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CRITICAL REVIEW

Systematic Review and Meta-analysis of Executive Functions in Preschool and School-Age Children With Neurofibromatosis Type 1

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Abstract

Objectives: Neurofibromatosis type 1 (NF1) is a genetic disorder in which the most frequent complication in children is learning disabilities. Over the past decade, growing arguments support the idea that executive dysfunction is a core deficit in children with NF1. However, some data remain inconsistent. The aim of this study was to determine the magnitude of impairment for each executive function (EF) and clarify the impact of methodological choices and participant's characteristics on EFs. **Methods:** In this meta-analysis, 19 studies met the selection criteria and were included with data from a total of 805 children with NF1 and 667 controls. Based on the Diamond's model (2013), EF measures were coded separately according to the following EF components: working memory, inhibitory control, cognitive flexibility, planning/problem solving. The review protocol was registered with PROSPERO (International prospective register of systematic reviews; CRD42017068808). **Results:** A significant executive dysfunction in children with NF1 is demonstrated. Subgroup analysis showed that the impairment varied as a function of the specific component of executive functioning. The effect size for working memory and planning/problem solving was moderate whereas it was small for inhibitory control and cognitive flexibility. Executive dysfunction seems to be greater with increasing age whereas assessment tool type, intellectual performance, attention deficit hyperactivity disorder and control group composition did not seem to affect EF results. **Conclusions:** EF deficits are a core feature in children with NF1 and an early identification of executive dysfunctions is essential to limit their impact on the quality of life. (*JINS*, 2018, *24*, 977–994)

Keywords: Neurodevelopmental disorders, Genetic disorders, Learning disabilities, Executive control, Frontal lobe, Behavior regulation

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a rare autosomal dominant genetic disorder, with a prevalence of 1 in 3000–4000 (National Institute of Neurological Disorders and Stroke, 2011). Diagnostic criteria for the disorder were established by the National Institutes of Health (NIH, 1988). A diagnosis of NF1 is made when two or more of the following criteria are met: a first degree relative with NF1, six or more cafe au lait patches, axillary or inguinal freckling, two or more neurofibromas or one plexiform neurofibroma, optic glioma, two or more Lisch nodules, or distinctive osseous lesions. Nonetheless, learning disabilities are the most frequent complication in children with NF1, varying from 30% to 65% (Cutting, Clements, Lightman, Yerby-Hammack, & Denckla, 2004).

Cognitive impairment has often been inconsistent, and a specific cognitive phenotype associated with NF1 remains unclear (Levine, Materek, Abel, O'Donnell, & Cutting, 2006). Most studies have shown a general intellectual functioning within the average range, although somewhat lower than children in normative samples or comparison groups (Lehtonen, Howie, Trump, & Huson, 2013). Cognitive disturbances in children with NF1 are heterogeneous and affect language, reading, spelling, mathematical skills, praxis and visuo-spatial

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abilities, memory, attention, and executive functions (EFs) (Cutting et al., 2004; Levine et al., 2006). Executive functioning refers to a superordinate capacity underlying goal-directed behavior, which is particularly important in novel or demanding situations (Shallice & Burgess, 1991; Stuss, 1992). It is usually considered to be mediated by the prefrontal cortex and its subcortical connections.

Over the past 10 years, an increasing body of evidence has suggested that executive dysfunction is a core deficit in children with NF1 (Plasschaert et al., 2016; Ribeiro, Violante, Bernardino, Edden, & Castelo-Branco, 2015; Roy et al., 2010, 2012, 2015). Thus, some cognitive impairments, which have been considered as a hallmark deficit of children with NF1, are reinterpreted in the light of executive dysfunction (Van Eylen et al., 2017). Table 1 shows an overview of studies investigating EF in children with NF1 and included in the meta-analysis.

Several questions emerge from this overview that we aim to study in this meta-analysis. The first objective of this study is to determine whether all aspects of executive functioning are impaired to a similar degree for each aspect of EFs. In fact, papers simultaneously studying all EFs remain scarce. Furthermore, a diversity of measures (tasks or questionnaires) is generally used to investigate EFs (see Table 1) and depending on the study considered, the same measurement may refer to different EFs. Indeed, studies are rarely theoretically guided, and, if so, the theoretical model used varies from one study to another. The first aim of this meta-analysis was thus to collect all published EF-related data and to combine the results with a statistical approach to enable the generalization of findings. This is all the more important as clinical sample sizes in studies are relatively small due to the scarcity of NF1. EF measures were coded separately according to Diamond's model of EFs (2013).

In this recent model, three core EFs are described: inhibitory control, working memory, and cognitive flexibility. Inhibitory control is the ability to control one's attention (interference control – selective or focused attention), thoughts (interference control – cognitive inhibition), or behavior (response inhibition – self-control and discipline). Working memory is defined as the ability to keep in mind information and mentally working with or updating it. Two types are distinguished: verbal working memory and visual-spatial working memory. Cognitive flexibility refers to the ability to switch between mental sets or strategies.

Diamond showed the specific development of each of the executive components and their increasingly complex relationships. Working memory and inhibitory control support one another and co-occur. They develop early but show a prolonged developmental progression. Cognitive flexibility builds on the other two and arises much later in development. These three core EFs underpin the establishment of "higher-level executive functions" such as reasoning, problem solving, and planning. In the current meta-analysis, we divided the analysis into four domains. We considered different sets of tasks that address aspects of one of the three domains (working memory, inhibitory control, cognitive flexibility) and the possibility that planning/problem-solving does not overlap with the other three. Indeed, the literature data and our clinical experience seem to indicate that this last domain does not subsume the first three factors.

The second aim was to ascertain whether executive dysfunction may be explained by methodological choices (control group composition, tool types used to assess EFs). First, the composition of the control group (community controls versus siblings) could influence the results of cognitive assessment. For example, a recent study by Lehtonen et al. (2015) revealed how a healthy control group may differ from a sibling group, although both are matched with the NF1 group by age and socio-economic status. Indeed, calculations of estimated marginal means in the analysis of variance (ANOVA) with IQ as a covariate revealed differences between the community comparisons and each of the other groups (sibling and NF1 groups), leading to the exclusion of the community group for this study. Finally, contrary to performance-based tests, a questionnaire is an ecological assessment based on child's behavior rating in daily life. Some studies have arrived at different conclusions depending on the tool used to investigate EFs (e.g., Lorenzo, Barton, Arnold, & North, 2013). Data collection from performance-based tests on the one hand, and from questionnaires on the other hand, will allow us to determine whether the results from the two tools assessing executive functioning in a complementary manner are similar.

The third question was whether the executive dysfunction may be explained by participants' selection criteria (age, IQ, neurological history, attention deficit hyperactivity disorder [ADHD]). First, we know that the rudiments of EF emerge before early childhood and continue to be reinforced significantly throughout childhood and adolescence (Best & Miller, 2010). Due to this extensive development window, it is reasonable to hypothesize that the developmental changes in children with NF1 do not follow the same curve as healthy children. Thus, differences between patients and children without NF1 may change with advancing age, especially as the structure of EF changes during its development (Lee, Bull, & Ho, 2013). Thereby, the very broad range of subject ages in some studies (e.g., Ferner, Hughes, & Weinman, 1996) can limit the accuracy of conclusions.

Second, considering IQ in inclusion criterion may induce a selection bias (Dennis et al., 2009). Indeed, while IQ monitoring provides a degree of certainty concerning the specificity of neuropsychological disorders in children with NF1, weaknesses in intellectual ability can be the result of cognitive function impairments, which are frequently observed in children with NF1 (Cutting, Koth, & Denckla, 2000). Thus, executive dysfunction could contribute to the weakening of IQ insofar as the relationship between these two components appears to be narrow for some authors (e.g., Diamond, 2013).

Third, neurological history co-occurrence such as prematurity, epilepsy, brain injury, tumors of the central nervous system also contribute to increase the risk of executive dysfunction because these medical contexts are characterized by probable dysexecutive functioning (Roy, 2015). Thus, results

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Table 1. Overview of studies included in the meta-analysis

Studies	Groups	Task	Assessed construct (as mentionned in the study)	Variables	Group differences
Chaix et al., 2018	NF1 = 75 Controls = 75	Corsi blocks	Visuospatial memory	Forward span	—
				Backward span	NF1 < C
		CPT II	Sustained attention	Omissions score	—
			Inhibition	Commissions score	—
Galasso et al., 2014	NF1 = 18 Controls = 18	TOL	Planning efficiency	Total score	NF1 < C
			Psychomotor speed	Total time	NF1 > C
Gilboa et al., 2014a	NF1 = 30 Controls = 30	ROCF	Cognitive planning	Copy score	NF1 < C
Gilboa et al., 2014b	NF1 = 29 Controls = 27 (with some siblings)	Key search test (BADS-C)	Planning of action and monitoring own performance	Standard score	NF1 < C
		Playing cards (BADS-C)	Flexibility and inhibition	Standard score	—
		Six parts (BADS-C)	Ability to distribute the execution of several tasks in a limited period of time	Standard score	—
		Water test (BADS-C)	Plan of action to solve a problem	Standard score	NF1 < C
		Zoo Map 1 (BADS-C)	Spontaneous planning	Standard score	—
		Zoo Map 2 (BADS-C)	Ability to follow a concrete imposed strategy	Standard score	—
		BRIEF	EF	8 scales	NF1 > C (Initiate; Working Memory; Plan/ Organise; Organisation of Materials)
Huijbregts et al., 2015	NF1 = 15 Controls = 18	BRIEF DEX	EF	GEC Total score	NF1 > C —
Lehtonen et al., 2015	NF1 = 49 Siblings = 19	Spatial Span Task	Working memory	Span length Total usage errors	— —
		Spatial Working Memory	Ability to retain spatial information in working memory, and to use this information to work towards a goal	Total errors Strategy	NF1 > Siblings —
		BRIEF	EF	8 scales + 3 indexes	NF1 > norms (8 scales + 3 indexes)
Loitfelder et al., 2015	NF1 = 14 Controls = 30	BRIEF DEX	EF	Total Behavior Cognition Emotion Total	NF1 > C NF1 > C NF1 > C NF1 > C NF1 > C

Table 1. (*Continued*)

Studies	Groups	Task	Assessed construct (as mentionned in the study)	Variables	Group differences
Lorenzo et al., 2011	NF1 = 33 Controls = 38	BRIEF-P	EF	3 indexes + GEC	—
Lorenzo et al., 2013	NF1 = 43	BRIEF-P	EF	3 indexes + GEC	—
	Controls = 43	Delay Alternation	Nonverbal working memory	Correct responses	—
				Correct alternations	—
				Maximum correct alternations	—
				Maximum perseverative errors	—
				Win-stay errors	—
				Lose-stay errors	—
		Shape School (A and B)	Response inhibition	Efficiency A and B	NF1 < C
		Verbal fluency (NEPSY)	Rapid word generation	Standard score	NF1 < C
		Visual attention (NEPSY)	Visual selective attention	Standard score	—
		TOH	Spatial planning/organization	Z score	—
Mazzocco et al., 1995	NF1 = 19 Siblings = 19	Digit span (WISC R)	Intellectual fonctionning	Standard score	NF1 < siblings
		WCST	Mental flexibility and perseverative response patterns	% perseverative response	—
				Number of categories	NF1 < siblings
		TOVA	Attention	Omissions	NF1 > siblings
				Commissions	—
				Mean reaction time	—
				Reaction time variability	—
		ROCF	Visuospatial	Copy score	—
		Word fluency	Language	Category	—
Payne et al., 2011	NF1 = 199 Siblings = 55	BRIEF	EF	8 scales + 2 indexes + GEC	NF1 > Siblings (8 scales + 2 indexes + GEC)
		CCT		Z score	—
		COWAT		Z score	NF1 < siblings
		Digit Span		Standard score	—
		Score ! (TEA-Ch)		Standard score	—
		Tower		Z score	—
		Sky search Score !(TEA-Ch)	Selective attention	Standard score	—
		Sky search Dual task (TEA-Ch)	Divided attention	Standard score	—

Table 1. (*Continued*)

Payne et al., 2012	NF1 = 49 without ADHD + 35 with ADHD Controls = 30	Spatial Working Memory	Working Memory	Between group-errors (total)	NF1 > C ; NF1 + ADHD > C
				Strategy score	—
		Stop Signal Task	Inhibition	Proportion of successful stops	—
				Mean go reaction time	—
				Direction errors	—
				SSRT	NF1 > C ; NF1 + ADHD > C
Plasschaert et al., 2016	NF1 = 42 Controls = 52 ASD = 52	BRIEF	EF	Total score + 4 scales: inhibition, shift, working memory, plan/ organize	NF1 > C[a] NF1 < ASD[a] (except working memory)
		Design fluency	Spatial working memory	Correct responses condition 1	NF1 < C
		Flanker	Inhibition	Inhibition cost reaction time	NF1 > C[a]
				Inhibition cost error %	—
		Go/No-Go	Inhibition	% No-go errors	NF1 > C
		Spatial Span (WNV-NL)	Spatial working memory	Correct trials	NF1 < C[a] ; NF1 < ASD
		Spatial working memory (CANTAB)	Spatial working memory	Total errors	NF1 > C
		Switch task	Cognitive flexibility	Switch cost reaction time	—
				Switch cost error %	—
		Tower (D-KEFS)	Planning	Move accuracy ratio	NF1 > C[a]
		Use of objects	Generativity	Number of correct responses	NF1 < C[a]
		WCST-WCTS	Cognitive flexibility	Switch cost reaction time Perseverative errors	NF1 > C[a]
Pride et al., 2010	NF1 = 46 Controls = 30	BRIEF	EF	8 scales + 2 indexes + GEC	NF1 > C (Shift, Emotional Control, Monitor, BRI Index, GEC)
Remigereau et al., 2017	NF1 = 18 Controls = 20	ROCF	Planning ability	Planning Index	NF1 > C
		Stroop	Inhibition	Stroop effect (time)	—
		Verbal fluency	Flexibility and generation of ideas	Number of words	—
		BRIEF	EF	2 indexes + GEC	NF1 > norms (MI index)
Riva et al., 2017	NF1 = 16 Controls = 16 Siblings = 16	Key search test (BADS-C)	EF	Standard score	NF1 < C
		Playing cards (BADS-C)		Standard score	—
		Six parts (BADS-C)		Standard score	—
		Water test (BADS-C)		Standard score	—
		Zoo Map 1 and 2 (BADS-C)		Standard score	—

Table 1. (*Continued*)

Studies	Groups	Task	Assessed construct (as mentionned in the study)	Variables	Group differences
Roy et al., 2010	NF1 = 22 without ADHD + 14 with ADHD Controls = 36	Labyrinthes (WISC III)	Planning	Errors	NF1 > C ; NF1 + ADHD > C
		ROCF		Formulation	NF1 < C ; NF1 + ADHD < C
				Execution	NF1 + ADHD < C
		Tower (NEPSY)		Moves number	NF1 + ADHD > C ; NF1 + ADHD > NF1
				Broken rules	NF1 > C ; NF1 + ADHD > C
Roy et al., 2012	NF1 = 30 Controls = 60	Brixton	Reactive flexibility	Total score	NF1 < C[a]
		MCST	Reactive flexibility	Correct responses	NF1 < C[a]
		Design fluency	Spontaneous flexibility	Number of designs	—
		Word fluency	Spontaneous flexibility	Number of words	—
Ullrich et al., 2010	NF1 = 10 Siblings = 6	Arena Mazes	Spatial learning	Path length	—
				Latency	—
				Dwell time	NF1 < Siblings
		Spatial working memory (CANTAB)	Working memory problems	Errors	NF1 > normes
		BRIEF	EF	2 indexes + GEC	NF1 > siblings (MI index, GEC)

CPT II = Continuous Performance Test; TOL = Tower of London; ROCF = Rey-Osterrieth Complex Figure; BADS-C = Behavioral Assessment of the Dysexecutive Syndrome in Children; BRIEF = Behavior Rating Inventory of Executive Functioning; EF = executive function; DEX = Dysexecutive Questionnaire; GEC = Global Executive Composite; BRIEF-P = Behavior Rating Inventory of Executive Function – Preschool; NEPSY = Developmental Neuropsychological Assessment; WISC = Wechsler Intelligence Scale for Children; TOH = Tower of Hanoi; WCST = Wisconsin Card Sorting Test; TOVA = Test of Variables of Attention; CCT = Children's Category Test; COWAT = Controlled Oral Word Association Test; TEA-Ch = Test of Everyday Attention for Children; ADHD = attention deficit and hyperactivity disorder; SSRT = Stop Signal Reaction Time; ASD = autism spectrum disorder; WNV-NL = Wechsler Nonverbal Scale of Ability—Dutch version; CANTAB = Cambridge Neuropsychological Test Automated Battery; D-KEFS = Delis–Kaplan Executive Function System; WCST-WCTS = Wisconsin Card Sorting Test with Controlled Task Switching; BRI = Behavioral Regulation Index; MI = Metacognitive Index; MCST = Modified Card-Sorting Test.
[a]Group differences remains after IQ as covariable.

concerning EF in some studies should be considered with caution because neurological history co-occurrence is not always considered in exclusion criteria or is not specified in the study methodology (e.g., Bluschke, Von der Hagen, Papenhagen, Roessner, & Beste, 2017a; Casnar & Klein-Tasman, 2016; Rowbotham, Pit-Ten Cate, Sonuga-Barke, & Huijbregts, 2009).

Fourth, the prevalence of ADHD in children with NF1 has been estimated at approximately 30–50% (Pride, Payne, & North, 2012). ADHD is more generally associated with executive dysfunction. It is accepted that difficulties in EFs are components of a complex cluster of underlying impairments that result in ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). Nevertheless, several studies in children with NF1 have shown that executive dysfunction is only partially related to ADHD (Hyman, Shores, & North, 2005; Galasso et al., 2014; Pride et al., 2012; Roy et al., 2010, 2012), although a few studies indicated some poorer EF scores in children with NF1 and ADHD than in children with NF1 only (Pride et al., 2012; Roy et al., 2010).

In summary, in view of the heterogeneity of results between studies and diversity of methodological choices that can explain them, the aim of this meta-analysis, based on the recent Diamond model of EFs (2013), was (1) to specify the degree of impairment for each aspect of EFs namely: working memory, inhibitory control, cognitive flexbility, and planning/problem solving; (2) to investigate the impact of methodological choices: assessment tool format (questionnaire versus performance-based test) and control group composition (percentage of siblings in the control group) on EF performance; and (3) to analyze the impact of participant characteristics (age, intellectual abilities, percentage of ADHD). The theoretical and clinical implications of the results are important. From a theoretical standpoint, these findings will clarify our knowledge of executive dysfunction in children with NF1 and answer the current debate around the independence of EF impairment from other cognitive characteristics. From a clinical standpoint, these findings will serve to guide neuropsychological assessments and rehabilitative interventions.

METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Shamseer et al., 2015) and Gates and March's (2016) recommendations were followed to conduct this study.

Eligibility Criteria

To be eligible for the current meta-analysis, studies had to fulfill seven criteria: (1) patients included were all diagnosed with NF1 according to the National Institutes of Health Diagnostic Criteria (NIH, 1988), (2) participants were aged between 2 and 18 years, (3) patients with NF1 were compared to a control group matched at least by age and gender, (4) patients had no neurological history other than NF1, (5) at least one neuropsychological task or questionnaire was used to assess EFs, (6) data reported were sufficient to calculate the effect size (ES), and (7) the study was published in English.

Search Strategy and Data Extraction

The literature search was conducted in May 2017 on four computerised databases (Pubmed, Scopus, PsycARTICLES and Cochrane Library). The following combinaison of keywords was used: ("neurofibromatosis type 1") and ("children" or "preschooler" or "toddler") and ("executive", "neuropsychology", "neurocognitive", or "cognitive"). The reference sections of publications found through our search were checked to identify missing studies. When data were missing in studies, the authors were contacted to collect them.

Initial searches were carried out by two authors (M.L.B. and A.R.) who screened search results for initial eligibility based on titles and abstracts according to the inclusion criteria. The potentially eligible studies were further assessed using the full text. Nine authors were contacted to obtain further information or missing data. Six responded favorably to this request. All selected studies were conducted in accordance with the Helsinki Declaration and/or approved by an institutional review board.

From each study, the following data were extracted for each group: number of participants (sample size was extracted for each task) and age (mean and standard deviation). When data were available, the full-scale IQ (FSIQ) (mean and standard deviation [SD]), percentage of ADHD in NF1 group and the composition of the control group (percentage of siblings within control group) were also extracted.

We coded EF measures separately when assessing one of the following EF components: working memory, inhibitory control, cognitive flexibility, and planning/problem solving. For each test, we selected one variable as a most appropriate measure of EF. This coding, which was intended to be the least arbitrary possible, was guided by literature data and our clinical experience with children. Table 2 summarizes executive tasks and related variables used in the current meta-analysis.

Mean and standard deviation were extracted for each group (NF1 and control). When studies reported results on different NF1 groups compared to the same control group, we averaged means and *SD*s across subgroups of patients. This was the case for Payne, Arnold, Pride, and North (2012), who examined the impact of ADHD on the cognitive functioning of children with NF1 by comparing two NF1 subgroups (with and without ADHD) to a group of unaffected controls. When many control groups (siblings and community group) were reported in a study (e.g., Lehtonen et al., 2015; Riva et al., 2017), the control groups were combined following established statistical procedures (Higgins, Thompson, Deeks, & Altman, 2003).

Data Analysis

Data analysis was carried out with Comprehensive Meta-Analysis software suite version 3 (Biostat, Englewood, NJ).

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Table 2. Executive function tasks and outcome measures used in the meta-analysis

EF tasks	*k*	Outcome measure	EF tested, based on Diamond's model (2013)
Digit Span	2	Standard score	Verbal working memory
Spatial working memory	3	Total errors[a]	Visual-Spatial Working Memory
Spatial Span	3	Correct trials; span length	
Delay Alternation	1	Correct responses (*Z*-score)	
Stroop	1	Stroop effect time (time "interference situation" minus time "Naming situation")[a]	Inhibitory control: interference control (cognitive inhibition)
Shape School	1	Condition B efficiency (*Z*-score)	
Flanker	1	Inhibition cost error % (error % incompatible trials minus error % compatible trials)[a]	Inhibitory control: interference control (selective or focused attention)
Visual Attention (NEPSY)	1	Standard score	
Sky Search (TEA-Ch)	1	Standard score	
Score! (TEA-Ch)	1	Standard score	
CPT II	1	Commissions score	
Go/No-Go	1	% no-go errors[a]	Inhibitory control: response inhibition (self-control and discipline)
Stop Signal Task	1	Proportion of successful stops	
Verbal fluency	4	Number of correct words; Correct words (z score)	Cognitive flexibility
WCST-WCTS	1	Perseverative errors[a]	
MCST	1	Number of correct responses	
Switch task	1	Switch cost error % (switch trial error % minus maintain trial error %)[a]	
Uses of objects	1	Number of correct responses	
Design fluency	2	Number of correct and unique designs	
Playing cards	2	Standard score	
Brixton	1	Total score	
CCT	1	Number of errors (*Z*-score)	
Tower of London	3	Total score; mean number of moves[a]; standard score (z score)	Planning/ problem solving
Tower of Hanoi	2	Move accuracy ratio (actual number of moves divided by the number of minimally required moves)[a]; score based on number of trials required for solution (*Z*-score)	
Water test (BADS-C)	2	Standard score	
Key Search (BADS-C)	2	Standard score	
Zoo map 1 (BADS-C)	2	Standard score	
Six Parts (BADS-C)	2	Standard score	
Mazes	1	Total errors[a]	
ROCF	3	Copy score or planning index[a]	
Arena Mazes	1	Path length[a]	
BRIEF	6	GEC[a]	EF
BRIEF-P	2	GEC[a]	
DEX	2	Total[a]	

EF = executive functions; *k* = number of samples; TEA-Ch = Test of Everyday Attention for Children; CPT II = Continuous Performance Test; WCST-WCTS = Wisconsin Card Sorting Test with Controlled Task Switching; MCST = Modified Card-Sorting Test; CCT = Children's Category Test; BADS-C = Behavioral Assessment of the Dysexecutive Syndrome in Children; ROCF = Rey-Osterrieth Complex Figure; BRIEF = Behavior Rating Inventory of Executive Functioning; BRIEF-P = Behavior Rating Inventory of Executive Function – Preschool; DEX = Dysexecutive Questionnaire.
[a]The sign of effect size was reversed.

We conducted a random-effects meta-analysis because it does not require the assumption of a common effect size (ES), allowing us to generalize beyond the studies (Borenstein & Higgins, 2013).

From the software, we obtained Hedge's *g* for the overall effect, which is less biased for small sample sizes (Borenstein, Hedges, Higgins, & Rothstein, 2009). The direction of ES was coded in such a way that a negative score reflects poorer performance for the children with NF1. The sign of ES had to be reversed for some variables (i.e., error and time variables) to avoid obtaining a positive g when children with NF1 made more mistakes or had a longer response time than the

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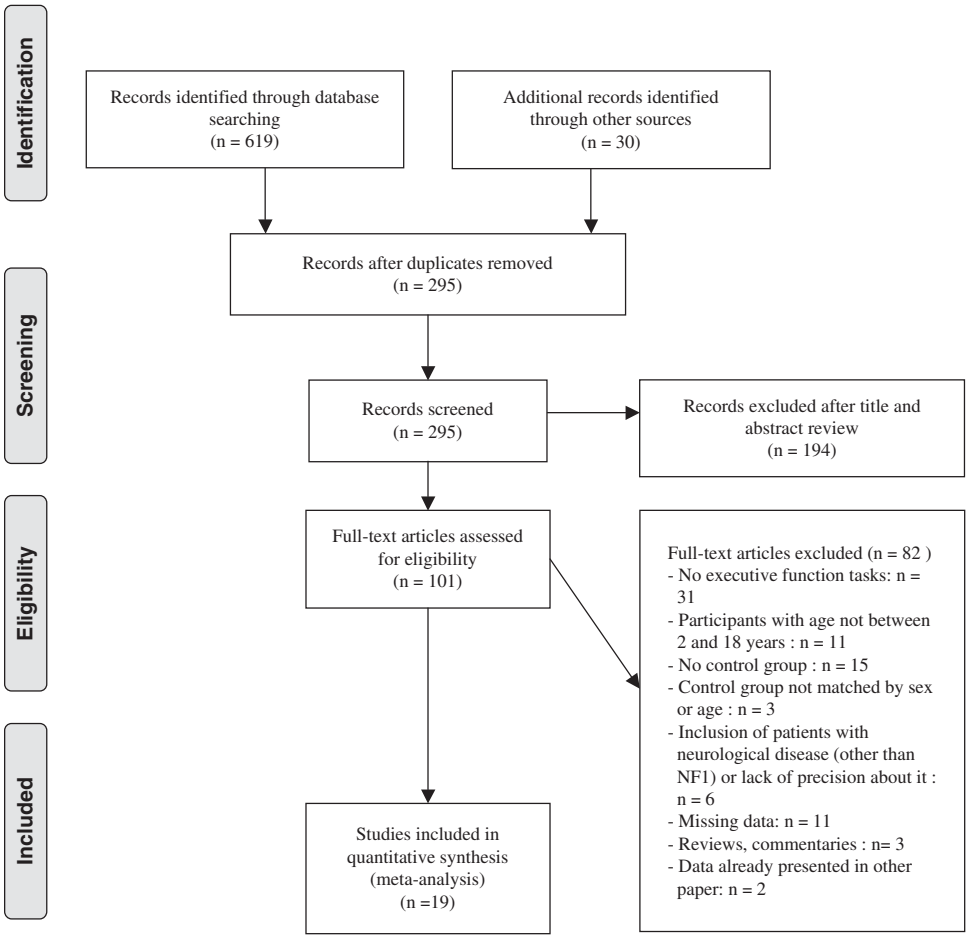

Fig. 1. Flow diagram of the study selection process.

control group (see Table 2). When several tasks were used to evaluate the same EF in a sample, the mean of EF scores was used to calculate one ES per sample.

We also obtained an heterogeneity statistic (Cochran's Q-test) for each ES. The alpha level was set at $p = .10$. If p-value was less than 0.10, we concluded that the heterogeneity observed between samples could not be exclusively due to within-sample error. We calculated I^2, which is a measure of true-effect variance to error variance (Borenstein, Higgins, Hedges, & Rothstein, 2017). An I^2 index around 25%, 50%, or 75% would mean, respectively, a low, moderate, or high heterogeneity (Higgins et al., 2003). We also calculated tau^2, which is an estimate of the variance of true effects (Borenstein et al., 2017). A meta-regression was performed, using the mixed-effects model when Q statistic indicated a significant between-sample heterogeneity. The aim of meta-regression analyses was to examine the influence of study characteristics (variable moderators) on ES. The R^2 index, which quantifies the proportion of variance explained by the covariate, was also reported.

To detect publication bias, the Fail-Safe Number (FSN) was calculated (Rosenberg, 2005). The FSN estimates the number of missing studies with null results we would need to include in the analysis before the p-value became non-significant ($p > .05$). The results of a meta-analysis can be considered robust if the FSN is greater than $5k + 10$, where k is the number of samples included in the analysis (Rosenthal, 1991). For the overall ES of EF, we used a funnel plot and Egger's test was used to test for funnel plot asymmetry because there were more than 10 studies (Sterne et al., 2011).

RESULTS

Study Selection

The literature search resulted in 19 studies that satisfied the selection criteria with data from a total of 805 NF1 and 667 controls. See Figure 1 for a flow diagram of studies' selection process. Sample characteristics are summarized in Table 3.

Overall Effect of EF

The overall effect of EF was moderate and statistically significant ($k = 19$; $g = –0.74$; 95% confidence interval [CI] [–0.95; –0.53]; $Z = –6.82$; $p < .0001$), suggesting an overall executive deficit in children with NF1 relative to controls. The Q-test, however, was significant ($Q(18) = 59.38$; $p < .0001$) and heterogeneity across studies was moderate ($I^2 = 69.99\%$; $tau^2 = 0.14$). The funnel plot revealed asymmetry (Figure 2);

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Table 3. Summary of samples characteristics selected in the meta-analysis.

	Neurofibromatosis type 1 group				Control group				
Studies	*N*	Patients with ADHD (%)	Mean age (*SD*)	Mean FSIQ (*SD*)	*N*	Mean age (*SD*)	Mean FSIQ (*SD*)	Test measurement to obtain the FSIQ	Siblings (%)	Number of EF tasks
Chaix et al., 2017	75	—	10 (1.3)	89.2 (12)	75	10 (1.2)	98.4 (15.1)	WISC-IV	—	2
Galasso et al., 2014	18	0	11 (2.87)	101.61 (12.19)	18	11.22 (2.8)	100.89 (8.66)	WISC-III	0	1
Gilboa et al., 2014a	30	—	12.25 (2.5)	—	30	12.33 (2.42)	—	—	—	1
Gilboa et al., 2014b	29	17.25	12.3 (2.6)	98.96 (12.77)	27	12.4 (2.5)	107.19 (12.08)	WISC-R95 (vocabulary + block design)	—	5
Huijbregts et al., 2015	15	40	12.9 (2.6)	—	18	13.8 (3.6)	—	—	—	2
Lehtonen et al., 2015	49	6.67	11.75 (3.17)	90.9 (13.3)	48	11.63 (2.58)	108.33 (16.14)	WASI	39.58	2
Loitfelder et al., 2015	14	—	12.49 (2.65)	—	30	12.3 (2.94)	—	—	—	2
Lorenzo et al., 2011	33	—	2.5 (0)	—	38	2.5 (0)	—	—	0	1
Lorenzo et al., 2013	43	—	3.35 (0.06)	96.2 (13.68)	43	3.35 (0.04)	112.18 (10.27)	WPPSI-III	0	6
Mazzocco et al., 1995	19	—	9.9 (2.4)	96.4 (13)	19	10.1 (2.5)	108.2 (11.2)	WISC-R	100	1
Payne et al., 2011	199	29.7	10.62 (2.28)	89.9 (13.4)	55	10.1 (2.6)	102.6 (13)	WISC-III/IV	100	7
Payne et al., 2012	83	2 samples confounded (with and without ADHD) : 40.96	10.86 (2.33)	86.87 (10.43)	30	10 (2.67)	105.3 (11.5)	WISC-IV	0	2
Plasschaert et al., 2016	42	—	12.48 (3.08)	89.73 (12.16)	52	12.27 (2.65)	109.91 (10.86)	Abbreviated WISC-III NL	0	10
Pride et al., 2010	46	—	12.51 (1.8)	89.7 (14.1)	30	13.4 (2.1)	106 (11)	Abbreviated WISC-III	0	1
Remigereau et al., 2017	18	22.2	10.42 (2.42)	—	20	10.42 (1.92)	—	—	0	3
Riva et al., 2017	16	0	10.67 (2.25)	97.31 (11.57)	32	11.55 (2.21)	111.79 (9.80)	WISC-III	50	5
Roy et al., 2010	36	38.89	9.62 (1.74)	92.28 (13.88)	36	9.62 (1.7)	102.82 (9.84)	WISC-III	0	3
Roy et al., 2012	30	36.67	9.58 (1.67)	90.2 (12.4)	60	9.58 (1.58)	103 (8.7)	WISC-III	0	4
Ullrich et al., 2010	10	27.27	12.08 (2.04)	—	6	12.7 (1.7)	—	—	100	2

N = sample size; ADHD = attention deficit hyperactivity disorder; *SD* = standard deviation; FSIQ = Full Scale Intellectual Quotient; EF = executive function; WISC = Wechsler Intelligence Scale for Children; WASI = Wechsler Abbreviated Scale of Intelligence; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

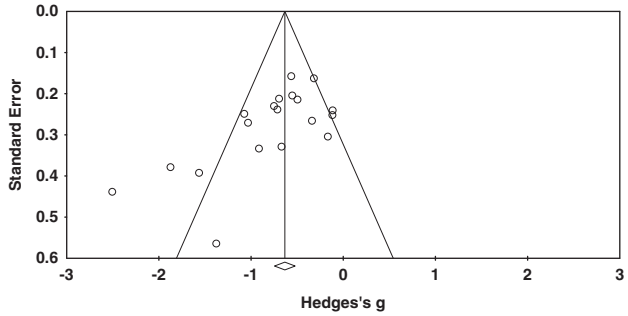

Fig. 2. Funnel plot of standard error by Hedges's *g*.

thus, an Egger's test of publication bias was conducted and was significant (Egger's intercept = –3.75; $p < .01$). There are several possible explanations for funnel plot asymmetry such as the heterogeneity between studies (Sterne et al., 2011).

A statistical comparison of "Assessment Tool Type" failed to reveal any significant differences ($p = .21$) between the performance-based test (k = 15; g = –0.65; 95% CI [–0.86; –0.45]; $Z = –6.18$; $p < .0001$) and the questionnaire format (k = 8; g = –0.98, 95% CI [–1.45; –0.51]; $Z = –4.10$; $p < .0001$). Heterogeneity was moderate for the performance-based test (Q(14) = 35.47; $p < .0001$; $I^2 = 60.53\%$; $tau^2 = 0.09$) and high for the questionnaire format (Q(7) = 42.95; $p < .0001$; $I^2 = 83.70\%$; $tau^2 = 0.36$).

The subgroup analysis between EF domains was significant ($p = .08$), demonstrating differential effects across EFs.

EF Domain-Specific Effects

Small to moderate ESs were observed for each of EF (see Figure 3).

Working Memory

The overall ES for working memory tasks was significant and moderate (k = 7; g = –0.63; 95% CI [–0.87; –0.39]; $Z = –5.20$; $p < .0001$). The Q-test was significant (Q(6) = 14.24; $p < .03$) and the I^2 test indicated ($I^2 = 57{,}85\%$; $tau^2 = 0.06$) moderate heterogeneity between samples. The FSN was 113, indicating results are robust. Nine tasks were used to assess working memory: two to assess verbal working memory (k = 2; g = –0,89; 95% CI [–1.17; –0.61]) and seven to assess visual-spatial working memory (results for two samples were pooled) (k = 5; g = –0.54; 95% CI [–0.82; –0.26]). A significant difference was observed between these two modalities ($p = .08$) at the expense of the verbal working memory.

Inhibitory Control

The ES for inhibitory control was significant but small (k = 6; g = –0.37; 95% CI [–0.56; –0.17]; $Z = –3.62$; $p < .0001$). Results were homogeneous (Q(5) = 9.27; $p = .21$; $I^2 = 30.01\%$; $tau^2 = 0.02$). The FSN was 24, below the estimations of Rosenthal's formula (40). Therefore, results were not robust. ES did not differ according to the subcomponents of inhibitory control ($p = .96$): interference control (cognitive inhibition) (k = 2; g = –0.41;, 95% CI [–0.93; 0.11]), interference control (selective or focused attention) (k = 4; g = –0.33; 95% CI [–0.58; –0.08]) and response inhibition (self-control and discipline) (k = 2; g = –0.37; 95% CI [–0.80; 0.07]).

Cognitive Flexibility

The ES for flexibility was significant but small (k = 7; g = –0.30; 95% CI [–0.56; –0.05]; $Z = –2.32$; $p = .02$). The

Study name	Outcome	Subgroup within study	Hedges's g	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Gilboa et al., 2014b	Playing cards (BADS-C)	Cognitive flexibility	0,13	-0,38	0,65	0,51	0,61	13,00
Lorenzo et al., 2013	Verbal fluency (NEPSY)	Cognitive flexibility	-0,48	-0,96	-0,00	-1,97	0,05	14,15
Payne et al., 2011	COWAT	Cognitive flexibility	-0,02	-0,31	0,28	-0,10	0,92	20,26
Plasschaert et al., 2016	Combined	Cognitive flexibility	-0,60	-1,02	-0,19	-2,85	0,00	16,11
Remigereau et al., 2017	Verbal fluency	Cognitive flexibility	-0,20	-0,82	0,43	-0,61	0,54	10,44
Riva et al., 2017	Playing cards (BADS-C)	Cognitive flexibility	-0,18	-0,77	0,41	-0,60	0,55	11,17
Roy et al., 2012	Combined	Cognitive flexibility	-0,75	-1,20	-0,29	-3,23	0,00	14,87
			-0,30	-0,56	-0,05	-2,32	0,02	
Galasso et al., 2014	TOL	Planning/problem solving	-2,50	-3,36	-1,64	-5,69	0,00	7,35
Gilboa et al., 2014a	RCF	Planning/problem solving	-1,03	-1,56	-0,50	-3,79	0,00	10,44
Gilboa et al., 2014b	Combined	Planning/problem solving	-0,45	-0,98	0,07	-1,69	0,09	10,52
Lorenzo et al., 2013	TOH	Planning/problem solving	0,00	-0,46	0,46	0,00	1,00	11,14
Payne et al., 2011	Combined	Planning/problem solving	-0,43	-0,73	-0,13	-2,83	0,00	12,70
Plasschaert et al., 2016	Tower (D-KEFS)	Planning/problem solving	-0,54	-0,96	-0,13	-2,60	0,01	11,67
Remigereau et al., 2017	ROF	Planning/problem solving	-1,08	-1,75	-0,41	-3,16	0,00	9,07
Riva et al., 2017	Combined	Planning/problem solving	-0,16	-0,76	0,44	-0,52	0,61	9,75
Roy et al., 2010	Combined	Planning/problem solving	-1,07	-1,56	-0,58	-4,28	0,00	10,87
Ullrich et al., 2010	Arena Mazes	Planning/problem solving	-0,53	-1,50	0,45	-1,06	0,29	6,48
			-0,72	-1,06	-0,38	-4,19	0,00	
Chaix et al., 2017	CPT II	Inhibitory control	-0,20	-0,51	0,12	-1,20	0,23	22,87
Lorenzo et al., 2013	Combined	Inhibitory control	-0,09	-0,60	0,42	-0,35	0,72	11,94
Payne et al., 2011	Combined	Inhibitory control	-0,60	-0,90	-0,30	-3,91	0,00	24,37
Payne et al., 2012	Stop Signal Task	Inhibitory control	-0,15	-0,56	0,27	-0,69	0,49	16,21
Plasschaert et al., 2016	Combined	Inhibitory control	-0,49	-0,90	-0,08	-2,36	0,02	16,52
Remigereau et al., 2017	Stroop	Inhibitory control	-0,72	-1,36	-0,07	-2,19	0,03	8,09
			-0,37	-0,56	-0,17	-3,62	0,00	
Chaix et al., 2017	corsi	Working memory	-0,43	-0,75	-0,11	-2,63	0,01	17,39
Lehtonen et al., 2015	Combined	Working memory	-0,55	-0,95	-0,15	-2,67	0,01	14,76
Lorenzo et al., 2013	Delay alternation	Working memory	0,00	-0,46	0,46	0,00	1,00	13,15
Mazzocco et al., 1995	Digit span (WISC R)	Working memory	-0,91	-1,57	-0,25	-2,72	0,01	8,70
Payne et al., 2011	Digit span	Working memory	-0,88	-1,19	-0,57	-5,62	0,00	17,90
Payne et al., 2012	Spatial Working Memory	Working memory	-0,84	-1,27	-0,41	-3,82	0,00	13,96
Plasschaert et al., 2016	Combined	Working memory	-0,86	-1,29	-0,44	-4,00	0,00	14,14
			-0,63	-0,87	-0,39	-5,20	0,00	

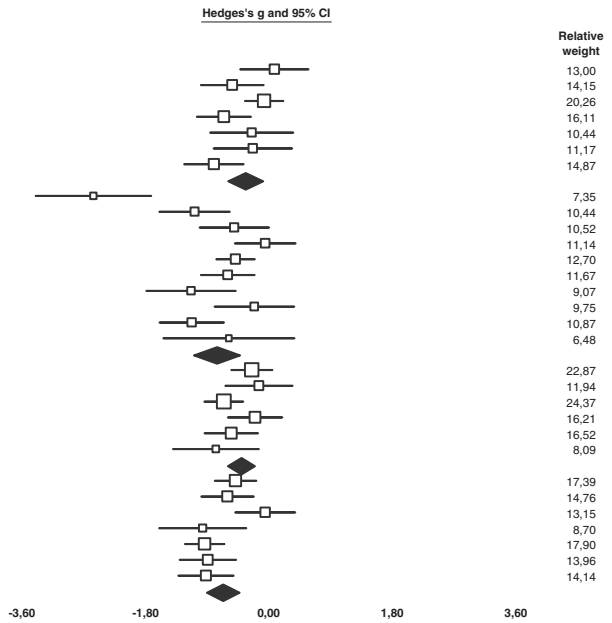

Fig. 3. Forest plot of studies group by EF process.

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Table 4. Meta-regression results

Moderator		Executive functions	*k*	Coefficient	95% CI	*Z*	*p*	R^2
Age	Overall EF	NF1 group (range: 3.35 to 12.9)	19	–0.09	[–0.16; –0.02]	–2.47	0.01	0.23
	Working memory	NF1 group (range: 3.35 to 12.48)	7	–0.09	[–0.16; –0.03]	–2.84	<0.01	0.93
	Cognitive flexibility	NF1 group (range: 3.35 to 12.48)	7	0.03	[–0.06; 0.13]	0.66	0.51	0
	Planning/problem solving	NF1 group (range: 3.35 to 12.48)	10	–0.08	[–0.20; 0.05]	–1.18	0.24	0.02
QI	Overall EF	Mean FSIQ NF1 group (range: 86.87 to 101.61)	13	–0.03	[–0.09; 0.03]	–1.05	0.29	0
	Working memory	Mean FSIQ NF1 group (range: 86.87 to 96.40)	7	0.05	[–0.02; 0.13]	1.44	0.15	0.33
	Cognitive flexibility	Mean FSIQ NF1 group (range: 89.73 to 98.96)	6	0.04	[–0.04; 0.12]	0.94	0.35	0
	Planning/problem solving	Mean FSIQ NF1 group (range: 89.73 to 101.61)	7	–0.06	[–0.17; 0.05]	–1.08	0.28	0
% ADHD within NF1 group	Overall EF	NF1 group (range: 0 to 40.96)	11	–0.00	[–0.02; 0.02]	–0.02	0.99	0
	Working memory	NF1 group (range: 6.67 to 40.96)	Not enough studies					
	Cognitive flexibility	NF1 group (range: 0 to 38.89)	5	–0.01	[–0.03; 0.02]	–0.76	0.45	0
	Planning/problem solving	NF1 group (range: 0 to 38.89)	7	0.01	[–0.03; 0.05]	–0.57	0.57	0
% of siblings within control group	Overall EF	NF1 group (range: 0 to 100)	13	0.00	[–0.01; 0.01]	0.09	0.93	0
	Working memory	NF1 group (range: 0 to 100)	6	–0.00	[–0.01; 0.00]	–0.97	0.33	0
	Cognitive flexibility	NF1 group (range: 0 to 100)	6	0.01	[0.00; 0.01]	2.81	0.01	1
	Planning/problem solving	NF1 group (range: 0 to 100)	8	0.01	[–0.01; 0.02]	1.01	0.31	0

k = number of samples; CI = confidence interval; NF1 = neurofibromatosis type 1; FSIQ = Full-Scale Intellectual Quotient; EF = executive functions.

Q-test revealed moderate heterogeneity between studies (Q(6) = 12.74; $p = .05$; $I^2 = 52.91\%$; $tau^2 = 0.06$). The results are not considered to be robust (FSN = 14).

Planning/Problem Solving

The overall ES for planning/problem solving tasks was significant and moderate (k = 10; g = –0.72; 95% CI [–1.06; –0.38]; $Z = -4.19$; $p < .0001$). There was a significant between-sample heterogeneity (Q(9) = 36.81; $p < .0001$; $I^2 = 75.55\%$; $tau^2 = 0.21$). A publication bias was unlikely (FSN = 161).

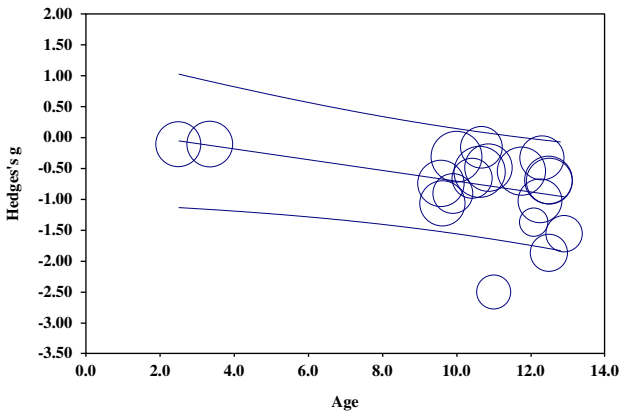

Fig. 4. Regression of Hedges's *g* on age for overall EF.

Moderator Analysis

A significant heterogeneity across overall EF studies and within working memory, cognitive flexibility and planning/problem solving studies was observed, so effects of different variable moderators were assessed (age, IQ, ADHD, percentage of siblings within control group) to determine whether there was a relationship between these variables and the NF1 executive performance (Table 4). No meta-regression was performed for inhibitory control because *Q* statistics indicated homogeneity of the results.

Age

The overall EF meta-regression was significant (regression coefficient = –0.09, 95% CI [–0.16; –0.02]; $Z = -2.48$; $p = .01$), suggesting that age has an effect on ES (Figure 4). Furthermore, meta-regressions were performed separately for specific EFs. The working memory meta-regression was significant (regression coefficient = –0.09, 95% CI [–0.15; –0.03]; $Z = -2.85$; $p < .01$): age was negatively associated

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with working memory performances. No significant association was observed for cognitive flexibility ($p = .51$) and planning/problem solving ($p = .24$).

IQ

The effect of FSIQ (NF1 FSIQ) was assessed and showed that NF1 FSIQ has no effect on the ES of overall EF ($p = .29$), working memory ($p = .15$), cognitive flexibility ($p = .35$), and planning/problem solving ($p = .28$).

ADHD

No association was found between the percentage of ADHD in children with NF1 and ES concerning overall EF ($p = .53$), cognitive flexibility ($p = .38$), and planning/problem solving ($p = .57$). A meta-regression was not possible for working memory because not enough studies with the ADHD variable were available.

Percentage of Siblings Within the Control Group

No association was observed between the overall EFs and the percentage of siblings within the control group ($p = .93$). Control group composition did not seem to influence working memory ($p = .33$) or planning/problem solving ES ($p = .31$). Nevertheless, an association between the percentage of siblings within the control group and cognitive flexibility was observed (regression coefficient = 0.01; 95% CI [0.00; 0.01]; $Z = 2.81$; $p = .01$): the percentage of siblings within the control group was positively associated with cognitive flexibility performances.

DISCUSSION

The aim of this meta-analysis was to determine the magnitude of impairment for each EF, namely working memory, inhibitory control, cognitive flexbility, and planning/problem solving and to clarify the impact of assessment tool format, control group composition, and participant characteristics (age, intellectual abilities, percentage of ADHD) on EFs.

Executive Function Impairments in Children With Neurofibromatosis Type 1

The first question was whether all aspects of executive functioning are similarly impaired. The results demonstrated EF deficits in children with NF1 with moderate ES. These findings are consistent with past research that showed executive dysfunction in children with NF1 (Plasschaert et al., 2016; Ribeiro et al., 2015; Roy et al., 2010, 2012, 2015). However, a heterogeneity was observed across studies. Subgroup analyses showed that ES varied with the specific component of executive functioning. Individual analyses by function showed that working memory and planning/problem solving are more affected than inhibitory control and cognitive flexibility. ES for working memory and planning/problem solving are moderate, whereas the ES for inhibitory control and cognitive flexibility are small. Nevertheless, all ESs are significant. Results for inhibitory control and cognitive flexibility should be considered with caution because the results are not assumed to be robust.

Moreover, working memory deficits vary according to the type of working memory. While the working memory deficit appears to be global, the magnitude of the ES for verbal working memory is larger than that of visual-spatial working memory, which are, respectively, large and moderate. Differences between the two modalities could be due to the psychometric properties of EF tasks. Indeed, in the current meta-analysis, the verbal working memory was assessed solely with the digit span task. This measure is perhaps more sensitive than other working memory tasks, irrespective of the type of working memory assessed. Inhibitory control did not vary according to its component aspects. Indeed, the ES is homogeneous for "cognitive inhibition" and "selective or focused attention." Nevertheless, heterogeneity between studies for overall EF, working memory, cognitive flexibility, and planning/problem solving studies was observed, thus prompting us to question the influence of moderator variables.

Moderator Variables of Executive Functions

The second question was whether the degree of executive dysfunction is governed by methodological choices (tool type used to assess EFs, composition of control group). There was no significant difference between the assessment tool with a medium ES for performance-based test and a large ES for questionnaire format, contrary to some studies that noted an inconsistency between cognitive test scores and questionnaires (e.g., Payne, Hyman, Shores, & North, 2011). On the meta-analysis level, conclusions concerning executive dysfunction from the two assessment tools appear to be similar. It must be kept in mind, however, that these are two different assessment tools used to assess executive functioning in a complementary manner, one with a behavioral approach and the other with a performance-based test.

Control group composition and especially the percentage of siblings within healthy controls seems not to be linked to the ES of EF. To our knowledge, no study to date has investigated this question. Nevertheless, our findings are contrary to some studies that observed a difference between a sibling group and a healthy control group (e.g., Lehtonen et al., 2015; Riva et al., 2017). In the meta-analysis, only one significant relationship between this moderator variable and cognitive flexibility performances was observed: the higher the proportion of siblings in the control group is high, the smaller the ES. This could be explained by the fact that family environments (Bernier, Carlson, & Whipple, 2010; Rhoades, Greenberg, Lanza, & Blair, 2011) could also

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influence EFs, which are expected to be similar in NF1 patients and their siblings. In a complementary way, the education level of parents and parental socioeconomic status may also have an impact on EF development (Er Rafiqi, Roukoz, Le Gall, & Roy, 2017; Noble, Norman, & Farah, 2005). Nevertheless, this result should be considered with caution because this association is only observed for one domain of EF and the number of samples included in this analysis is relatively small.

The third question was whether the executive dysfunction may be explained by participant selection criteria (age, IQ, neurological history, ADHD). To our knowledge, the influence of age on EF from early childhood to adolescence has never been studied. Only one publication conducted a longitudinal study of a cohort of children with NF1 with some EF tasks (Hyman et al., 2003). Concerning cognitive flexibility, the results fail to show a decrease in the gap between children with NF1 and controls with advancing age. In this meta-analysis, an age effect was observed on the ES of overall EF and working memory: executive dysfunction and more particularly working memory seems to be more important when age increases. Thus, executive dysfunction seems to be long-lasting, worsening with advancing age, at least up to adolescence.

These findings can be justified insofar as EFs are increasingly necessary in everyday life, with growing autonomy requirements. Thus, while an EF deficit can pass unnoticed or be of low intensity in younger children, this deficit may become increasingly noticeable during childhood and adolescence, as and when educational and social requirements increase. Data from functional questionnaires tend to reinforce these results. Indeed, while parents did not notice any difference in behavior and executive functioning in younger children (30 and 40 months) (Lorenzo, Barton, Acosta, & North, 2011; Lorenzo et al., 2013), an emerging executive dysfunction was reported between 3 and 5 years (Casnar & Klein-Tasman, 2016; Sangster, Shores, Watt, & North, 2011). In school-aged children, EF impairment reported by parents is very significant (Champion, Rose, Payne, Burns, & North, 2014; Lehtonen et al., 2015; Loitfelder et al., 2015; Payne et al., 2011; Plasschaert et al., 2016; Pride et al., 2010; Roy et al., 2015; Ullrich, Ayr, Leaffer, Irons, & Rey-Casserly, 2010).

Additionally, these findings consolidate the hypothesis of lasting executive dysfunction in NF1, which is probably due to an atypical development of fronto-sub-cortical circuits. These data are contrary to the temporary developmental shift of EFs assumed by some authors (Itoh et al., 1994), especially since, despite heterogeneous results, some studies have shown an executive deficit in adults with NF1 (Descheemaeker, Plasschaert, Frijns, & Legius, 2013; De Souza Costa et al., 2014; Ferner et al., 1996; Pavol et al., 2006).

No relationship between FSIQ in children with NF1 and EFs was noted. These results recall some previous studies which concluded that EF deficits do not appear to be a side effect of a lower IQ (Plasschaert et al., 2016). These findings strengthen the idea that executive dysfunction is specific and not due to the slightly decreased general intellectual functioning. More generally, these results raise questions concerning the link between EF and intelligence in a neurodevelopmental disorder such as NF1, despite the supposed close ties between EF and fluid intelligence in healthy subjects such as proposed by Diamond (2013).

The meta-analysis shows no association between the percentage of ADHD in the NF1 group and the ES of EF. These results are consistent with previous studies suggesting that executive dysfunction is only partially related to ADHD (Galasso et al., 2014; Hyman et al., 2005; Roy et al., 2010, 2012). ADHD comorbidity is frequently reported in children with NF1, with an estimated prevalence of 30–50% (Pride et al, 2012). The high co-occurrence of ADHD and NF1 testify to semiological proximity. Nevertheless, these findings question the semiological proximity between ADHD and NF1, because executive dysfunction is observed in children with NF1, with or without ADHD. They confirm the presence of executive impairment independently of ADHD symptoms and the specific nature of dysexecutive syndrome in children with NF1. In addition to this observation, these results show a limited repercussion of ADHD in other cognitive domains such as EF. This brings into question the important role attributed to ADHD in the cognitive phenotype of children with NF1. In this context, the results underline the need to study EF in children with NF1, even when ADHD is excluded. Monitoring in schooling and care should not be limited to patients with ADHD symptoms.

Finally, the children included in this meta-analysis did not have a neurological history co-occurrence that could explain or accentuate the executive dysfunction observed among children with NF1. This finding is important because the inconsistency of methodologies used between studies in the scientific literature (children with or without neurological history co-occurrence) could contribute to the heterogeneity of conclusions concerning EF in children with NF1.

Other characteristics specific to NF1, such as T2 hyperintensities (T2H), could not be studied in this meta-analysis, whereas some studies have examined the relationship between neuropsychological impairment and T2H in NF1 (Levine et al., 2006). T2H are often present in individuals with NF1, at approximately 43% to 79% (Cutting et al., 2004; Levine et al., 2006). Only a small number have examined the impact of T2H on EFs (Roy et al., 2015). Roy et al. (2015) compared EF performance in children with and without T2H in 36 school-age children with NF1 (7–12 years). The presence, number, size, and the main cerebral locations of hyperintensities were considered. Results showed that the presence, number, and size of the T2H, as they are currently measured, would be independent of executive functioning. It may also be of interest to study other topics, such as the link between EF and optic pathway gliomas, considering the high prevalence in children with NF1 (approximately 15–20%) (Gutmann et al., 2017). Neuropsychological profile and, more specifically, EF in children with NF1 and optic pathway gliomas are rarely studied, probably because optic pathway gliomas are often treated and the type of treatment itself

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(chemotherapy, radiotherapy, surgery) also interferes with cognitive functions (Lacaze et al., 2003).

Executive Functions at the Interface With Higher Functions in Children With Neurofibromatosis Type 1

The EF deficit in children with NF1 may have a negative impact on their daily life, particularly on higher functions. Thus, Remigereau et al. (2017) showed that praxis difficulties disappeared when executive dysfunctions (planning and inhibitory control) were controlled. Gilboa, Josman, Fattal-Valeski, Toledano-Alhadef, and Rosenblum (2014) observed that planning underlies poor writing quality in children with NF1.

Similarly, Van Eylen et al. (2017) found no differences between children with NF1 and controls for any of the visuoperceptual measures when statistically checking for EF confounders (inhibitory control, cognitive flexibility, working memory). These results suggest that reduced visuoperceptual performances in children with NF1 arise from confounding EF impairments and not from visuoperceptual impairments *per se*. In a complementary manner, other studies show that executive dysfunction is observed even when basic skills such as visuospatial ability is taken into consideration (Roy et al., 2010, 2012). Roy et al. (2010) demonstrated that lower Rey-Osterrieth Complex Figure scores are due to a weakness in planning in children with NF1 and cannot be attributed to deficits in either IQ or visuospatial skills. Moreover, these findings emphasize the need for caution with analyses of scores because one neuropsychological task usually assesses several cognitive functions. It is thus essential to propose several tasks to reach a conclusion concerning the nature of impairment.

Another study suggested that the social functioning impairment suffered by children with NF1 is likely to be a result of deficits in higher-order functions rather than of basic face recognition (Lehtonen et al., 2015). Concerning theory of mind, a deficit is observed in children with NF1 but appears to be independent of other cognitive abilities such EF impairments (Payne, Pride, & North, 2016). This conclusion, however, was derived from only one study, EF measurement was indirect and not all theory of mind aspects were evaluated. These results should be considered with all the more caution as a link between theory of mind and EF has been demonstrated in many medical contexts (for a review, see Moreau & Champagne-Lavau, 2014).

Finally, executive dysfunction in children with NF1 partially accounts for their academic achievement difficulties (Gilboa, Rosenblum, Fattal-Valevski, Toledano-Alhadef, & Josman, 2014).

These data provide an additional argument for considering that EF disorders are the source of several learning disabilities in children with NF1. Contrasting these data with other clinical contexts (e.g., Krivitsky, Walsh, Fisher, & Berl, 2016), for which executive impairment seems to be a core feature of cognitive phenotype, seems to be important to improve our knowledge of executive dysfunction in pediatric medical conditions.

Limitations and Future Directions

The current meta-analysis had several limitations. From a methodological standpoint, the number of studies included in this meta-analysis was relatively small, particularly for preschool-aged children. For example, only two studies involving preschool children were included in the current meta-analysis, both of these were carried out by the same authors and toddlers come from one group (Lorenzo et al., 2011, 2013). Thus, the effect of age on the magnitude of the EF deficit needs to be explored with further studies in preschool children, especially since there is an age gap from 3 to 9 in this meta-analysis. Even if an effect of age should be observed on cognitive flexibility and planning/problem solving if the age effect on the overall EF and working memory was solely due to this gap, we cannot fully rule out an effect of age on the other EF domains. These are very important to improve our knowledge of the development of EF in children with NF1, especially since neuropsychological tests are now available. It would also be interesting to confirm this finding with longitudinal studies to observe EF development at the group level as well at the individual level.

Moreover, the small number of studies did not allow us to eliminate those conducted by the same research team. We cannot, therefore, eliminate the fact that school-age children may have been included in several studies at different ages.

Concerning the relationship between intellectual performance and EFs, we have considered the possibility that the FSIQ and working memory may be confounded because, some of FSIQ provided by the meta-analysis was obtained with the Wechsler Intelligence Scale for Children, with Digit Span among subtests. Nevertheless, no effect of FSIQ on the ES of working memory nor of overall EF, cognitive flexibility or planning/problem solving could be found. Thus, we can consider reasonably that executive dysfunction is not due to the slightly decreased general intellectual functioning.

Furthermore, due to the lack of data, some variables such socioeconomic status, specific and preferential location of T2H, or gender influence upon ES in the meta-analysis, could not be analyzed, whereas these variables could have an impact on the development of EF (Roy et al., 2012, 2015).

We also decided to exclude studies in languages other than English. The number of non-English studies we came across in our searches, however, was small.

Additionally, we used the FSN to detect publication bias. The FSN estimates the number of missing studies with null results that we would need to incorporate in the analysis before the *p*-value became non-significant. Nonetheless, it is quite unlikely that all unpublished studies would have a null effect.

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On a clinical level, these findings emphasize the need for patients with NFl to undergo a full early neuropsychological assessment, as recommended by Ferner et al. (1996) to detect early signs of executive dysfunction and to alert the child's entourage. In this way, learning disabilities and behavioral problems in children with NF1 could be anticipated. Moreover, while the meta-analysis did not reveal significant differences between performance-based tests and ratings of EF measurement, it would seem essential to study EF with the two assessment tools because they are complementary and probably assess different aspects of cognitive and behavioral functioning (Toplak, West, & Stanovich, 2013).

On a theoretical level, the results of this meta-analysis consolidate the biological hypothesis of an atypical development of fronto-sub-cortical circuits in children with NF1. Indeed, executive functioning is associated with a large cerebral network with a preponderant role of the prefrontal cortex and its subcortical connections. These data echo recent studies that observed some differences in neurophysiological processes between adolescents with NF1 and controls in a Go/No-Go task (Bluschke, Von der Hagen, Papenhagen, Roessner, & Beste, 2017b). These findings should encourage future neurophysiological studies to focus on EF studies which will enrich our knowledge of this topic. These data are reminiscent of the preponderance of T2H in fronto- sub-cortical networks, which could represent cumulative risk factors for executive dysfunction (Roy et al., 2015)

CONCLUSION

To conclude, the current meta-analysis demonstrated EF deficit in children with NF1 compared with controls matched by age and gender. Subgroup analyses showed that impairment varies by specific component of executive functioning. Working memory and planning/problem solving appear to be more affected than inhibitory control and cognitive flexibility. Executive dysfunction and more specifically working memory seems to be more important with increasing age, probably due to the growing autonomy requirements of everyday life. EF performances do not seem to be affected by intellectual performance, ADHD, tool type used to assess EFs, or the percentage of siblings within control groups. Early identification of executive dysfunctions to reduce long-term impact is essential. In fact, these disorders may be a complication affecting the quality of life in NF1, with repercussions on other cognitive abilities (praxis, visuospatial skills), social functioning, and academic achievements.

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