patients were able to be administered the WISC-III supplementary subtests. Therefore, the freedom from distractibility factor and the processing speed factor, for whose calculation the supplementary subtests are required, were excluded from statistical analyses.

Demographic and clinical characteristics of the whole sample and of the male and female groups were analyzed by descriptive statistics. The following demographic and clinical characteristics other than gender were considered for this study: age at diagnosis, age at evaluation, time since diagnosis, tumor location, radiotherapy, chemotherapy, socio-economic status (SES), special educational needs. Moreover, for supratentorial patients, we also collected tumor lateralization. The SES was

calculated according to Hollingshead's classification (ranging from a minimum of 1 to a maximum of 9) [31].

Statistical analyses

Differences between groups were analyzed by independent sample *t* tests (two-tailed) for continuous variables and by χ^2 for categorical variables.

Stepwise multiple regressions were performed to predict VIQ and performance intellectual quotient (PIQ) based on gender and the other main risk factors for neurocognitive impairment (tumor location, age at diagnosis, time since diagnosis, radiotherapy, and chemotherapy). They were calculated both for the whole sample and for the supratentorial and infratentorial groups separately. In the second case, tumor location was excluded from independent variables. The stepping method criteria considered a probability of *F* set at $p = 0.05$ for entry and at $p = 0.10$ for removal.

General linear models were used to test differences between groups on cognitive subtests, inserting as covariates those demographic or clinical characteristics that differed between the compared groups.

The significance level for all analyses was set at $p < 0.05$, two-tailed.

Results

Distribution of clinical and demographic variables based on gender

171 children, 100 males and 71 females, participated in the study at a mean time from diagnosis of 3.89 years (SD = 2.33) and at a mean age at evaluation of 10.81 years (SD = 2.90 years). Males and females did not significantly differ with respect to the following risk factors: age at diagnosis, $t(169) = 0.20$, $p = 0.85$; age at evaluation, $t(169) = -0.06$, $p = 0.95$; time since diagnosis, $t(169) = -0.38$, $p = 0.70$; chemotherapy, $\chi^2(1, 171) = 1.08$, $p = 0.30$; radiotherapy, $\chi^2(1, 171) = 1.13$, $p = 0.29$; SES, $t(169) = 0.24$, $p = 0.81$; special educational needs, $\chi^2(1) = 0.75$, $p = 0.39$. Significant differences based on gender were instead observed regarding tumor location, $\chi^2(1, 171) = 7.16$, $p < 0.01$: specifically, 46.5% of female children had supratentorial tumors and 53.5% had infratentorial tumors; differently, 23% of male children had supratentorial tumors and 77% of them had infratentorial tumors. Complete demographic and clinical data of the whole sample are reported in Table 2.

Distribution of clinical and demographic variables based on tumor location

Between the two tumor location groups, a significant difference was found with respect to having received chemotherapy, $\chi^2(1) = 4.12$, $p = 0.04$, which was received by 55% of children with infratentorial tumor and by 22% of children with supratentorial tumor. A significant difference was also found for radiotherapy, $\chi^2(1) = 9.33$, $p < 0.01$, which was received by 52.4% of children with infratentorial tumor and by 18.2% of children with supratentorial tumor. No between-group differences were found for the following variables: age at diagnosis, $t(169) = -1.03$, $p = 0.31$, age at evaluation, $t(169) = 0.18$, $p = 0.86$; time since diagnosis ($t(169) = 1.86$, $p = 0.06$; special educational needs, $\chi^2(1) = 0.15$, $p = 0.70$; SES, $t(169) = 0.24$, $p = 0.81$. In the supratentorial group, tumor laterization was not different between males and females, $\chi^2(2) = 1.86$, $p = 0.39$: 4 males had a bilateral tumor, 14 a tumor in the right hemisphere, and 5 a tumor in the left hemisphere; 9 females had a bilateral tumor, 14 a tumor in the right hemisphere, and 10 a tumor in the left hemisphere.

Table 3 depicts demographic and clinical data of children in the whole group and in the supratentorial and infratentorial tumor location groups.

Effects of gender on cognitive performance

In the whole group, males and females exhibited an intellectual functioning within the borderline range (≤ 85). However the VIQ in male children fell within the average range. Table 4 depicts the means and SDs of all IQs and WISC-III subtests in male and female children.

In the whole sample, the prediction model (stepwise multiple regression) for PIQ was statistically non-significant. The prediction model for VIQ was significant ($F(1, 169) = 7.96$, $p < 0.01$) and accounted for approximately 40% of the variance of VIQ ($R^2 = 0.05$, adjusted $R^2 = 0.04$). Gender was the only predictor ($b = -0.23$, $t = -2.89$, $p < 0.01$). The verbal subtests that resulted to be significantly different between males and females, controlling for the covariate tumor location, were the following: Information, Similarities, Arithmetic, and Digit Span (see Table 4), with females obtaining lower scores.

In the supratentorial group, the prediction model (stepwise multiple regression) for PIQ was statistically non-significant. The prediction model for VIQ was significant ($F(1, 54) = 4.99$, $p = 0.03$) and accounted for approximately 70% of the variance of VIQ ($R^2 = 0.09$, adjusted $R^2 = 0.07$). Gender was the only predictor ($b = -10.90$, $t = -2.24$, $p = 0.03$).

Females showed a lower performance on the Information, Similarities, Arithmetic, and Digit Span subtests.

In the infratentorial group, stepwise multiple regressions for PIQ and VIQ were statistically non-significant. However, at *t* tests, females showed a lower performance on the Information and Arithmetic subtests (Table 4).

Table 1 Cognitive processes inferred by WISC-III intellectual quotients and cognitive subtests

	Inferred cognitive processes
VIQ	Crystallized intelligence, knowledge application
Subtests	
Information	General cultural knowledge
Similarities	Abstract reasoning and logical thinking
Arithmetic	Numerical accuracy and mental arithmetical ability
Vocabulary	Knowledge of word meanings and verbal fluency
Comprehension	Social and practical judgment
Digit span	Short-term verbal memory and attention
PIQ	Fluid reasoning
Subtests	
Picture completion	Visual discrimination
Coding	Visual-motor coordination, fine-motor dexterity, and processing speed
Picture arrangement	Sequential logic
Block design	Visual abstract ability and visuospatial problem-solving
Object assembly	Visual analysis and construction of objects
Symbol search	Visual-perceptual discrimination and speed of processing
Mazes	Visual-motor coordination, planning ability, and perceptual organization

VIQ verbal intellectual quotient, *PIQ* performance intellectual quotient

The VIQ is derived from scaled scores of all the Verbal subtests, except Digit Span

The PIQ is derived from scaled scores of all the Performance subtests except Mazes and Symbol Search

Differences in cognitive functioning based on tumor location

General linear models assessing differences on WISC-III subtests between supratentorial and infratentorial patients, with chemotherapy and radiotherapy as covariates, revealed no significant difference for any subtests (all $F < 1.85$ and all $p > 0.18$), except Coding, in which infratentorial patients performed significantly worse than supratentorial patients, $F(3, 166) = 5.87$, $p = 0.02$. Moreover, on this subtest, infratentorial

Table 2 Demographic and clinical characteristics of participants

	Whole sample ($N = 171$)	Males ($N = 100$)	Females ($N = 71$)		
	M (SD)/N (%)	M (SD)/N (%)	M (SD)/N (%)	t/χ^2	p
Age at diagnosis [years]	6.91 (3.66)	6.95 (3.66)	6.85 (3.68)	0.20	0.85
Age at evaluation [years]	10.81 (2.90)	10.79 (2.95)	10.82 (2.85)	− 0.06	0.95
Time since diagnosis [years]	3.89 (2.33)	3.83 (2.41)	3.97 (2.22)	− 0.31	0.70
SES	52.30(19.95)	52.70 (21.50)	51.90 (18.40)	0.24	0.81
Tumor location				7.16	< 0.01
Supratentorial	56 (32.7%)	23 (23.0%)	33 (46.5%)		
Infratentorial	115 (67.3%)	77 (77.0%)	38 (53.5%)		
Radiotherapy (yes)	120 (70.2%)	73 (73.0%)	47 (66.2%)	1.13	0.29
Chemotherapy (yes)	132 (77.2%)	80 (80.0%)	52 (73.2%)	1.08	0.30
Diagnosis				1.77	0.62
Medulloblastoma	71 (41.5%)	44 (44.0%)	27 (38.0%)		
Astrocytoma	40 (23.4%)	20 (20.0%)	20 (28.2%)		
Ependymoma	27 (15.8%)	17 (17.0%)	10 (14.1%)		
Other*	33 (19.3%)	1 (19.0%)	14 (19.7%)		
Special educational needs (yes)	91 (53.2%)	56 (56.0%)	35 (49.3%)	0.75	0.39

SES socio-economic status; p values refer to the comparisons between males and females

Table 3 Demographic and clinical characteristics of participants in the supratentorial and infratentorial groups

Supratentorial patients ($N = 56$)	Whole group	Males ($N = 23$)	Females ($N = 33$)		
	M (SD)/N (%)	M (SD)/N (%)	M (SD)/N (%)	t/χ^2	p
Age at first diagnosis (years)		6.30 (4.37)	6.64 (3.67)	−0.31	0.76
Age at evaluation (years)		10.66 (2.76)	11.01 (2.72)	−0.47	0.64
Time since diagnosis (years)		4.35 (2.67)	4.36 (1.93)	−0.02	0.99
SES	5.27 (2.15)	5.39 (2.46)	5.18 (1.94)	0.36	0.72
Radiotherapy		14 (60.87)	17 (51.5%)	0.48	0.49
Chemotherapy	38 (70.4%)	16 (69.60)	22 (66.6%)	0.05	0.82
Diagnosis				2.18	0.54
Medulloblastoma	5 (9.0%)	1 (4.3%)	4 (12.1%)		
Astrocytoma	20 (37.0%)	7 (30.4%)	13 (39.4%)		
Ependymoma	9 (16.7%)	5 (21.7%)	4 (12.1%)		
Other*	22 (40.7%)	10 (43.5%)	12 (36.4%)		
Special educational needs	31 (57.4%)	13 (56.5%)	18 (54.5%)	0.02	0.88
Infratentorial patients ($N = 115$)	Whole group	Males ($n = 77$)	Females ($n = 38$)		
	M (SD)/N (%)	M (SD)/N (%)	M (SD)/N (%)	t/χ^2	p
Age at first diagnosis (years)		7.16 (3.45)	7.03 (3.73)	0.18	0.86
Age at evaluation (years)		10.83 (3.01)	10.66 (2.99)	0.29	0.77
Time since diagnosis (years)		3.67 (2.33)	3.63 (2.42)	0.11	0.92
SES	51.91 (18.44)	51.95 (18.21)	51.84 (19.15)	0.03	0.98
Radiotherapy		59 (77.6%)	30 (78.94%)	0.03	0.87
Chemotherapy	94	64 (83.1%)	30 (78.95%)	0.30	0.59
Diagnosis				1.23	0.75
Medulloblastoma	66 (57.4%)	43 (55.8%)	23 (60.5%)		
Astrocytoma	20 (17.4%)	13 (16.9%)	7 (18.4%)		
Ependymoma	18 (15.7%)	12 (15.6%)	6 (15.8%)		
Other*	11 (9.5%)	9 (11.7%)	2 (5.3%)		
Special educational needs	60 (52.2%)	43 (55.8%)	17 (44.7%)	1.26	0.26

t/χ^2 and p values refer to the comparisons between males and females

male children showed a significantly lower performance than infratentorial female children (Table 3).

Discussion

Our study included 58.7% male and 41.3% female children. The percentages of survivors' distribution based on gender are in line with epidemiological data on pediatric brain tumors: indeed, according to the WHO classification of CNS tumors in childhood and adolescence, the prevalence of this illness is higher for boys (i.e., [32, 33]). However, in the infratentorial group, females were about half of males. This unbalance in gender distribution could have affected results and thus was taken into account while discussing them.

The intellectual functioning of male and female participants fell approximately within the borderline range. An influence of gender was found on the VIQ, with females having lower scores both in the whole sample and in the infratentorial and supratentorial groups separately (Table 4). An association between VIQ and female gender has been previously reported in a study [15] on children with brain tumor and was interpreted by the authors as a finding by chance or, alternatively, the indication of a gender-mediated risk of selective neurocognitive deficits. The results of our study seem to support the second hypothesis, at least for patients with supratentorial tumor, for whom gender represented the only significant predictor among other main risk factors. Male and female supratentorial children did not differ in the prevalence of the tumor in the left hemisphere, which serves as a hint to exclude the role of tumor lateralization. Moreover, no gender differences in the average socio-economic status and percentage of special educational needs were found, ruling out that the verbal impairment of females could be attributed to a poorer family environment [34] or to a worse global functioning.

The higher vulnerability of females with respect to the VIQ, which reflects crystallized knowledge, could be explained by the fact that girls may be more adversely affected by damage to

Table 4 Differences in cognitive functioning between males and females in the whole sample and in the supratentorial and infratentorial groups

Whole sample	*N*	Males = 100 *M* (SD)	*N*	Females = 71 *M* (SD)	*F*	*p*	η_p^2
FSIQ	100	85.68 (20.94)	71	80.70 (23.22)	2.60	0.11	0.02
VIQ	100	91.84 (20.28)	71	83.18 (19.03)	7.95	< 0.01	0.05
PIQ	100	82.81 (19.68)	71	82.65 (24.52)	0.05	0.83	0.00
Verbal subtests							
Information	100	9.27 (3.81)	71	7.01 (3.11)	15.86	< 0.01	0.09
Similarities	100	9.35 (3.01)	71	8.21 (3.09)	5.89	0.02	0.03
Arithmetic	100	8.57 (4.11)	71	6.46 (3.46)	12.09	< 0.01	0.07
Vocabulary	100	8.90 (3.28)	71	7.99 (3.07)	3.53	0.06	0.02
Comprehension	100	7.84 (3.31)	71	7.90 (3.10)	0.01	0.97	0.00
Digit span	97	8.80 (3.62)	70	7.60 (3.71)	4.85	0.03	0.03
Performance subtests							
Picture completion	100	8.57 (3.24)	71	8.49 (4.09)	0.17	0.68	0.00
Coding	100	5.62 (3.61)	71	6.41 (3.89)	0.63	0.43	0.00
Picture arrangement	100	7.85 (3.74)	71	7.27 (4.68)	1.13	0.29	0.01
Block design	100	8.46 (3.48)	71	8.04 (3.89)	0.46	0.50	0.00
Object assembly	100	7.11 (3.34)	71	7.41 (3.74)	0.18	0.67	0.00
Mazes	95	8.80 (4.04)	68	7.75 (3.79)	2.43	0.12	0.02
Symbol search	69	6.45 (3.69)	60	6.80 (4.08)	0.11	0.74	0.00
Supratentorial patients		Males = 23		Females = 33			
		M (SD)		*M* (SD)	*t*	*p*	*d*
FSIQ	23	91.04 (17.97)	33	80.12 (21.20)	2.02	0.05	− 0.56
VIQ	23	93.96 (19.37)	33	83.06 (16.90)	2.24	0.03	− 0.60
PIQ	23	89.87 (17.43)	33	81.82 (24.34)	1.36	0.18	− 0.39
Verbal subtests							
Information	23	9.35 (3.40)	33	7.00 (2.88)	2.78	< 0.01	− 0.75
Similarities	23	9.70 (2.56)	33	8.18 (2.66)	2.12	0.04	− 0.58
Arithmetic	23	9.04 (3.52)	33	6.36 (3.11)	3.01	< 0.01	− 0.81
Vocabulary	23	9.22 (3.47)	33	8.00 (2.93)	1.41	0.16	− 0.38
Comprehension	23	8.22 (3.14)	33	8.00 (2.93)	0.26	0.79	− 0.07
Digit span	23	9.83 (3.01)	32	7.34 (3.74)	2.61	0.01	− 0.74
Performance subtests							
Picture completion	23	9.96 (3.12)	33	8.27 (3.71)	1.77	0.08	− 0.49
Coding	23	7.91 (3.46)	33	6.27 (4.29)	1.49	0.14	− 0.42
Picture arrangement	23	8.83 (3.90)	33	7.18 (4.68)	1.38	0.17	− 0.38
Block design	23	8.91 (3.26)	33	7.64 (3.81)	1.30	0.19	− 0.36
Object assembly	23	7.57 (2.95)	33	7.36 (3.56)	0.22	0.82	− 0.06
Mazes	23	8.87 (3.95)	31	7.45 (3.86)	1.32	0.19	− 0.36
Symbol search	16	7.56 (2.56)	27	6.67 (4.32)	0.75	0.46	− 0.26
Infratentorial patients		Males = 77		Females = 38			
		M (SD)		*M* (SD)	*t*	*p*	*d*
FSIQ	77	84.08 (21.60)	38	81.21 (25.12)	0.63	0.53	− 0.12
VIQ	77	91.21 (20.62)	38	83.29 (20.93)	1.93	0.06	− 0.38
PIQ	77	80.67 (19.92)	38	83.37 (24.98)	− 0.72	0.48	0.12
Verbal subtests							
Information	77	9.25 (3.94)	38	7.03 (3.34)	2.97	< 0.01	− 0.61
Similarities	77	9.25 (3.12)	38	8.24 (3.46)	1.57	0.11	− 0.31
Arithmetic	77	8.43 (4.29)	38	6.55 (3.78)	2.29	0.02	− 0.47

Table 4 (continued)

Vocabulary	77	8.81 (3.24)	38	7.97 (3.22)	1.29	0.19	− 0.26
Comprehension	77	7.73 (3.37)	38	7.82 (3.32)	− 0.13	0.89	0.03
Digit span	74	8.49 (3.74)	38	7.82 (3.73)	0.90	0.37	− 0.18
Performance subtests							
Picture completion	77	8.16 (3.18)	38	8.68 (4.44)	− 0.73	0.46	0.14
Coding	77	4.96 (3.39)	38	6.53 (3.55)	− 2.28	0.02	0.45
Picture arrangement	77	7.55 (3.67)	38	7.34 (4.74)	0.26	0.79	− 0.05
Block design	77	8.32 (3.55)	38	8.39 (3.97)	− 0.09	0.92	0.02
Object assembly	77	6.97 (3.46)	38	7.45 (3.93)	− 0.65	0.51	0.13
Mazes	72	8.78 (4.10)	37	8.00 (3.76)	0.97	0.34	− 0.22
Symbol search	53	6.11 (3.93)	33	6.91 (3.95)	− 0.91	0.37	0.20

FSIQ full scale intellectual quotient, *VIQ* verbal intellectual quotient, *PIQ* performance intellectual quotient

white matter due to the illness and treatments, as suggested in a previous study on female children with lymphoblastic leukemia [20]. The Authors reported that oncological treatments affecting white matter integrity could have more disrupting effects in females, since myelination occurs less in female than in male children. Thus, females are more likely to display a clinically relevant reduction of intact white matter after the oncological care programs. Since neural connections linking different areas of the cerebral cortex are myelinated, we may hypothesize that deficits in crystallized knowledge found in female patients could be the effect of alterations of associative networks linked by axonal fibers. Accordingly, integrity of white matter has been reported to be necessary for adequate proficiency in higher level cognition [5].

The greater vulnerability of girls with supratentorial tumor with respect to VIQ could be interpreted from a neuroanatomical perspective. Indeed, the presence of damage to circuitry close to the verbal areas or, however, to the neuroanatomical areas responsible for the main core cognitive domains contributing to language could be hypothesized to be the main cause of the larger verbal-related risk of children with tumor in this location. In line with this hypothesis, a previous study [35] indicated that the occurrence of a tumor in the mesial regions of the temporal lobes is associated with severely impaired verbal intellectual outcomes, thus supporting the possibility that anomalies in neural networks conducting to these supratentorial areas may be associated with lower verbal performance. Another study [23] found deficits in encoding new words in children with supratentorial tumor but not in those with infratentorial tumor, supporting the greater risk for verbal weaknesses in case of tumors located over the tentorium. Alternatively, it could be that the smaller number of females in the infratentorial group led to detect more limited significance.

Specifically, girls with supratentorial tumors showed lower scores than males on the WISC-III subtests Information, Similarities, Arithmetic, and Digit Span, while girls with infratentorial tumors on the Information and Arithmetic subtests (Table 3). Taken together, findings indicate that the whole girls had more limited general culture and more difficulties in learning and recalling facts (Information) and were less competent at solving arithmetical problems, probably because of more difficulties at managing the verbal requests. In children with supratentorial tumor, the verbal proficiency of females could be further worsened by difficulties in keeping the verbal key information online to perform complex tasks (Digit Span) and impairments with logical thinking, concept formation, and verbal abstract reasoning (Similarities). In absence of a more comprehensive neurocognitive assessment, it is reckless to sustain whether the verbal deficit of females could be ascribed to more specific core cognitive abilities rather than to a general language impairment. However, it could likely be that such a deficit may be the consequence of a memory delay, which might not only be limited to working memory (Digit Span subtest in female children with supratentorial tumor) but also extended to long-term memory. This hypothesis could account for the difficulties of females in storing the verbal items indefinitely, thus providing an explanation for the impairment on the Information and Similarities subtests. It could also justify their weakness on the Arithmetic subtest, as this task requires an accurate retrieval of numerical concepts and calculation procedures, together with problem-solving abilities. Correlations among WISC-III subtests reported in the WISC-III manual [36] reveal that the subtests Information, Similarities, and Arithmetic show the strongest correlations between each other among the verbal subtests. This could support our interpretation on the fact that these subtests rely on common cognitive processes, which we mostly attributed to long-term memory. In contrast, no gender-based differences were found on the Vocabulary subtest. This finding could be interpreted considering our hypothesis on the vulnerability of females to white matter damage. In fact, in terms of cognitive abilities, the Vocabulary subtest requires semantic-lexical retrieval, suggesting that, also in this case, memory abilities play a crucial role. However, neuroanatomically, it could be that the knowledge of word meaning relies on more limited intermodal connections than the cognitive abilities tested by the Information, Similarities, and Arithmetic subtests, which

require to integrate more complex sources of information and to elaborate it abstractly. Consequently, we may speculate on the fact that the Vocabulary subtest relies at a lower extent than the verbal subtests found to be impaired on the myelinated networks, which may have spared females from having a worse performance than males in this task. This hypothesis seems to be supported by previous research indicating that vocabulary knowledge is associated with grey matter density, possibly suggesting that white matter plays a minor role for this ability [37]. Finally, the hypothesis of memory difficulties of females could also explain the absence of differences between male and female children in the Comprehension subtest. Indeed, this task strongly relies on judgment, inference, and concrete problem-solving abilities, supposedly requiring the intervention of long-term memory at a lower extent as compared to the Information, Similarities, and Arithmetic subtests.

Limitations of this study should be acknowledged. First, this study was retrospective; therefore, male and female children were not preliminarily balanced with respect to sample size and demographic and clinical characteristics, which could have generated interfering effects on results. In particular, due to the imbalanced numerosity of male and female patients with infratentorial tumor, our finding on the potential greater cognitive impairment of female children with supratentorial tumor should be considered with caution. Moreover, we cannot rule out that certain variables not considered in this study (e.g., radiotherapy and chemotherapy type, dose and duration, and radiotherapy fractioning) may have had an influence on findings. Third, we assessed cognitive functioning by using WISC-III only, a fact that could have provided a limited overview of cognitive differences between males and females. As described above, language difficulties should be associated with subtler cognitive deficits, which could be worthwhile to investigate by more specific instruments. In particular, our findings suggest to carefully test memory abilities. Finally, we could only speculate on the possible neuroanatomical features responsible for the differences found between males and females. Therefore, our interpretations should be considered with caution, giving to future research the assignment to test and verify the hypotheses suggested in this study.

In conclusion, females showed more impairments than males at performing tasks requiring the manipulation of the verbal oral information. This seems to suggest the presence of a cognitive vulnerability associated with gender in pediatric brain tumor survivors. We delegate to future research a detailed assessment of core cognitive competencies underlying the verbal deficit of females, by using more specific cognitive tests. As linguistic abilities exert a mediating effect on communication [38, 39] and represent an important predictor of academic performance [40], it is possible that the verbal delay of females may have significant cascade effects on global functioning. With respect to interventions, a detailed analysis of the cognitive profile of children, highlighting cognitive strengths and weaknesses in the distinct cognitive domains, should be the first step to develop targeted and individualized rehabilitation treatments. In this regard, this study suggests that neurorehabilitation interventions tapping language abilities could be of main relevance for female children with brain tumor in order to prevent long-term shortfalls in daily life. Finally, neuroanatomical variants based on gender, possibly responsible for the differences in cognitive functioning, should be investigated through advanced neuroimaging techniques. In particular, the higher vulnerability of females with respect to white matter damage should be verified.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent In our Scientific Institute, at the moment of the clinical evaluation of children, parents are proposed to sign an informed consent to allow data treatment for research. Informed consent was obtained from all parents of individual participants included in the study.

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