

## Quality of survival and cognitive performance in children treated for medulloblastoma in the PNET 4 randomized controlled trial

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### Abstract

**Background.** The relationship between direct assessments of cognitive performance and questionnaires assessing quality of survival (QoS) is reported to be weak-to-nonexistent. Conversely, the associations between questionnaires evaluating distinct domains of QoS tend to be strong. This pattern remains understudied.

**Methods.** In the HIT-SIOP PNET4 randomized controlled trial, cognitive assessments, including Full Scale, Verbal and Performance IQ, Working Memory, and Processing Speed, were undertaken in 137 survivors of standard-risk medulloblastoma from 4 European countries. QoS questionnaires, including self-reports and/or parent reports of the Behavior Rating Inventory of Executive Function (BRIEF), the Health Utilities Index, the Strengths and Difficulties Questionnaire, and the Pediatric Quality of Life Inventory, were completed for 151 survivors. Correlations among direct cognitive assessments, QoS questionnaires, and clinical data were examined in participants with both assessments available ( $n = 86$ ).

**Results.** Correlations between direct measures of cognitive performance and QoS questionnaires were weak, except for moderate correlations between the BRIEF Metacognition Index (parent report) and working memory ( $r = .32$ ) and between health status (self-report) and cognitive outcomes ( $r = .35-.44$ ). Correlations among QoS questionnaires were moderate to strong both for parent and self-report ( $r = .39-.76$ ). Principal Component Analysis demonstrated that questionnaires and cognitive assessments loaded on 2 separate factors.

**Conclusions.** We hypothesize that the strong correlations among QoS questionnaires is partially attributable to the positive/negative polarity of all questions on the questionnaires, coupled with the relative absence of disease-specific questions. These factors may be influenced by respondents' personality and emotional characteristics, unlike direct assessments of cognitive functioning, and should be taken into account in clinical trials.

## Key words

everyday executive functioning | intellectual ability | medulloblastoma | outcome | quality of survival

Medulloblastoma, the most common primary malignant brain tumor of the central nervous system among children,<sup>1-3</sup> carries long-term implications for patients' survivorship, such as neurological and cognitive deficits,<sup>4,5</sup> auditory and endocrine impairments,<sup>6,7</sup> and the perception of reduced health-related quality of life (HRQoL).<sup>8</sup> Increased survival rates of patients with medulloblastoma have led to the recognition of the importance of comprehensive assessments aimed at providing a more complete description of survivors' quality of survival (QoS) across several domains of functioning, including an individual's perception of his or her cognitive performance, health status, behavior, and HRQoL. Thus, besides progression-free survival and treatment-related effects, assessments of clinical outcomes should incorporate not only direct measures of performance and clinician reports, but also questionnaires reflecting the patients' and caregivers' perspectives of outcomes.<sup>9</sup>

QoS is a term intended to integrate overall outcomes, including medical complications, cognitive deficits, psychosocial impairments in different domains (eg, academic achievement, independence, professional and social integration, activity limitations or participation restrictions), and self- and/or proxy-reported HRQoL.<sup>10-15</sup> Awareness of the importance of multidimensional assessments based on different informants has led to efforts among European countries to reach consensus regarding the domains of functioning and measures to be included in clinical trials aimed at evaluating the effects of brain tumors and their treatment.<sup>16</sup> This international agreement was intended to increase robustness of data collection in clinical trials to support better-informed treatment and rehabilitation decisions. This consensus established that the assessment of QoS in clinical trials should include demographic, endocrine, and other medical information, direct measures of cognitive functions and questionnaire-based assessments of health status, behavior, HRQoL, and executive functioning in everyday life.<sup>16</sup>

Objective evaluation of cognitive functions pertains to the results of neuropsychological assessment (eg, intellectual ability, specific cognitive functions). "Health status" refers to clinical outcomes (eg, ataxia, cerebellar mutism, among others), which can be evaluated objectively through medical examination, but can also be assessed through questionnaire reports.<sup>17</sup> HRQoL is a multi-dimensional concept referring specifically to the subjective view of the individual survivor about his or her life situation. HRQoL is questionnaire-based and includes physical, social, cognitive, and emotional functioning dimensions.<sup>11,16</sup>

Although an increasing number of studies on the effects of brain tumors have included information about direct assessments of cognitive functioning together with questionnaire measures of QoS, there remains a dearth of information regarding the specific associations between direct assessments of cognitive functioning and

questionnaire-based assessments of QoS.<sup>18</sup> Associations of questionnaire-based reports with direct assessments generally tend to be absent or weak.<sup>19-22</sup> Furthermore, the associations between assessments of the same cognitive functions with standardized tests and with self or parent/caregiver questionnaires, are generally absent, weak, or moderate.<sup>9,21-24</sup> For example, a divergence between direct assessment and questionnaire-based scores of executive function has been consistently observed in patients with traumatic brain injury<sup>25</sup> and cancer.<sup>26-28</sup> Previous reports have nevertheless highlighted the usefulness of questionnaire-based assessments in the screening of cognitive deficits in survivors of childhood brain tumors.<sup>29</sup> On the other hand, correlations between scores on different questionnaires assessing various domains of QoS have been moderate or strong. For example, a previous study of participants in the same clinical trial from which the current study sample is drawn found strong correlations between questionnaires assessing different constructs of QoS, ranging from .56 (parent report of behavior vs health status) to .85 (self-report of HRQoL vs health status).<sup>11</sup>

Independent of the assessment method used, QoS following childhood medulloblastoma is known to be influenced by demographic (eg, age at diagnosis), medical (eg, post-operative cerebellar mutism, ataxia), and treatment-related factors (eg, radiation dose and volumes).<sup>30</sup> Thus, the influence of these factors should be considered when examining QoS.

Taking into account the scarcity of studies examining the specific association between direct assessments of cognitive functioning and questionnaire-based assessments of QoS, the present exploratory study aimed to contribute to the extant literature in 2 ways. First, we sought to explore the extent to which scores on direct measures of cognitive functioning were associated with scores on questionnaire-based measures of QoS, including health status, behavior, HRQoL, and executive function. More specifically, we wanted to examine the associations between directly measured and questionnaire-based measures of cognitive functioning. Further, given the importance of cognitive impairments following childhood medulloblastoma and their impact on academic achievement and overall independence in adult life, we wished to determine whether scores on direct measures of cognitive function were correlated with HRQoL. A second aim was to examine the association of direct and questionnaire-based measures with clinical outcomes known to have an impact on QoS. Third, we aimed to analyze the pattern of associations between questionnaire-based reports assessing different constructs of QoS. According to a previous report,<sup>11</sup> we expected these correlations to be strong and, therefore, we sought to present a reasonable hypothesis for this pattern of associations.

## Materials and Methods

### Patients

The participants were selected from the HIT-SIOP PNET4 phase III European randomized controlled treatment trial (RCT) for M0 medulloblastoma conducted in 10 countries between 2001 and 2006<sup>31</sup>. This cross-sectional study aimed to evaluate QoS by means of questionnaires assessing health status, behavior, HRQoL, and executive function. For this purpose, 244 event-free survivors at the time of the cross-sectional follow-up<sup>11,32</sup> were eligible for participation. Details of these participants have been described elsewhere.<sup>11,32</sup> Although the original PNET 4 protocol did not include systematic cognitive assessment, 4 countries (France, Germany, Italy, and Sweden) collected prospective or cross-sectional direct measures of cognitive function between 2004 and 2013<sup>32</sup>. From the original sample of 244 event-free survivors, 137 (56%) participants from France, Germany, Italy, and Sweden had direct cognitive measures and 151 (62%) had data on at least one of the questionnaire-based measures. The analyses reported in the present work were based on participants with both direct cognitive assessment and questionnaire-based QoS data available ( $n = 86$ ).

### Procedure

As part of PNET 4, all participating countries obtained ethical approval and eligible participants provided informed consent to undergo cognitive and questionnaire assessments.

### Measures

The questionnaire-based assessments were collected in a similar way in the 4 participating countries. Information regarding standard demographics and secondary clinical outcomes was obtained through the Medical Examination Form addressed to clinicians and the Medical Educational Employment and Social<sup>33</sup> (MEES) questionnaire addressed to parents and adult participants. Executive function, health status, behavior, and HRQoL in participants aged <18 years at assessment were measured 1) through parent-report booklets containing the Behavior Rating Inventory of Executive Function<sup>34</sup> (BRIEF, normative  $M[SD] = 50[10]$ , clinical cut-off for cognitive impairments:  $\geq 65$ ); the Health Utilities Index<sup>17</sup> (HUI3, scale fixed points: 0 = "dead," 1 = "perfect health"); the Strengths and Difficulties Questionnaire<sup>35</sup> (SDQ,  $M[SD] = 8.4[5.8]$ , clinical cut-off for behavioral difficulties: high to very high:  $\geq 90^{\text{th}}$  percentile); and the Pediatric Quality of Life Inventory<sup>36</sup> (PedsQL,  $M(SD) = 81.3(15.9)$ , clinical cut-off for low HRQoL:  $\leq 65.42$ <sup>37</sup>), and 2) through self-report booklets containing the HUI3, SDQ, and PedsQL, if participants were aged 11 to 17 years; for participants aged  $\geq 18$  years, these assessments comprised self-report booklets of the BRIEF-A and the HUI3. The European Organization for Research and Treatment of Cancer Quality of Life measure (EORTC QLQ-C30)<sup>38</sup> was also used, but was not analyzed in the present work due to the small sample size ( $n = 22$ ).

The direct assessments of cognitive outcomes were different, although comparable, according to the participant's age and country.<sup>32</sup> For France, Italy, and Sweden, Full Scale Intelligence Quotient (FSIQ), Performance IQ (PIQ), Verbal IQ (VIQ), Working Memory Index (WMI), and Processing Speed Index (PSI) corresponded to the standard scores obtained from age-appropriate Wechsler Intelligence Scales.<sup>39–42</sup> For Germany, with the exception of PSI (data not collected), FSIQ, PIQ, VIQ and the WMI were converted to standard scores ( $M[SD] = 100[15]$ ) from the participants' performances in the Raven's Colored and Standard Progressive Matrices,<sup>43,44</sup> the vocabulary subtests of the Wechsler Scales or Kaufmann Assessment Battery for Children<sup>45</sup> (K-ABC I/II, Riddles subtest), and the Number Recall test of the K-ABC I/II, respectively. For this subgroup, PIQ was considered as FSIQ. These assessments allowed to derive 5 measures of cognitive performance (normative  $M[SD] = 100[15]$ ), specifically FSIQ, PIQ, and VIQ, as well as WMI and PSI. The performances in all the cognitive assessments were similar according to the participants' sex, age, and country.<sup>32</sup>

### Statistical Analyses

Pearson's  $r$  was used to examine correlations among the parent- and the self-report versions of the questionnaires, and between parent- and self-reports and the direct assessments of cognitive functioning. For the purpose of the present study, we opted to change the sign of the standardized scores of the HUI3 and the PedsQL questionnaires. Hence, higher scores in all the questionnaires indicated poorer levels of health status, behavior, executive functioning, and HRQoL, as opposed to IQ assessments in which higher scores reflected superior levels of intellectual functioning. For the BRIEF, we opted to analyze not only the Global Executive Composite (GEC), but also the Behavioral Regulation Index (BRI) and the Metacognition Index (MI), which allowed us to consider separately the cognitive and behavioral aspects assessed by the BRIEF. However, for participants over 18 years, the associations of the self-report version of the BRIEF with the cognitive outcomes and the remaining QoS questionnaires were not explored due to the small number of participants over 18 years with available BRIEF self-reports. When numbers were too low, the correlation was not reported (eg, N/A in Tables 2 and 3). The lowest sample size used for a correlation was  $n = 46$ .

Subsequently, we performed a Principal Component Analysis (PCA) with varimax rotation using the 6 questionnaire-derived measures (parent reports and self-reports of BRIEFGEC, BRI and MI, HUI3, SDQ, and PedsQL) together with the 4 directly assessed cognitive outcomes (VIQ, PIQ, WMI, and PSI). We then converted the standardized scores of the questionnaires into a single composite z-score where  $M = 0$  and  $SD = 1$ . Univariate analyses ( $t$  tests) were then used to examine differences in this composite z-score and in FSIQ according to secondary clinical outcomes derived from the Medical Examination form.<sup>24</sup> We only report here clinical complications significantly or marginally significantly associated with FSIQ or questionnaire-based composite score. The complications included reports of postsurgical ataxia of any kind and the presence

of cerebellar mutism. We adopted a  $P < .01$  for statistical significance to adjust for multiple testing, although values between  $P > .01$  and  $P < .05$  were considered to be marginally significant.

## Results

Table 1 depicts the descriptive characteristics and the number of participants with available data for each direct and questionnaire-based measure. Group comparisons indicated that participants ( $n = 86$ ) and nonparticipants (event-free survivors of the original sample,  $n = 158$ ) were similar regarding sex and cognitive, questionnaire-based, and secondary clinical outcomes. However, participants tended to be younger at diagnosis ( $M = 9.1$  vs  $10.9$ ,  $P < .01$ ), at the neuropsychological assessment ( $M = 13.9$  vs  $16.8$ ,  $P < .01$ ), and to present shorter intervals between diagnosis and assessments ( $M = 4.8$  vs  $5.8$ ,  $P < .01$ ).

The distribution of the 5 direct measures of cognitive outcomes and the 6 QoS outcomes derived from the 4 questionnaires (Executive functioning [BRIEF GEC, BRI and MI]; health status [HUI3]; behavior [SDQ]; HRQoL [PedsQL]) used in the analyses described subsequently indicated considerable variability and the number of observations for each outcome was large enough to deduce meaningful results (Table 1). The HUI3 scores tend to be highly skewed and, therefore, both Pearson and Spearman correlation coefficients were derived whenever this outcome was used in the analyses. The questionnaire-based indicators and the cognitive outcomes assessed directly were similar with respect to gender, country, age at diagnosis, and age at assessment (data not shown). The interval between direct cognitive measures and QoS questionnaire assessments ranged from 0 to 4.4 years and 43 participants (50%) had both assessments performed within a 1-year range.

There were moderate-to-strong statistically significant positive correlations between all the QoS questionnaires assessed either by parent or self-reports (Table 2). The

**Table 1** Demographic characteristics and descriptive statistics of direct and questionnaire-based outcomes

		N	Mean	SD	Min	Max
<b>Age at diagnosis (years)</b>		86	9.1	3.2	4	16.3
<b>Age at direct neuropsychological assessment (years)</b>		86	13.9	4.4	6.2	24.9
<b>Time since diagnosis (years)</b>		86	4.8	2.6	.6	9.7
<b>Interval between direct and questionnaire assessments (years)</b>		86	1.5	1.5	0	4
<b>Males, n (%)</b>		60 (69.7)				
<b>Direct measures</b>						
FSIQ		86	89.7	19.7	40	137
VIQ		73	96.9	18.4	47	140
PIQ		85	90.1	19.4	40	140
WMI		83	92.1	14.7	56	120
PSI		64	78.5	16.0	50	103
<b>Questionnaire-based measures</b>						
Executive function (BRIEF)						
<i>Global Executive Composite</i>	Parent report	65	55.8	10.3	34	87
	Self-report	17	48.8	11.7	34	72
<i>Behavioral Regulation Index</i>	Parent report	65	53.9	11.9	36	94
	Self-report	17	50.2	12.5	35	70
<i>Metacognition Index</i>	Parent report	65	56.0	10.2	34	78
	Self-report	17	47.9	9.9	36	70
Health status (HUI3)	Parent report	58	.8	.2	.1	1
	Self-report	62	.8	.2	.1	1
Behavior (SDQ)	Parent report	64	9.7	5.3	0	23
	Self-report	54	9.7	5.5	0	21
HRQoL (PedsQL)	Parent report	67	67.5	17.7	26.1	100
	Self-report	56	74.3	16.7	34.8	100

BRIEF: Behavior Rating Inventory of Executive Function; HUI3: Health Utilities Index; SDQ: Strengths and Difficulties Questionnaire; PedsQL: Pediatric Quality of Life Inventory; FSIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; WMI: Working Memory Index; PSI: Processing Speed Index.

**Table 2** Pearson's correlations among questionnaire-based measures of executive function, health status, behavior, and health-related quality of life

	Parent-report scores									
	BRIEF BRI		BRIEF MI		HUI3		SDQ		PedsQL	
	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>
BRIEF GEC	.82***	65	.91***	65	.45***	54	.63***	61	.64***	64
BRIEF BRI			.58***	65	.54***	54	.68***	61	.66***	64
BRIEF MI					.33*	54	.56***	61	.57***	64
HUI3							.55***	57	.70***	57
SDQ									.76***	64
	Self-report scores									
BRIEF GEC	N/A		N/A		N/A		N/A		N/A	
BRIEF BRI			N/A		N/A		N/A		N/A	
BRIEF MI					N/A		N/A		N/A	
HUI3							.59***	54	.67***	53
SDQ									.66***	53

\* $P < .05$ ; \*\*\* $P < .001$ ; N/A = not analyzed due to small sample size of BRIEF self-reports for patients aged >18 years ( $n = 17$ ); BRIEF: Behavior Rating Inventory of Executive Function; GEC: Global Executive Composite; BRI: Behavioral Regulation Index; MI: Metacognition Index; HUI3: Health Utilities Index; SDQ: Strengths and Difficulties Questionnaire; PedsQL: Pediatric Quality of Life Inventory.

exception to this pattern was observed for the weak association of marginal significance observed between parent reports of the HUI3 and the BRIEF MI. The associations between the VIQ, PIQ, WMI, and PSI were moderate to strong ( $r$  range, .33 to .66;  $P < .01$  in all cases, results not shown).

The correlations between the questionnaires and the direct assessments of cognitive function were generally weak and nonsignificant ( $r < -.30$ , cf. Table 3). For parent reports, the correlation coefficients ranged from weak to moderate, albeit marginally significant between the BRIEF BRI and FSIQ ( $r = -.25$ ), the WMI and the BRIEF GEC ( $r = -.29$ ), the BRI (  $r = -.26$ ) and MI ( $r = -.32$ ), as well as the HUI3 scores ( $r = -.28$ ). For self-reports, there were moderate statistically significant correlations between the HUI3 scores and FSIQ, VIQ, PIQ, WMI, and PSI ( $r$  range,  $-.35$  to  $-.44$ ). A moderate correlation of marginal significance was also observed between the SDQ scores and the PSI. Correlations between the PedsQL and any of the directly assessed measures of cognitive functioning were weak and fell short of statistical significance.

Further, correlations between direct testing (WMI) and parent-reports (BRIEF-Working Memory subscale) of a single specific cognitive construct, namely working memory, was moderate ( $r = -.46$ ,  $P < .001$ ), and the correlations between WMI (direct testing) and overall health status assessed through parent-report and through self-report were weak and moderate, respectively (HUI3;  $r = -.28$ ;  $P = .036$  and  $r = -.39$ ;  $P = .002$ ).

We also undertook an analysis of the correlations taking into account the differences between a) the time since diagnosis and psychometric assessment, b) the time since diagnosis and questionnaire assessment, and c) the delay between direct and questionnaire assessments. The pattern of results in all 3 cases was unchanged from that presented in Table 3 and is not reported here. In particular, for the group of 43 participants who had both

assessments performed within a 1-year range, the correlations remained weak.

### Principal Component Analysis of the Questionnaire-based Measures and the Direct Assessments of Cognitive Performance

The PCA of 5 of the questionnaire-derived outcomes (BRIEF BRI, BRIEF MI, HUI3, SDQ, and PedsQL) together with 4 of the cognitive outcomes (VIQ, PIQ, WMI, and PSI) revealed 2 separate factors (Table 4). The 5 questionnaire-based outcomes loaded heavily onto the first factor, while the 4 direct measures of cognitive outcomes loaded heavily on to the second factor. These 2 factors together accounted for 67% of the total variance (Factor 1 = 45% and Factor 2 = 22%). Based on the results of the PCA, we computed a composite z-score from the combined scores of all the questionnaires. The internal consistency of this composite score was excellent (normalized Cronbach's alpha reliability = .88). The same analyses were performed separately for parent- and self-reports and results remained unchanged.

### Differences in Questionnaire-based Measures and Direct Assessments of Cognitive Performance According to Secondary Clinical Outcomes Assessed Directly

The results of the univariate analyses indicated a moderate difference in the FSIQ according to the presence vs absence of postsurgical ataxia of any kind before radiotherapy (M[SD] = 86.1[19.05] vs 95.8[17.7], difference 9.7, 95% confidence interval (CI):  $-1.03$  to  $-18.4$ ,  $t = -2.2$ ,  $P = .03$ ) or presence vs absence of postoperative cerebellar mutism (M[SD] = 77.2[12.5] vs 90.5[19.9], difference 13.4, 95% CI:  $-2.99$  to  $29.8$ ,  $t = 1.6$ ,  $P = .1$ ). There were non-significant

**Table 3** Pearson's correlations between parent reports and direct measures of cognitive function

	Parent-report scores											
	BRIEF GEC		BRIEF BRI		BRIEF MI		HUI3		SDQ		PedsQL	
	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>	<i>r</i>	<i>n</i>
FSIQ	-.13	65	-.25 *	65	-.07	65	-.24	58	-.12	64	-.18	67
VIQ	-.19	56	-.24	56	-.15	56	-.21	50	-.14	56	-.15	59
PIQ	-.07	65	-.18	65	-.05	65	-.18	58	-.05	64	-.10	67
WMI	-.29 *	63	-.26 *	63	-.32 *	63	-.28 *	57	-.22	63	-.23	66
PSI	.004	54	.06	54	-.06	54	-.25	51	-.02	56	-.01	56
	Self-report scores											
FSIQ	N/A		N/A		N/A		-.41***	62	-.08	54	-.23	56
VIQ	N/A		N/A		N/A		-.44***	54	-.22	46	-.21	48
PIQ	N/A		N/A		N/A		-.35**	62	.01	54	-.14	56
WMI	N/A		N/A		N/A		-.39**	60	-.22	53	-.24	55
PS	N/A		N/A		N/A		-.44***	54	-.32*	47	-.21	46

\* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .001$ ; N/A = not analyzed due to small sample size of BRIEF self-reports for patients aged >18 years ( $n = 17$ ); BRIEF: Behavior Rating Inventory of Executive Function; GEC: Global Executive Composite; BRI: Behavioral Regulation Index; MI: Metacognition Index; HUI3: Health Utilities Index; SDQ: Strengths and Difficulties Questionnaire; PedsQL: Pediatric Quality of Life Inventory; FSIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; WMI: Working Memory Index; PSI: Processing Speed Index. Higher scores in all the questionnaires indicate poorer levels of executive functioning, health status, behavior, and HRQoL.

differences in the composite z-scores reflecting all the questionnaires according to the presence or absence of postsurgical ataxia ( $M[SD] = 1.1[3.2]$  vs  $-.6[3.9]$ , difference 1.7, 95% CI:  $-4$  to  $3.7$ ,  $t = -1.61$ ,  $P = .12$ ) or postoperative cerebellar mutism ( $M[SD] = -1.9[4.2]$  vs  $.3[3.9]$ , difference 2.2, 95% CI:  $-2.5$  to  $6.9$ ,  $t = -.94$ ,  $P = .35$ ). In addition, individual analyses of the questionnaires indicated a marginal association between the presence or absence of ataxia and the BRIEF BRI ( $M[SD] = 55.84[11.39]$  vs  $50[11.24]$ , difference 5.83, 95% CI:  $.38$  to  $11.29$ ,  $t = 2.14$ ,  $P = .04$ ).

## Discussion

This study found few relationships between directly measured cognitive functioning and the majority of questionnaire-based measures of QoS, specifically executive function, health status, behavior, and HRQoL. Contrary to our expectations, we did not find strong relationships between directly measured cognitive functioning and HRQoL. Self-reported health status was moderately related to the different domains of directly measured cognitive functioning, while parent-reported health status was weakly related to directly measured working memory, which in turn was weakly related to parent-report of executive functioning. The relationship between direct assessments and questionnaire responses of single domains, such as working memory, was moderate and of similar magnitude to the relationship between directly measured working memory and self-report health status.

These results align well with the findings from several studies of patients treated for brain tumors<sup>8,20,21,46</sup> and might suggest that self-report measures of general health

such as the HUI3 could provide a parsimonious screening tool for identifying patients for more comprehensive cognitive assessments.<sup>47</sup> Other studies have reported a significant association between questionnaire scores and direct assessments<sup>48</sup> or proposed the use of QoS questionnaires as screening tools for the presence of neuropsychological deficit.<sup>29,49</sup> However, this was based on observations in a mixed sample of children (malignant and benign brain tumors,<sup>48</sup> brain tumors and healthy controls<sup>29,49,50</sup>), which may have increased the estimates of sensitivity and specificity of questionnaires compared to that which applies to a population of medulloblastoma survivors. Several reports have underlined the absence of significant intercorrelations<sup>8,9,21,51</sup> between direct assessments and questionnaire scores and it seems that patients whose direct assessments suggest cognitive compromise do not necessarily present behavioral or cognitive difficulties on questionnaires by self- or proxy-report.

This lack of association contrasts with the strong correlations observed between the different domains conceptualized under the term QoS, which typically includes questionnaire-based information relative to health status, behavior, executive function, and HRQoL.<sup>11,16</sup> The robust association between these different constructs suggests the existence of a common factor sustaining the significant co-variance observed among these measures. An analogy can be traced with IQ, in which all specific IQ measures (eg, verbal, performance, working memory, processing speed) tend to be highly correlated because they are supposed to share a common factor of "general intelligence" measured by the FSIQ. The results from the present exploratory study allow us to hypothesize that questionnaire-based measures might share a common factor, which could be related

**Table 4** Principal component analysis with varimax rotation of the questionnaire- and the performance-based outcomes

	Factor1	Factor2
BRIEF BRI	.83	-.13
BRIEF MI	.68	-.07
HUI3	.76	.16
SDQ	.88	-.15
PedsQL	.89	.15
VIQ	-.18	.88
PIQ	-.04	.83
WMI	-.28	.77
PSI	-.06	.71
Proportion of variance explained	45%	22%

BRIEF: Behavior Rating Inventory of Executive Function; BRI: Behavioral Regulation Index; MI: Metacognition Index; HUI3: Health Utilities Index; SDQ: Strengths and Difficulties Questionnaire; PedsQL: Pediatric Quality of Life Inventory; FSIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; WMI: Working Memory Index; PSI: Processing Speed Index.

to common characteristics of all the items of all the QoS questionnaires used in the present study.

First, these questionnaire-based measures are structured with a positive/negative wording of all the items: presence/absence or degree of a presence of a difficulty or a symptom, or a desirable trait. For example, respondents are typically asked to rate a particular symptom according to their positive or negative character (ie, absence or presence of symptoms). Second, the questionnaires used to assess QoS in the present study were developed to cover a broad range of concerns and to be used with a variety of clinical populations. Therefore, they include a collection of symptoms, some of which are general and not specific to medulloblastoma (eg, “having hurts or aches” [PedsQL] vs “able to hear with or without hearing aid” [HUI3]). In the same vein, the items of these questionnaires overlap frequently, as do the scale scores computed from these items, such as the emotional indices derived within the HUI3, PedsQL, SDQ, and BRIEF scoring metrics.

Given these shared characteristics, respondent-related factors could explain the associations between QoS questionnaires. Personality and emotional factors, which tend to relate poorly with direct assessments of cognitive difficulties, have been shown to influence symptom reporting.<sup>26–28,52,53</sup> Such respondent-related factors might underlie the robust associations observed among the questionnaire-based measures of QoS, when questionnaires are completed by the same respondent or even different respondents that share the same context (eg, family).

Previous studies have provided empirical support for this argument. Following chemotherapy in women with breast cancer, Biglia et al<sup>26</sup> demonstrated that a patient’s emotional status influenced both symptom reporting and self-reported cognitive dysfunction, but not direct assessment of cognitive function. In the same vein, Pullens et al<sup>28</sup> observed that anxiety, depression, and psychological distress were the main factors associated with self-reported cognitive

dysfunction, but not with direct assessments of executive functioning. Similar findings have also been observed when parental questionnaires were used to assess children’s cognitive functioning. In a recent study of children with neurofibromatosis type 1, the overall positive or negative view of the parents with respect to the child’s abilities and difficulties was strongly associated with a number of questionnaire-based measures, but not with the results of the comprehensive neuropsychological assessment.<sup>54</sup> Hooper et al<sup>55</sup> presented evidence that parents of children with encephalitis exhibited clinical levels of anxiety and depression, and that these factors were strongly associated with their own perception of cognitive dysfunction in their children. Hermelink et al<sup>56</sup> observed that patients’ symptom reporting is influenced by “negative affectivity,” a personality trait characterized by the stable tendency to experience negative emotions. The patients exhibiting higher levels of negative affectivity tended to manifest more pessimistic self-appraisals of cognitive functioning, independently of the presence of cognitive dysfunction assessed directly. An opposite pattern can be observed in individuals that tend to focus on positive outcomes of stressful past events (ie, positive thinking), who evidence increased reports of perceived well-being compared to individuals characterized by negative thinking.<sup>57</sup> Interestingly, negative affectivity has been reported to influence symptom reporting particularly if the symptoms are vague.<sup>56</sup> On the contrary, when the disease and its treatment symptoms were clear, distinct, and nonoverlapping with vague symptoms (eg, headaches, cough, lapses), patients tended to report disease-specific symptoms accurately and independently of the presence or absence of negative affectivity.<sup>52</sup>

The influence of personality and psychological factors on symptom reporting has been perceived by the authors of some of these questionnaires. The BRIEF, for instance, includes validity scales that acknowledge that a high degree of negativity underlying the respondent’s answers may cast doubt on its validity. In addition, efforts have also been made to render some instruments (eg, the PedsQL<sup>58</sup>) specific to certain clinical populations.

The influence of these factors on questionnaire-based assessments might contribute to a reduction in the specificity of these questionnaires intended to assess distinct dimensions of QoS, such as health status, behavior, HRQoL, or executive function, and also provides a plausible explanation for the lack of association between questionnaire-reported QoS and direct assessments of cognitive functioning. Direct testing and questionnaires represent very different approaches towards assessment of outcomes following childhood medulloblastoma. Most studies looking at the links between cognitive tests of executive functioning and the BRIEF questionnaire (designed to assess everyday executive functioning) have consistently reported similar results.<sup>23,24</sup> Indeed, although both aspects are significantly impacted by brain injury, they are not correlated even though they were developed to measure the same construct. The authors of a comprehensive literature review conducted on this topic<sup>23</sup> concluded that this often-cited absence of interrelations indicates that they evaluate different underlying aspects of executive functioning. While direct assessments are more likely to capture processing efficiency in optimal conditions, reports of cognitive

functioning might provide a more accurate indication of executive performance in everyday situations of real-life environments. Although questionnaires provide less information regarding core cognitive processes, they might provide a more global and ecologically valid picture of everyday functioning.<sup>24</sup> Hence, both methods of measurement should be conceptualized as distinct but complementary measures of cognitive functioning. For instance, it is important to assess the parent's point of view about their child when cognitive impairments are detected, as rehabilitation interventions will require parental collaboration. It is also important to bear in mind respondent characteristics when questionnaire-based measures only are used in clinical trials.

The relatively high quality-of-life scores of cancer patients in self-reports has been partially attributed to response-shift,<sup>59,60</sup> that is, the adjustment of the internal norm by patients experiencing extreme negative situations, such as cancer. For instance, when patients with cancer are asked to judge their well-being, they tend to choose a comparative reference group of patients whose clinical situation is worse. A consequence of this shift of the internal norm is that HRQoL or psychological distress are not measured on the same scale in patients and in healthy controls. It is worth noting that in a recent study,<sup>49</sup> HRQoL tended to increase with time in children treated for medulloblastoma, in contrast with the well-known decrease of IQ over time in the same population.<sup>61,62</sup>

In a recent literature review of factors influencing QoS, the negative influence of postoperative cerebellar mutism and persisting ataxia on subsequent cognitive functioning, language skills, and academic achievement has been repeatedly reported. Similarly, in the present study, the association of these complications was moderate with IQ measures, whereas it was nonsignificant with the questionnaire-based measures. However, a negative influence of postoperative complications on QoS assessed through questionnaires has been reported, although their influence on psychosocial domains seems to be less pronounced and has been less frequently studied.<sup>30</sup>

Some limitations should be taken into account regarding the interpretation of these results. The direct assessments of cognitive functioning were different in the participating countries and, therefore, they might be tapping separate underlying constructs of cognitive function. Consensus regarding the standardized instruments used to directly assess cognitive functioning should follow the one reached regarding the domains of QoS to be assessed in European clinical trials.<sup>16</sup> Despite these differences, nearly half of the participants in the present study were evaluated with the same instrument (ie, Wechsler Intelligence Scales<sup>39-42</sup>), and shared-method variance might have contributed to the loading estimates of the cognitive measures into the same factor. However, previous reports have presented evidence that IQ and neuropsychological tests aimed at evaluating specific cognitive constructs (eg, memory, attention) loaded into the same factor, although they did not correlate with questionnaire-based measures.<sup>54</sup> Further, the rate of participants who had both cognitive and questionnaire-based assessments available was relatively low (35%).

This reduced sample size limited our analysis of the relationships among the different questionnaires assessing QoS, results of cognitive assessments, and clinical data. In addition, the noninclusion of observations referring to HRQoL in participants aged  $\geq 18$  years limited the analysis of these data and the reliability of our findings in these subgroups. It was not possible to analyze the directionality of effects between respondents' personality and emotional characteristics and children's outcomes, such as the possibility that children's poor health status, emotional and behavioral difficulties, executive dysfunction, and lower quality of life may have a negative effect on the respondents' reporting of symptoms. Finally, the exploratory approach used in the present study might benefit from confirmatory studies. However, our findings are consistent with studies of patients with comparable pathologies.<sup>11,20-22,25,27</sup>

Future studies examining the clinical outcomes of patients treated for medulloblastoma could first include multiple informants (eg, patients, parents, and teachers) in order to help identify co-variance among different measures completed by the same respondent or by respondents who share a single context (eg, the home environment), and second include measures of respondent factors, such as emotional distress of patients and caregivers, contributing to variance in questionnaire scores. In addition, the possible role of vague questions in generic questionnaires suggests that the development of disease-specific instruments should be pursued.

The implications of the weak associations observed between direct measures and QoS questionnaires may suggest dilemmas of practical clinical importance: for example, when questionnaire and cognitive assessment scores point to conflicting conclusions in a clinical trial, which conclusion should be preferred?

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