Review

The Executive Profile in Brief of Patients and/or Survivors of Central Nervous System Tumors in Children and Adolescents? A Review and Meta-Analysis

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The Executive Profile in BRIEF of Patients and/or Survivors of Central Nervous System Tumors in Children and Adolescents? A Review and Meta-Analysis

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Abstract: Background: This review aimed to determine whether executive dysfunction is a characteristic of survivors of central nervous system tumors in children and adolescents, including Astrocytoma, Neurofibromatosis-1, Medulloblastoma, and Pilocytic Astrocytoma. Method: A review and meta-analysis of executive function assessed with BRIEF in individuals with these tumor types. Results: A total of 48 articles were obtained, which allowed for tracking the evolution of research on the topic and selecting those suitable for a subsequent meta-analysis. Of these, 8 studies were included in the meta-analysis. Effect sizes were analyzed using the standardized mean difference (Cohen's d). The forest plot showed an average effect size of $d = 0.40$ (95% CI = 0.27–0.53). Conclusions: Executive deficits are observed in individuals with brain tumors or survivors, significantly affecting their academic, social, and emotional lives. Early identification, along with educational and neuropsychological support, is essential to preventing these deficits from interfering with academic, personal, and professional functioning.

Keywords: astrocytoma; BRIEF; executive function; neurofibromatosis-1; medulloblastoma; pilocytic astrocytoma

1. Introduction

Survivors of central nervous system tumors are at high risk of experiencing a variety of late effects that may impact physical, motor, and cognitive functioning. (Benzing et al. 2022) and influence their academic, personal, and professional performance in both the short and long term.

Cancer treatment-related factors have been linked to deficits in executive functions (EF) among survivors (Vega, Dumas, y Newhouse 2017).

Thus, cancer and its treatments, particularly chemotherapy, are associated with impairments in executive functions such as attention, memory, and working memory (Yao, Bernstein, y Rich 2017) (Pendergrass, Targum, y Harrison 2018) (Williams, Janelsins, y Van Wijngaarden 2016) (Wang et al. 2016). Focusing on pediatric cancer survivors, especially those treated for brain tumors, they exhibit significant executive function deficits, according to parent reports using the BRIEF (Roche et al. 2020) (Peterson y Jacobson 2021) (Gorsi y Trask 2018) (de Vries et al. 2018). Inhibition appears to be relatively protected from the effects of chemotherapy, while impairments in cognitive flexibility and information updating are more common. (Yao et al. 2017). Working memory is frequently reported as the most affected subscale in children treated for brain tumors (Roche et al. 2020) (de Vries et al. 2018).

Long-term survivors of central nervous system tumors, especially older adults, show persistent deficits in processing speed, attention, and working memory, which are crucial for executive functions (Peterson y Jacobson 2021).

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A diagnosis at an earlier age and an evaluation at an older age are associated with higher levels of executive function difficulties reported by parents (Roche et al. 2020) when using informant scales.

Several studies (Roche et al. 2020) (Loughan, Braun, y Lanoye 2020) Several studies suggest that cancer and its treatments can negatively impact executive function, and BRIEF is a tool used to assess these cognitive impairments. BRIEF is effective in identifying deficits in executive functions in daily life, but it does not always correlate strongly with performance-based executive function measurements (de Vries et al. 2018) both the parent and teacher versions of BRIEF provide valuable perspectives, although the teacher version may correlate better with some executive function tasks. Next, we focus on some of them, specifically.

Neurofibromatosis-1

Neurofibromatosis type 1 (NF1) is a hereditary genetic disorder characterized by the formation of tumors (neurofibromas) in the nerve tissues of the skin, cranial nerves, and spinal cord.

The diagnosis is made in patients who meet certain clinical criteria proposed by the National Institute of Health (Jacobsen et al. 2022).

If one of the parents has NF1, there is a 50% chance that their children will inherit the disease. It can also arise spontaneously due to a genetic mutation.

NF1 is caused by issues in the gene that produces the protein neurofibromin.

NF1 is defined if the patient presents two or more of the following signs: (i) Six or more café-au-lait spots larger than 5 mm in prepubertal individuals or larger than 15 mm after puberty; (ii) Two or more neurofibromas of any type or one or more plexiform neurofibromas; (iii) Freckles in the axillary or inguinal region (Crowe's sign); (iv) Optic nerve glioma; (v) Two or more Lisch nodules (iris hamartomas); (vi) A distinctive bone lesion: sphenoid wing dysplasia or pseudoarthrosis of long bones; (vii) A first-degree relative (parent, sibling, or child) affected.

Symptoms vary widely and may include "café-au-lait" spots, skin neurofibromas, optic gliomas, seizures, freckles in the axillae, and plexiform and nodular tumors. Symptoms can cause cosmetic issues, pain, and nerve damage depending on the location of the tumors.

(Lehtonen et al. 2013) It analyzes studies on children with NF1 and their executive functions, particularly planning and inhibitory control. The results show that children with NF1 perform significantly worse on planning tasks, such as the Tower of London, and inhibitory control tasks, such as the Stroop task. Although some studies did not find marked deficits in executive functions, the majority highlight issues with attention, cognitive control, and working memory.

Astrocytoma

It is a type of brain tumor that originates in astrocytes, cells that are part of the brain's supportive tissue. Astrocytomas are glial tumors, and their severity varies depending on the type and location. Astrocytomas can be low or high grade (more aggressive), and treatment depends on the grade and location of the tumor.

This is a type of low-grade astrocytoma (less aggressive) that generally occurs in areas of the brain such as the cerebellum or brainstem. It is often found in children and young adults. Pilocytic tumors tend to grow slowly and have a relatively good prognosis when surgically removed.

Astrocytomas are a type of brain tumor that can affect cognitive functions, including executive function.

Studies have shown that children who survive a pilocytic astrocytoma (PA) often show more deficient executive function compared to those who survive medulloblastoma, despite the latter group having received more intensive treatments, such as chemotherapy and radiotherapy. This suggests that the tumor itself, rather than the treatment, may significantly impact cognitive abilities in PA survivors (Holland et al. 2024).

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Research indicates that children treated for cerebellar astrocytomas show deficits in executive functions, such as attention and motor speed, compared to standard norms. These deficits are observed even when the treatment is limited to surgery, highlighting the potential cognitive impact of the tumor's presence and location. (Rønning et al. 2005).

Given the differential impact of astrocytomas on executive function, it is essential to develop specific rehabilitation strategies that address the particular cognitive deficits in affected individuals. This approach could help improve the quality of life and functional outcomes for survivors (Vaquero et al. 2008).

Research highlights the significant impact of astrocytomas on executive function and the importance of understanding these effects to improve patient care and outcomes.

Medulloblastoma

It is a type of brain tumor that originates in the cerebellum, the part of the brain that controls balance and coordination. It is one of the most common brain tumors in childhood. It is often considered a malignant tumor and can spread to other parts of the brain or spinal cord.

Medulloblastoma is a common pediatric brain tumor that often leads to long-term neurocognitive deficits, particularly affecting executive function.

Survivors of pediatric medulloblastoma frequently experience disruptions in executive function, showing deficits in cognitive flexibility, attention, and working memory. These deficits are often related to a decrease in the integrity of white matter in the brain, particularly in the frontal lobes (Brinkman et al. 2012) (Law et al. 2017) (Glass et al. 2017).

It has been shown that children with medulloblastoma score lower in executive function and occupational performance compared to their peers with typical development (Önal y Huri 2021) (Law et al. 2017).

Different approaches to radiotherapy, such as hyperfractionated radiotherapy versus standard radiotherapy, have varying impacts on executive function. Hyperfractionated radiotherapy has been associated with better outcomes in executive function compared to standard radiotherapy, although it may lead to other side effects, such as growth disorders (Laprie, LaMarre, y Haas-Kogan 2014) (Kennedy, Molina, y Pedersen 2022) (Câmara-Costa et al. 2015).

Studies have shown that damage to white matter, particularly in the frontal regions, is associated with worse outcomes in executive function. This damage can occur as a result of the tumor itself or as a consequence of treatment, such as surgery and radiotherapy (Holland et al. 2024) (Glass et al. 2017).

It has been identified that disruption in the cerebro-cerebellar pathways affects executive function, particularly working memory, in children treated for medulloblastoma. This suggests that the cerebellum plays a significant role in cognitive processes beyond motor control (Law et al. 2017).

There is a need for specific cognitive interventions to address the particular executive function deficits observed in survivors of medulloblastoma. Client-centered and occupation-focused therapeutic interventions can help improve occupational performance and overall quality of life (Önal y Huri 2021).

Future research should focus on integrating advanced imaging techniques, such as diffusion tensor imaging, to better understand the long-term effects of medulloblastoma treatment on brain structure and function. This could guide the development of more effective cognitive rehabilitation strategies (Brinkman et al. 2012) (Law et al. 2017).

In conclusion, medulloblastoma and its treatment significantly affect the executive function of survivors, with various factors such as the type of treatment and the integrity of brain structure being key elements. Ongoing research and personalized interventions are essential to mitigate these effects and improve outcomes for survivors.

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Pilocytic Astrocytoma

Pilocytic astrocytoma (PA) is a type of brain tumor commonly diagnosed in children.

Children treated for PA often experience cognitive deficits despite having normal intelligence levels in long-term follow-ups. These difficulties include issues with sustained attention, processing speed, verbal intelligence, visuospatial memory, and executive function, especially in those with infratentorial tumors (Aarsen et al. 2009).

It has been reported that survivors of PA have poorer executive functioning compared to survivors of medulloblastoma (MB), according to parent evaluations. These difficulties affect various areas of executive function, with the exception of the ability to shift attention, which showed no significant differences from the normative average (Holland et al. 2024).

Parent evaluations indicate that survivors of PA experience more executive function difficulties compared to survivors of MB, which can impact their daily functioning and support needs. This underscores the importance of considering the parent's perspective in the assessment and management of cognitive deficits in children who have survived a brain tumor (Holland et al. 2024).

In conclusion, although children with pilocytic astrocytoma may have a normal intelligence quotient, they often face significant challenges in cognitive and executive function that can impact their academic and daily life.

The aim of this review is to investigate the impairment in executive functioning in individuals diagnosed with NF1, Astrocytoma, Medulloblastoma, and Pilocytic Astrocytoma, focusing on studies that used the BRIEF scales for the assessment of executive functioning (Gioia et al. 2000) (Roth, Isquith, y Gioia 2005) (Isquith et al. 2005) In its different versions. Our reason for including only BRIEF studies was to allow an ecological assessment of executive functions, thus ensuring homogeneity among them.

The degree of executive function impairment in individuals diagnosed with NF1, Astrocytoma, Medulloblastoma, and Pilocytic Astrocytoma will be significantly higher compared to patients in the normative population. This will be reflected in a higher score on the BRIEF scales, suggesting a greater impact of these conditions on executive functions. Additionally, it is expected that variations in executive functioning among these groups will be more pronounced in subscales related to inhibition, cognitive flexibility, and working memory, as these areas are commonly affected in brain tumors.

2. Materials and Methods

A review of executive functioning in individuals with NF1, Astrocytoma, Medulloblastoma, and Pilocytic Astrocytoma assessed using BRIEF (different versions) will be conducted, following the procedure outlined in the PRISMA guidelines *(Page et al. 2021).*

Eligibility Criteria for Studies and Selection Process

For the selection of keywords and, consequently, studies, the PICOS strategy (Participants, Interventions, Comparisons, Outcomes, Study design) was used (Santos, Pimenta, y Nobre 2007). The present work includes the following inclusion and exclusion criteria for review studies (see Table 1):

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Table 1. Inclusion and Exclusion Criteria for Review Studies.

Inclusion	Exclusion
Diagnosis: Individuals under 18 years of age of both sexes	Age at diagnosis: Adults
Exposed to a brain tumor during pediatric age and/or exposed to oncological treatments during the fetal period	Exposed to other types of tumors not related to the brain or central nervous system
Assessment of executive functioning using the BRIEF scales in their different versions and translations	Assessment of executive functioning using other instruments
Ex post facto studies (descriptive, comparative-causal)	Case studies

Search Strategy

The search strategy follows the guidelines established by the PRISMA statement. (Page et al. 2021). To this end, the databases PubMed, Springer Link, and Scopus were consulted, selecting articles published from 2010 to March 2024.

In the first stage, an initial bibliographic search was conducted using the following keywords in English: "cancer," "tumor," and "executive function." The studies were then categorized based on the type of tumor, and studies with diagnoses of NF1, Astrocytoma, Medulloblastoma, and Pilocytic Astrocytoma were selected.

A total of 78.933 articles were obtained, which allowed for tracking the evolution of research on the topic.

In the second stage, specific filters were applied according to each database: full text, empirical studies, English or Spanish language, and open access.

A total of 48 articles were obtained, which allowed for tracking the evolution of research on the topic and selecting those suitable for a subsequent meta-analysis.

Included Studies

A total of 48 studies were selected as the basis for this review. Of these, 8 studies were included in the meta-analysis with the following diagnosis: (i) NF1 (Beaussart-Corbat et al. 2021) (Casnar y Klein-Tasman 2016) (Gilboa et al. 2011) (Lorenzo et al. 2013) (Maier et al. 2020) (Payne et al. 2011), (ii) Astrocytoma (Bull et al. 2015), (iii) Medulloblastoma (Holland et al. 2024) and Pilocytic astrocytoma (Holland et al. 2024). Through an initial screening process, studies whose titles indicated no relevance to the research objective were excluded. Subsequently, a second screening and suitability assessment were conducted by reviewing the abstracts, ultimately selecting those that met the established criteria. The flowchart illustrating the study selection process can be seen in Figure 1. In total, the following were included for the meta-analysis: NF1 (6 studies), Astrocytoma-Medulloblastoma (1 study), and Medulloblastoma-Pilocytic astrocytoma (1 study). The studies included in the meta-analysis (8 studies) are presented in Table 2.

Table 2. Studies included in the meta-analysis.

Nº	Estudio	Journal/Oncology Specific	Título (BRIEF)	Country	Sample (n)	Cancer	Age (diagnosis and/or assessment)	Sex N(DT)	Methodology		Instrument	Specific results	Global results	Meta-analysis
1.	(Beaussart-Corbat et al. 2021)	Journal of Clinical and Experimental Neuropsychology / NO	NO	Francia	G. NF1: (n=33) G. Control: (n=52) Informants: Parents (n=31) Teachers: (n=18)	Neurofiromatosis type 1	3-5 years G. NF1: 56.67 (11.27) (months) G. Control: 55.75 (10.37) (months)	G. NF1: 17/16 (man/woman) G. Control: 27/25 (men/women)	**VI**: G. NF1 vs. G. Control **VD:** BRIEF-P intellectual competence (WPPSI-IV)	Comparative-causal	BRIEF-P Parents y Teachers	**Parents:** Flexibility Inhibition **Teachers:** Global, Inhibition y Emotional Control	> Early executive dysfunction in children with NF1 is supported, highlighting the need for early and systematic evaluation of executive functions (EF). > Both performance-based tests and questionnaires are complementary tools for investigating early EF dysfunction in children with NF1.	YES Informant: - Parents - Teachers
2.	(Casnar y Klein-Tasman 2016)	Journal of Pediatric Psychology / NO	NO	Wisconsin (EE.UU)	G. NF1: (n=26) G. Control: (n=37)	Neurofibromatosis Type 1	NF1: 4.53 (0.87) G. Control: 4.51 (0.89)	NF1 Mans: 17 (65%) Wome: 9 (34%) G. Control Men 23 (62%) Women: 14 (38%)	**VI:** G. NF1 vs. G. Control **VD:** Executive Functioning (BRIEF-P)	Comparative-causal	BRIEF-P	Executive Functioning	Dysfunction compared to the normative mean in the Working Memory (WM) scale and the Emerging Metacognition Index (EMI).	YES Informants: Parents
3.	(Gilboa et al. 2014)	Neuropsychological Rehabilitation /NO	NO	Israel	G. NF1: (n= 29) G. Control: (n=27)	Neurofibromatosis tipo I (NF1)	NF1: 12.3 (2.6) G. Control: 12.4 (2.5)	NF1 Men: 8 Women: 21 G. Control Men: 8 Women: 19	**VI:** G. NF1 vs. G. Control **VD:** BADS-C BRIEF-Parents ACES	Comparative-causal	BRIEF Parents	Academic performance predictor	Children with NF1 exhibit executive dysfunction, which partially explains their difficulties in academic performance.	YES Informants: Parents
4.	(Lorenzo et al. 2013)	The Journal of Pediatrics / NO	NO	Australia	G. NF1: (n=43) G. Control: (n=43)	Neurofibromatosis Tipo 1 (NF1)	G. NF1: 40.23 (0.72) months G. Control: 40.16 (0.48) months	G. NF1 H= 32 (74%) M= 11 (26%) G. Control Man= 32 (74%) Woman= 11 (26%)	**VI:** G. NF1 vs. G. Control **VD:** BASC – II BRIEF-P CADS-P	Comparative-causal	BRIEF-P Parents	Preschoolers' cognitive and executive profile	Young children with NF1 exhibit significantly lower intellectual functioning, expressive language, and visual perception. These difficulties can be detected in preschool age and are likely to impact learning and performance during the early school years.	YES Informants: Parents
5.	(Maier et al. 2024)	Child Neuropsychology / NO	NO	Australia	G. Control: (n=55) G. NF1	Neurofribromatosis tipo 1	Control: 11.81 (2.61)	Men= Control 22(40)	**VI:** G. NF1 vs. G. Control	Comparative-causal	BRIEF	FE global	This study provides evidence that visuospatial deficits are	YES Informants: Parents

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					(n=191) G. NF1 Typical: (n=41) G. NF1 Bordeline: (n=30) G. NF1 Impaired: (n=120)		NF1: 10.38 (2.36) NF1 Typical: 11.61 (2.75) NF1 Bordeline: 9.98 (2.29) NF1 Impaired: 10.06 (2.11)	NF1: 104 (54.45) NF1 Typical: 27 (65.85) NF1 Bordeline: 13 (56.67) NF1 Impaired 64: (53.33)	**VD:** RCFT, IQ, Visuospatial abilities, BRIEF, Torre de Londres, The Conners ADHD DSM-IV Scales (CDAS)				a key factor in the decreased performance on the RCFT in children with NF1 and that executive skills, as well as younger age, are also independent predictors of RCFT performance.	
6.	(Payne et al. 2011)	Child Neuropsychology / NO	NO	Australia	G. NF1: (n=199) G. Control: (n=55)	Neurofibromatosis Tipo 1	(6-16) G. NF1: 10.62 (2.28) G. Control: 11.24 (2.03)	G. NF1: Men: 108 Women: 91 G. Control: Men: 22 Women: 31	**VI;** G. NF1 vs. G Control **VD:** BRIEF, Conners`ADHD DSM-IV Scales (CADS), Wechsler Intelligence Scales for Children-Third Edition or Fourth Edition (WISC-III / WISC-IV)	Comparative-causal	BRIEF Parents and Teachers	Attention	The prevalence of functional and executive attention deficits was examined in a large sample of children with NF1, and the relationship between cognitive test scores and functional indices was evaluated. Our results suggest that, although the convergent validity between these two domains was relatively low, both have the ability to detect significant impairments and contribute important information to a child's clinical profile. We argue that neuropsychological assessments should include both cognitive and functional tests to provide more accurate and sensitive information about a child's strengths and weaknesses, guiding intervention programs effectively.	YES
7.	(Bull et al. 2015)	Neuro-Oncology / SI	NO	Londres	G. Cerebellar (N=72) G. Medulloblastoma (n= 37) G. Astrocitoma (n=35) G. Control (n= 38)	Tumor cerebral	8-14 years G. Cerebellar N: Medulloblastoma Age assessment: 10.2 (8-14) Diagnosis age:	G. Cerebellar G. Medulloblastoma Women: 13 (41%) G. Astrocitoma Women: 23 (68%) G. Control= Women:	**VI:** G. Cerebellar G. Medulloblastoma G. Astrocitoma G. Control **VD:** IQ BRIEF Parents y Teachers	Comparative-causal	BRIEF Parents and Teachers	Screening Discriminación de déficit cognitivo en el contexto educativo	The PedsQL reported by children and parents, as well as the BRIEF and SDQ reported by teachers, have moderately good accuracy in distinguishing between children with and	YES Informant: - Parents - Teachers

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							10.4 (8-14) Astrocitoma Age assessment: 10.4 (8-14) E Diagnosis age: 9.2 (5-14) G. Control= Diagnosis age: 10.4 (8-14)	19 (50%)	SDQ Parents Teachers Niño PedsQL Parents y Niño				without an FSIQ below 80.	
8.	(Holland et al. 2024)	Applied Neuropsychology: Child / NO	NO	USA	G. Meduloblastoma (n=36) G. Pilocytic Astrocytoma (n=20)	Tumor cerebral pediátrico: Meduloblastoma Pilocytic Astrocytoma	Meduloblastoma Diagnosis age: 8.55 (4.34) Age assessmen: 14.07 (3.45) Pilocytic Astrocytoma Diagnosis age: 5.40 (4.34) Age assessmen: 12.84 (2.67)	Meduloblastoma Men: 24 (66.7%) Women: 12 (33.3%) Pilocytic Astrocytoma Men: 11 (55.0%) Women: 9 (45.0%)	**VI:** Tipo de cáncer: G. Meduloblastoma G. Pilocytic Astrocytoma **VD:** BRIEF	Comparative-causal	BRIEF Parents	Sensibilidad, discriminación	Pan survivors demonstrate worse executive functioning than MB survivors.	YES Informants: Parents

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Figure 2 presents the procedure followed in the selection of the studies.

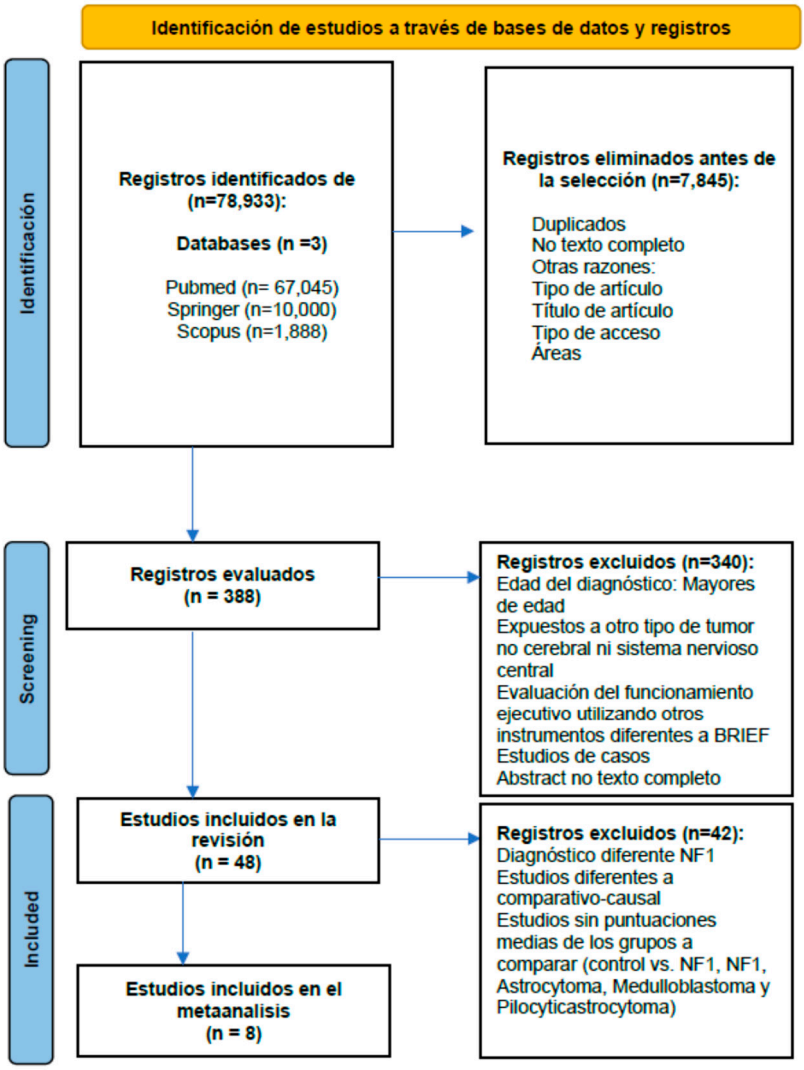

Figure 2. Forest plot (clinical scales and indices) based on the type of alteration.

Bias Assessment

The Newcastle-Ottawa Quality Assessment Scale tool has been selected (Wells et al. 2014). The selected articles present a low risk of bias (Table 3).

Table 3. Assessment of the risk of the included studies using the Newcastle-Ottawa Quality Assessment Scale.

Study	Tipo de estudio	Dimensions								Total	Risk
		1	2	3	4	5	6	7	8		
3	Comparative-causal	1	1	1	1	1	1	1	1	8	Low
5	Comparative-causal	1	1	1	1	1	1	1	1	8	Low
9	Comparative-causal	1	1	1	1	1	1	1	1	8	Low
16	Comparative-causal	1	1	1	1	1	1	1	1	8	Low
22	Comparative-causal	1	1	1	1	1	2	1	1	9	Low
29	Comparative-causal	1	1	1	1	1	2	1	1	9	Low
32	Comparative-causal	1	1	2	1	1	1	1	1	9	Low
35	Comparative-causal	1	1	1	1	1	2	1	1	9	Low

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Data Analysis

A meta-analysis was conducted using the SPSS program (Meta-analysis module). When using quantitative variables, mean differences were used. Cohen's d effect sizes were calculated (Cohen, Reference Cohen 1988). A Cohen's d effect size in the range of [0.2 – 0.35] was considered small, in the range of [0.35 – 0.65] moderate, and > 0.65 large. Statistical inferences were made based on the analysis of the 95% confidence intervals (CI). A random effects model was chosen, assuming that the effects are not the same across all studies.

3. Results

Table 4 presents the descriptive data of the two participant groups. The mean scores of the brain tumor group are higher than those of the control group.

Table 4. Paired sample statistics.

	Mean	**N**	**Standard deviation**	**Standard error mean**
Tumor Cerebral	54.23	75	4.87	.56
Control	50.04	75	4.38	.506

There are statistically significant differences between the group with various alterations related to central nervous system tumors and the control group in the mean BRIEF scores ($t = 5.80$; $p < 0.001$) (Table 5).

Table 5. Matched samples test.

	Paired differences							**Significance**	
				95% de intervalo de confianza de la diferencia					
	Mean	**Standard deviation**	**Standard error mean**	**Lower**	**Upper**	**t**	**gl**	**P of one factor**	**P of two factors**
M_TC - M_Control	4.19	6.25	.72	2.75	5.62	5.80	74	<.001	<.001

Table 6 presents the effect sizes for paired samples.

Table 6. Effect Sizes for Paired Samples.

			Standardizer (a)	**Point estimation**	**95% de intervalo de confianza de la diferencia**	
					Lower	**Upper**
Par 1	M_TC - M_Control	d de Cohen	6.25	.670	.418	.919
		corrección de Hedges	6.31	.664	.414	.910

(a) The denominator used in the estimation of effect sizes. Cohen's d uses the sample standard deviation of the mean difference. Hedges' correction uses the sample standard deviation of the mean difference, plus a correction factor.

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Effect Size Measures

Cohen's d effect sizes were calculated based on data from 8 studies that used BRIEF (in different versions) in 4.954 patients with various tumors affecting the central nervous system and 3.218 controls. Table 7 presents the detailed results of the meta-analysis for subgroups based on different clinical scales and indices, informant, and BRIEF version.

Table 7. Effect size estimates based on the type of alteration.

	Effect size	Standard error	Z	Sig. (two-tailed)	95% de intervalo de confianza de la diferencia	
					Lower	Upper
Astrocytoma_Medublalastoma	.486	.1682	2.893	.004	.157	.816
Medulloblastoma_Pilocyticastrocytoma	-.803	.0875	-9.173	.000	-.974	-.631
NF1	.606	.0474	12.781	.000	.513	.699
Global	.402	.0671	5.996	<.001	.271	.534

The model globally shows moderate executive deficits compared to the community sample (d = 0.402; p = 0.001; 95% CI [0.271 – 0.534]).

An analysis of the different clinical scales and indices indicates that significant executive deficits vary depending on the type of alteration: (I) Moderately significant compared to the community sample in: (i) NF1 (d = 0.606; p = 0.000; 95% CI [0.513 – 0.699]) y (ii) Astrocytoma_Medulloblastoma (d = 0.486; p = 0.004; 95% CI [0.157 – 0.816]). (II) Significantly high compared to the community sample in: Medulloblastoma_Pilocytic astrocytoma (d = -0.803; p = 0.000; 95% CI [0.974 – 0.631]).

Homogeneity and Heterogeneity

The heterogeneity test and the chi-square test were conducted. A significant heterogeneity of >40% suggests the presence of heterogeneity (Higgins y Thompson 2002). The presence and amount of statistical heterogeneity were assessed using the I^2 statistic, with significance set at p<.10. (Higgins 2003).

In Table A1, we present the results of the subgroup homogeneity test. The subgroup homogeneity test was: (i) It is significant for NF1 (χ^2_{61}= 197,452; p=.001). This means that the studies have heterogeneous results: (ii) Astrocytoma_Medulloblastoma: (χ^2_1= 0.003; p=.955) it is not significant; (iii) Medulloblastoma_Pilocyticastrocytoma: (χ^2_{10}= 7.247; p=.702) not significant; (iv) Global versions: (χ^2_{74}= 461.523; p=.000) it is significant.

Forest Plot

Figure 2 presents a forest plot of the effect sizes from the meta-analysis on differences between NF1 and control. The effect size index used in this meta-analysis was the standardized mean difference, Cohen's d, and was calculated such that positive values indicated a greater deficit in executive functioning in individuals diagnosed with NF1 compared to community samples.

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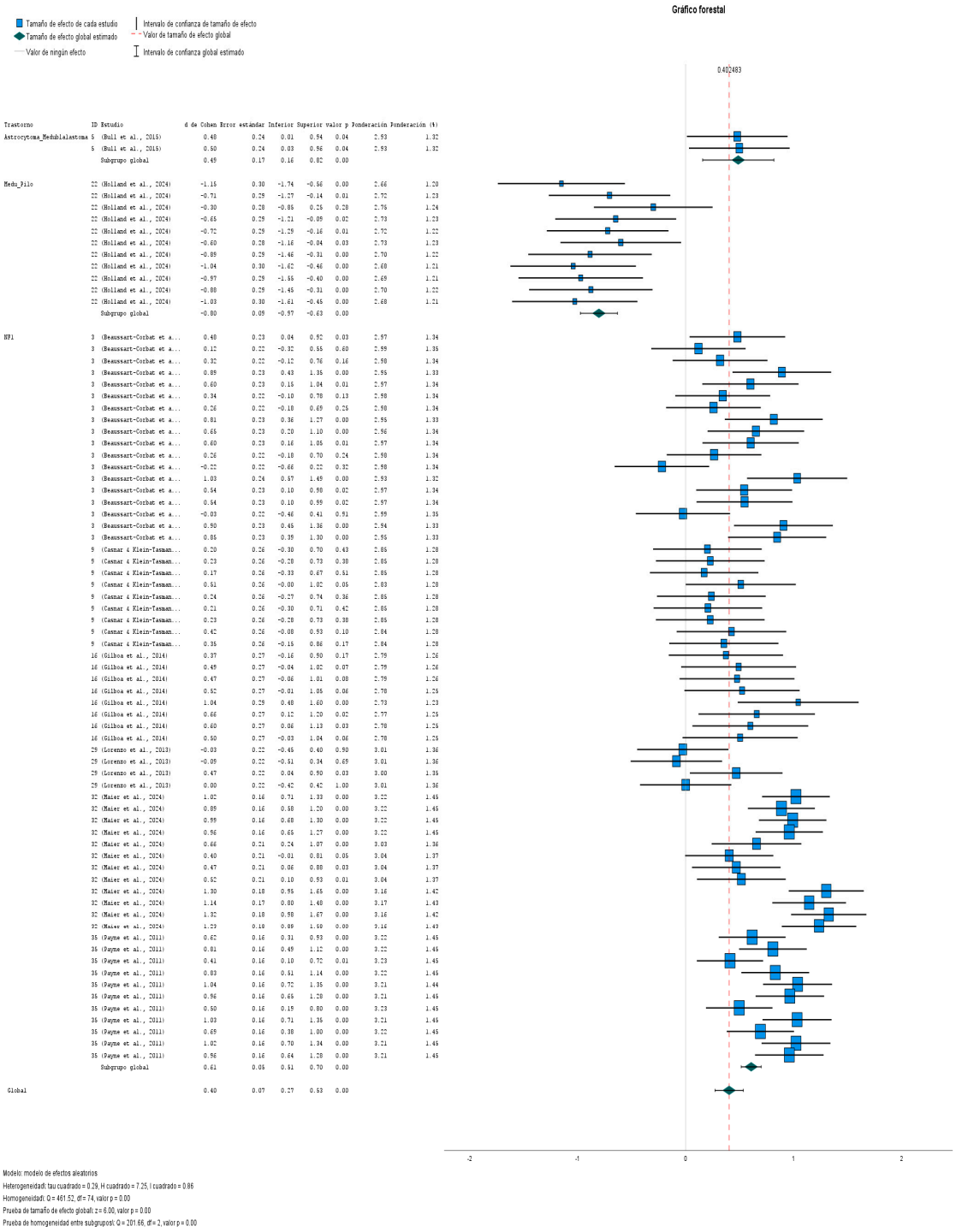

Figure 2. Forest plot (clinical scales and indices) based on the type of alteration.

In this study, the effect sizes of 75 studies (from 8 articles) were integrated using the standardized mean difference as the effect size index (Cohen's d).

At the bottom of the forest plot, the average effect size and its 95% confidence interval are shown. (d = 0.40; IC 95% = 0.27– 0.53).

With a Cohen's d of 0.40, according to Cohen's (1988) guidelines, this effect size reflects a medium relevance.

The homogeneity statistic reached statistical significance Q (74) = 461,52, p = .000.

The I^2 index was of high magnitude, I^2 = 86% (which is considered substantial heterogeneity), and the between-study variance reached the value $\tau 2 = 0.29$ ($\tau = 0.53$).

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Global Effect Size Test

The global effect size test (z = 5.996, p = 0.01) is below 0.05. There are statistically significant differences in executive functioning between patients with NF1, Astrocytoma_Medulloblastoma, Medulloblastoma_Pilocyticastrocytoma, and the community sample, with a clear trend of executive deficits toward the sample of participants with brain tumors.

Inverted Funnel

It shows an absence of asymmetry, so we can say that publication bias is not a threat to the validity of the results of this meta-analysis. The disaggregated data are presented because the different disorders do not have the same number of studies (Figure 3).

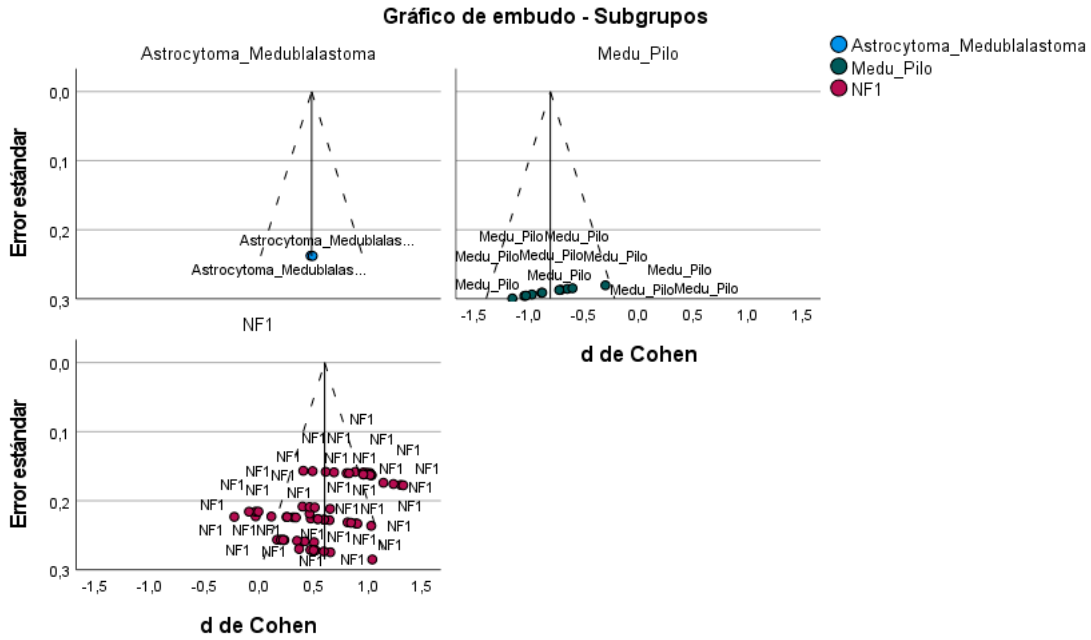

Figure 3. Funnel plot of all studies (based on the different disorders).

4. Results

The model proposed in the study shows moderate executive deficits overall when compared to the community sample (d = 0.402; p = 0.001; 95% CI 0.271 – 0.534). An analysis of the different clinical scales and indices reveals that significant executive deficits vary depending on the type of disorder: (I) Moderately significant when compared to the community sample in: (i) NF1 (d = 0.606; p = 0.000; 95% CI 0.513 – 0.699); (ii) Astrocytoma-Medulloblastoma (d = 0.486; p = 0.004; 95% CI 0.157 – 0.816). (II) Significantly high when compared to the community sample in Medulloblastoma_Pilocyticastrocytoma (d = -0.803; p = 0.000; 95% CI 0.974 – 0.631).

The interpretation of these results indicates that, overall, the model shows moderate executive deficits when compared to the community sample, with an effect size of 0.402, suggesting a significant difference, but not extremely high.

When analyzing the different groups, moderately significant executive deficits are observed in two specific conditions: (i) NF1: Shows an effect size of 0.606, with a $p < 0.001$, indicating a moderate impact on executive functions compared to the community sample; (ii) Astrocytoma-Medulloblastoma: Has an effect size of 0.486 and a p = 0.004, also suggesting moderate deficits, but less pronounced than in NF1.

On the other hand, significantly high executive deficits were found in the Medulloblastoma_Pilocyticastrocytoma group, with an effect size of -0.803 ($p < 0.001$). This indicates

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a substantially larger difference compared to the community sample, reflecting greater impairment in executive functions in this specific group.

In conclusion, although all groups show executive deficits to varying degrees, the impact is strongest in patients with Medulloblastoma_Pilocyticastrocytoma, while deficits in NF1 and Astrocytoma_Medulloblastoma are moderate.

Regarding the heterogeneity of the studies for NF1 ($\chi^2 61 = 197.452$; $p = 0.001$), the results are significant, indicating that the included studies have heterogeneous results. For the other disorders, Astrocytoma_Medulloblastoma ($\chi^2 1 = 0.003$; $p = 0.955$) and Medulloblastoma_Pilocyticastrocytoma ($\chi^2 10 = 7.247$; $p = 0.702$), the results are not significant, indicating homogeneity.

Globally ($\chi^2 74 = 461.523$; $p = 0.000$), the results are significant, showing that the included studies have heterogeneous results.

The model shows moderate executive deficits globally when compared to the community sample ($d = 0.402$; $p = 0.001$; 95% CI 0.271 – 0.534).

5. Conclusions

Our review and meta-analysis revealed that executive function impairments, assessed using BRIEF, were present in patients with various brain tumors analyzed.

Executive deficits were associated with high and moderately significant deficits across all related disorders. These results align with findings from other studies: (i) Individuals with NF1 often exhibit deficits in executive functions, including working memory, inhibitory control, cognitive flexibility, and planning. These deficits are typically accompanied by difficulties in attention, language, and visuospatial skills (Roy et al. 2021) (Glad et al. 2020) (Torres Nupan et al. 2017) (Law et al. 2017); (ii) Research indicates that pediatric survivors of pilocytic astrocytoma face significant challenges in executive functioning (Rønning et al. 2005) (Holland et al. 2024); (iii) Pediatric survivors of medulloblastoma often experience neurocognitive dysfunction, with a significant proportion presenting deficits in executive function. These deficits are associated with a reduction in white matter integrity in the brain, particularly affecting tasks related to attention shifting and cognitive flexibility (Brinkman et al. 2012) (Glass et al. 2017); (iv) Children treated for pilocytic astrocytoma often experience significant challenges in executive function. These include difficulties with sustained attention, processing speed, verbal intelligence, visuospatial memory, and naming, particularly in those with infratentorial tumors. Supratentorial hemisphere tumors are associated with additional problems in selective attention and executive function (Aarsen et al. 2009).

Only studies that used BRIEF in its different versions to assess executive function in survivors of brain tumors were included, making this, to our knowledge, the first review and meta-analysis focused on studies using a single instrument. Our reason for including only BRIEF studies was to allow for an ecological evaluation of executive functions, ensuring homogeneity among the studies. The magnitude of the executive deficits recorded in this research is, in general terms, in line with previously observed results. (Beaussart-Corbat et al. 2021).

Limitations

One limitation of the present review and meta-analysis is the lack of evaluation of the association between executive function and its impact on quality of life. The importance of considering this association was highlighted in a meta-analysis (Beaussart-Corbat et al. 2021).

6. Conclusions

Executive deficits are observed in individuals with brain tumors and/or survivors of brain tumors. These deficits can have a significant impact on the academic, social, and emotional life of individuals with various brain tumors, highlighting the importance of their evaluation. Early identification and educational and neuropsychological support are key to preventing these deficits from significantly interfering with their academic, personal, and professional functioning.

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Data Availability Statement: Sample and Syntax of the meta-analysis.

Conflicts of Interest: I am the co-author of the BRIEF-P adaptation and receive royalties as compensation.

Abbreviations

The following abbreviations are used in this manuscript:

ADHD-U	Attention Deficit Hyperactivity Disorder, Unmedicated
ALL	Acute Lymphoblastic Leukemia
BT	Brain Tumor
EPI	Epilepsy
H	Man
MCI	Mild Cognitive Impairment
NF1	Neurofibromatosis Type 1
OTC-D	Ornithine Transcarbamylase Deficiency
PA	Pilocytic astrocytoma
PBT	Pediatric Brain Tumors
STCP	Pediatric Brain Tumor Survivor
TBI	Traumatic Brain Injury
TCP	Primary Brain Tumors

Appendix A

Appendix A.1

Table A1. Effect size estimates for individual studies.

	ID	Effect size	Standard Error	Z	Sig. (two-tailed)	95% Confidence Interval		Weighting	Weighting (%)
						Inferior	Superior		
Astrocytoma_Medublalastoma	5	.477	.2376	2.007	.045	.011	.943	2.924	1.3
	5	.496	.2378	2.085	.037	.030	.962	2.923	1.3
Medulloblastoma_Pilocyticastrocytoma	22	-1.150	.2993	-3.844	<.001	-1.737	-.564	2.666	1.2
	22	-.705	.2867	-2.459	.014	-1.267	-.143	2.719	1.2
	22	-.300	.2803	-1.070	.284	-.849	.249	2.746	1.2
	22	-.648	.2855	-2.269	.023	-1.207	-.088	2.724	1.2
	22	-.722	.2871	-2.515	.012	-1.285	-.159	2.718	1.2
	22	-.601	.2846	-2.111	.035	-1.159	-.043	2.728	1.2
	22	-.885	.2912	-3.041	.002	-1.456	-.315	2.701	1.2
	22	-1.042	.2957	-3.522	<.001	-1.621	-.462	2.681	1.2
	22	-.972	.2936	-3.310	<.001	-1.547	-.396	2.690	1.2
	22	-.878	.2910	-3.017	.003	-1.448	-.308	2.701	1.2
	22	-1.027	.2953	-3.477	<.001	-1.605	-.448	2.683	1.2
NF1	3	.478	.2256	2.120	.034	.036	.920	2.973	1.3
	3	.118	.2227	.531	.596	-.318	.555	2.984	1.3
	3	.318	.2239	1.420	.156	-.121	.757	2.979	1.3

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	3	.890	.2328	3.823	<.001	.434	1.346	2.944	1.3
	3	.599	.2273	2.636	.008	.154	1.044	2.966	1.3
	3	.343	.2241	1.528	.126	-.097	.782	2.978	1.3
	3	.257	.2234	1.149	.251	-.181	.695	2.981	1.3
	3	.815	.2312	3.525	<.001	.362	1.268	2.950	1.3
	3	.649	.2281	2.848	.004	.202	1.096	2.963	1.3
	3	.601	.2273	2.644	.008	.156	1.047	2.966	1.3
	3	.263	.2235	1.175	.240	-.175	.701	2.981	1.3
	3	-.220	.2232	-.987	.324	-.658	.217	2.982	1.3
	3	1.031	.2362	4.366	<.001	.568	1.494	2.930	1.3
	3	.541	.2264	2.389	.017	.097	.985	2.969	1.3
	3	.544	.2264	2.404	.016	.101	.988	2.969	1.3
	3	-.025	.2226	-.113	.910	-.461	.411	2.985	1.3
	3	.904	.2331	3.879	<.001	.447	1.361	2.942	1.3
	3	.846	.2318	3.649	<.001	.392	1.300	2.948	1.3
	9	.201	.2565	.783	.433	-.302	.704	2.846	1.3
	9	.228	.2567	.887	.375	-.276	.731	2.846	1.3
	9	.170	.2564	.665	.506	-.332	.673	2.847	1.3
	9	.509	.2599	1.960	.050	-6.469E-5	1.019	2.832	1.3
	9	.237	.2568	.924	.355	-.266	.741	2.845	1.3
	9	.205	.2566	.800	.424	-.298	.708	2.846	1.3
	9	.227	.2567	.884	.377	-.276	.730	2.846	1.3
	9	.423	.2587	1.637	.102	-.084	.930	2.837	1.3
	9	.353	.2578	1.369	.171	-.152	.858	2.841	1.3
	16	.372	.2697	1.379	.168	-.157	.901	2.791	1.3
	16	.489	.2714	1.804	.071	-.042	1.021	2.784	1.3
	16	.475	.2712	1.752	.080	-.056	1.006	2.785	1.3
	16	.521	.2719	1.918	.055	-.012	1.054	2.782	1.3
	16	1.041	.2850	3.653	<.001	.483	1.600	2.727	1.2
	16	.657	.2745	2.394	.017	.119	1.195	2.771	1.2
	16	.598	.2733	2.188	.029	.062	1.134	2.776	1.3
	16	.504	.2716	1.854	.064	-.029	1.036	2.783	1.3
	29	-.027	.2157	-.124	.901	-.449	.396	3.012	1.4
	29	-.086	.2158	-.400	.689	-.509	.337	3.011	1.4
	29	.467	.2186	2.138	.032	.039	.896	3.000	1.4
	29	.000	.2157	.000	1.000	-.423	.423	3.012	1.4
	32	1.020	.1598	6.385	<.001	.707	1.333	3.215	1.4
	32	.886	.1581	5.599	<.001	.576	1.195	3.220	1.5
	32	.990	.1594	6.211	<.001	.678	1.302	3.216	1.4
	32	.958	.1590	6.025	<.001	.646	1.270	3.217	1.5

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	32	.655	.2117	3.095	.002	.240	1.070	3.027	1.4
	32	.403	.2084	1.933	.053	-.006	.811	3.040	1.4
	32	.468	.2091	2.239	.025	.058	.878	3.037	1.4
	32	.515	.2097	2.457	.014	.104	.926	3.035	1.4
	32	1.301	.1771	7.347	<.001	.954	1.648	3.156	1.4
	32	1.142	.1739	6.569	<.001	.802	1.483	3.167	1.4
	32	1.324	.1775	7.456	<.001	.976	1.672	3.154	1.4
	32	1.234	.1757	7.024	<.001	.890	1.578	3.161	1.4
	35	.615	.1581	3.892	<.001	.305	.925	3.221	1.5
	35	.807	.1600	5.042	<.001	.493	1.120	3.214	1.4
	35	.410	.1566	2.618	.009	.103	.717	3.225	1.5
	35	.829	.1602	5.173	<.001	.515	1.143	3.213	1.4
	35	1.035	.1629	6.356	<.001	.716	1.355	3.205	1.4
	35	.964	.1619	5.951	<.001	.646	1.281	3.208	1.4
	35	.495	.1571	3.152	.002	.187	.803	3.224	1.5
	35	1.031	.1628	6.329	<.001	.712	1.350	3.205	1.4
	35	.691	.1588	4.353	<.001	.380	1.002	3.218	1.5
	35	1.021	.1627	6.274	<.001	.702	1.340	3.205	1.4
	35	.959	.1618	5.923	<.001	.641	1.276	3.208	1.4

Appendix A.2

Table A2. Effect size estimates for cumulative analysis by subgroup.

						95% Confidence Interval		
	ID	Effect size	Standard Error	Z	Sig. (two-tailed)	Lower	Upper	Scalea
Astrocytoma_Medublalastoma	5	.477	.2376	2.007	.045	.011	.943	EF_Global
	5	.486	.1681	2.894	.004	.157	.816	EF_Global
Medulloblastoma_Pilocyticastrocytoma	22	-.705	.2867	-2.459	.014	-1.267	-.143	Emotional Control
	22	-.498	.2025	-2.460	.014	-.895	-.101	Flexibility
	22	-.670	.2104	-3.182	.001	-1.082	-.257	EF_Global
	22	-.742	.1686	-4.403	<.001	-1.073	-.412	Index Emerging Metacognition
	22	-.767	.1347	-5.696	<.001	-1.031	-.503	Behavioral Regulation Index
	22	-.828	.1274	-6.504	<.001	-1.078	-.579	Inhibition
	22	-.857	.1129	-7.591	<.001	-1.079	-.636	Initiative
	22	-.830	.1028	-8.070	<.001	-1.031	-.628	Working Memory
	22	-.836	.0969	-8.622	.000	-1.026	-.646	Monitoring
	22	-.811	.0918	-8.843	.000	-.991	-.632	Organization of Materials

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	22	-.803	.0874	-9.189	.000	-.974	-.632	Planificacion / Organizació
NF1	35	1.031	.1628	6.329	<.001	.712	1.350	Auto Monitoring
	3	.587	.4560	1.287	.198	-.307	1.481	Emotional Control
	16	.565	.2791	2.026	.043	.018	1.112	Emotional Control
	3	.494	.2166	2.281	.023	.070	.919	Emotional Control
	35	.480	.1670	2.873	.004	.152	.807	Emotional Control
	9	.445	.1468	3.031	.002	.157	.733	Emotional Control
	3	.430	.1281	3.359	<.001	.179	.681	Flexibility
	3	.346	.1358	2.547	.011	.080	.612	Flexibility
	35	.404	.1297	3.110	.002	.149	.658	Flexibility
	16	.412	.1187	3.467	<.001	.179	.644	Flexibility
	9	.393	.1111	3.538	<.001	.175	.611	Flexibility
	3	.407	.1027	3.964	<.001	.206	.608	Inhibitory Self-Control Index
	3	.404	.0954	4.233	<.001	.217	.591	Inhibitory Self-Control Index
	9	.392	.0907	4.328	<.001	.215	.570	Inhibitory Self-Control Index
	29	.363	.0892	4.070	<.001	.188	.538	Inhibitory Self-Control Index
	35	.405	.0918	4.407	<.001	.225	.584	EF_Global
	29	.380	.0897	4.237	<.001	.204	.556	EF_Global
	29	.353	.0886	3.986	<.001	.180	.527	Flexibility Index
	3	.349	.0845	4.135	<.001	.184	.515	Flexibility Index
	9	.345	.0811	4.247	<.001	.186	.504	Flexibility Index
	3	.327	.0794	4.120	<.001	.171	.483	Flexibility Index
	3	.342	.0770	4.435	<.001	.191	.493	EF_Global
	3	.362	.0763	4.748	<.001	.213	.512	EF_Global
	9	.363	.0736	4.924	<.001	.218	.507	EF_Global
	35	.392	.0758	5.171	<.001	.243	.540	Metacognition Index
	32	.425	.0800	5.318	<.001	.269	.582	Metacognition Index
	32	.429	.0771	5.570	<.001	.278	.581	Metacognition Index
	9	.430	.0747	5.752	<.001	.283	.576	Index Emerging Metacognition
	3	.443	.0732	6.047	<.001	.299	.586	Index Emerging Metacognition
	3	.458	.0722	6.336	<.001	.316	.599	Index Emerging Metacognition
	29	.458	.0700	6.553	<.001	.321	.596	Index Emerging Metacognition
	35	.467	.0679	6.885	<.001	.334	.600	Behavioral Regulation Index

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32	.484	.0675	7.177	<.001	.352	.617	Metacognition Index
16	.482	.0659	7.312	<.001	.353	.611	Inhibition
9	.475	.0647	7.341	<.001	.348	.602	Inhibition
35	.480	.0628	7.651	<.001	.357	.603	Inhibition
3	.481	.0612	7.859	<.001	.361	.601	Inhibition
3	.484	.0597	8.112	<.001	.367	.601	Inhibition
16	.486	.0585	8.306	.000	.371	.600	Initiative
35	.496	.0575	8.621	.000	.383	.609	Initiative
3	.505	.0568	8.889	.000	.394	.616	Working Memory
16	.515	.0565	9.111	.000	.404	.626	Working Memory
32	.529	.0565	9.350	.000	.418	.639	Working Memory
32	.532	.0553	9.619	.000	.423	.640	Working Memory
9	.532	.0543	9.802	.000	.425	.638	Working Memory
35	.544	.0542	10.034	.000	.438	.651	Working Memory
3	.554	.0539	10.268	.000	.448	.660	Working Memory
32	.570	.0552	10.316	.000	.462	.678	Working Memory
16	.569	.0543	10.475	.000	.463	.676	Monitoring
32	.579	.0539	10.747	.000	.473	.684	Monitoring
32	.577	.0529	10.915	.000	.473	.681	Monitoring
32	.592	.0539	10.973	.000	.486	.697	Monitoring
16	.592	.0531	11.156	.000	.488	.696	Organization of Materials
35	.590	.0520	11.354	.000	.488	.692	Organization of Materials
3	.591	.0511	11.563	.000	.491	.691	Planning/Organization
16	.592	.0504	11.760	.000	.493	.691	Planning/Organization
9	.587	.0499	11.754	.000	.489	.685	Planning/Organization
3	.586	.0491	11.938	.000	.490	.683	Planning/Organization
32	.592	.0485	12.227	.000	.497	.687	Planning/Organization
32	.589	.0478	12.339	.000	.496	.683	Planning/Organization
32	.599	.0479	12.516	.000	.505	.693	Planning/Organization
35	.606	.0474	12.783	.000	.513	.699	Planning/Organization

a. Accumulated analysis based on the variable classified in ascending order for each subgroup

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