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REVIEW ARTICLE

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A systematic review and meta-analysis of intellectual, neuropsychological, and psychoeducational functioning in neurofibromatosis type 1

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Abstract

Neurofibromatosis Type 1 (NF1) is a common genetic disorder frequently associated with cognitive deficits. Despite cognitive deficits being a key feature of NF1, the profile of such impairments in NF1 has been shown to be heterogeneous. Thus, we sought to quantitatively synthesize the extant literature on cognitive functioning in NF1. A random-effects meta-analysis of cross-sectional studies was carried out comparing cognitive functioning of patients with NF1 to typically developing or unaffected sibling comparison subjects of all ages. Analyses included 50 articles (Total N_{NF1} = 1,522; M_{Age} = 15.70 years, range = 0.52–69.60), yielding 460 effect sizes. Overall moderate deficits were observed [g = −0.64, 95% CI = (−0.69, −0.60)] wherein impairments differed at the level of cognitive domain. Deficits ranged from large [general intelligence: g = −0.95, 95% CI = (−1.12, −0.79)] to small [emotion: g = −0.37, 95% CI = (−0.63, −0.11)]. Moderation analyses revealed nonsignificant contributions of age, sex, educational attainment, and parental level of education to outcomes. These results illustrate that cognitive impairments are diffuse and salient across the lifespan in NF1. Taken together, these results further demonstrate efforts should be made to evaluate and address cognitive morbidity in patients with NF1 in conjunction with existing best practices.

KEYWORDS
academic, clinical assessment, cognitive, intelligence, research synthesis, NF1

1 | INTRODUCTION

Neurofibromatosis Type 1 (NF1), also known as von Recklinghausen's disease, is a common genetic multisystem disease found in ~1 in 2500 to 1 in 3000 people that affects the central and peripheral nervous system (Williams et al., 2009). NF1 is caused by mutations in the neurofibromin 1 (*NF1*) tumor suppressor gene located on chromosome 17, position q11.2, and can result in a heterogeneous symptom profile (Rasmussen & Friedman, 2000). NF1 is inherited in approximately half of cases and follows an autosomal dominant transmission pattern (DeBella et al., 2000). The remaining cases are sporadic of which ~80% are attributable to a paternal origin (Jadayel et al., 1990). De novo deletions of the NF1 gene, as opposed to a transmitted or sporadic mutation, occur in ~10% of cases and are most often maternally transmitted (Upadhyaya et al., 1998). The disease is highly penetrant such that 90% of cases are identified by age 7 and 100% of cases by age 19 (DeBella et al., 2000).

The characteristic somatic features include café-au-lait macules, cutaneous and plexiform neurofibromas, abnormal skin freckling, scoliosis, pseudarthrosis, and iris hamartomas (Gutmann et al., 1997).

Neurological complications often involve optic nerve gliomas (Gutmann et al., 1997), macrocephaly (Castle et al., 2003), epilepsy (Ostendorf et al., 2013), and multiple sclerosis (Ferner, 2007; Ferner et al., 1995). Attention-deficit/hyperactivity disorder (ADHD) and learning disabilities (LD) frequently co-occur in NF1, affecting approximately 40% and 30%–60% of patients respectively (Ferner, 2007). Recent epidemiological studies also report increased rates of autism spectrum disorder (ASD) in this population at a rate of 25%–30% (Garg et al., 2012; Garg et al., 2013).

Patients with NF1 face an increased risk for developing cognitive impairments, along with motor and behavioral dysfunction (Gutmann et al., 2012). NF1 is often characterized by intellectual abilities in the low average range (i.e., IQ ≈ 85–90); however, the base rates of intellectual disability are notably higher in NF1 than in the general population (i.e., 6%–7% vs. 2%; Lehtonen et al., 2013). Impairments in executive function are also a hallmark feature of the NF1 cognitive profile (Beaussart et al., 2018). Other areas of compromise include the domains of academic achievement, visuospatial ability, attention, and psychosocial functioning (Lehtonen et al., 2013). The appearance of these cognitive impairments closely proceed the onset of the hallmark features of this condition and often emerge in early childhood (ages 3–5 years; Williams et al., 2009), necessitating neuropsychological or psychoeducational evaluation for these patients.

Despite existing knowledge about the cognitive disruptions seen in NF1, summary characterization of cognitive functioning in this disease is needed given the breadth of deficits reported in the literature (cf. Beaussart et al., 2018; Lehtonen et al., 2013). Most studies document noticeable deficits in several domains in NF1, yet no clear cognitive profile emerges. A recent meta-analysis of the executive functions in children with NF1 revealed significant impairment across working memory, response inhibition, set-shifting, and planning/problem-solving (Beaussart et al., 2018), however, these deficits were not equal in magnitude and within-domain analyses showed heterogeneity among studies examined. A broader systematic review echoed these disparate findings in the executive function literature and noticed similar variability in other domains (Lehtonen et al., 2013).

The aim of the current meta-analytic review is to summarize cognitive functioning over the lifespan in patients with NF1. We examined intellectual, neuropsychological, and academic performance in both children, adolescents, and adults with NF1 relative to healthy unrelated age-matched typically developing and unaffected sibling comparison groups. Furthermore, we sought to identify the impact of various potential moderators, such as age and sex that may impact performance deficits in NF1.

2 | METHODS

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A complete PRISMA checklist is available in Appendix A.

2.1 | Search strategy

Articles were independently screened by four of the authors (CM, AM, JMJ, and AJDC) and identified through a computerized literature search using PubMed and PsychINFO databases using the search terms: ("neurofibromatosis type 1", OR "NF1", OR "von Recklinghausen's disease") AND ("neuropsychology", OR "cognitive", OR "intelligence", OR "achievement", OR "attention", OR "executive", OR "memory", OR "visual perceptual" OR "motor"). The search was limited to English articles published through June 30, 2021 that dealt with human subjects. Additionally, a thorough manual review of articles was performed utilizing cross-references from identified original articles and reviews. All articles of interest were retrieved without issue except one advanced online publication where the corresponding author was contacted.

2.2 | Eligibility criteria

Inclusion of studies followed these criteria: (1) were original English language research articles that enrolled human subjects; (2) utilized standard or experimental tasks of cognitive function in patients with NF1; (3) had a comparison group of typically developing or sibling participants with no history of NF1; and (4) provided data or statistical information that allowed for the calculation of effect size.

2.3 | Data extraction

Items extracted included: (1) study details (author, publication date, country of origin, and control group type); (2) participant characteristics (mean age at time of testing, sex distribution, educational attainment, and parental level of education among patients); (3) sample sizes; and (4) means and standard deviations of test scores, test statistics, and/or *p*-values. Cognitive functioning was defined broadly, examining effect sizes across 27 specific cognitive domains including: (1) general intelligence; (2) performance (nonverbal) intelligence; (3) verbal intelligence; (4) math; (5) reading; (6) writing; (7) verbal long-term memory; (8) nonverbal long-term memory; (9) verbal short-term memory; (10) nonverbal short-term memory; (11) verbal working memory; (12) nonverbal working memory; (13) processing speed; (14) attention; (15) response inhibition; (16) interference control; (17) set-shifting; (18) planning; (19) phonemic fluency; (20) semantic fluency; (21) nonverbal fluency; (22) expressive language; (23) receptive language; (24) visuospatial abilities; (25) motor function; (26) decision-making; and (27) emotion. Assignment of cognitive tests to selected domains was guided by the classifications made in source articles. In the absence of assignment in source articles, tests were assigned to domain based on discussions between authors. All effect sizes were coded so that a negative value indicated worse performance by the NF1 group.

2.4 | Statistical analysis

Mean differences contrasting patients with NF1 from healthy comparison subjects on measures of cognitive functioning were standardized by calculating Hedge's g (Hedges, 1981) with a large sample approximation of effect size variances (Borenstein, 2009). Effect sizes were categorized as small ($g \geq 0.2$), medium ($g \geq 0.5$), or large ($g \geq 0.8$) according to Cohen (1988) and were calculated from either: (1) means, standard deviations, and sample sizes; (2) independent samples t statistics; (3) univariate F statistics; (4) z statistics; or (5) p-values. Formula available in Borenstein (2009) and Friedman (1982) were used to convert and standardize effect sizes to Hedge's g. Random-effects models with a restricted maximum-likelihood estimator of heterogeneity (Viechtbauer, 2005) were utilized in all analyses. To formally test for heterogeneity across studies, the Cochran Q statistic (Cochran, 1950) and the I^2 statistic (Higgins & Thompson, 2002) were employed. Effect size moderators were assessed with Cochran's Q tests and linear mixed effect approaches. The alpha level was set to 0.05 for all analyses and post-hoc pairwise contrasts were Holm-adjusted where appropriate. All analyses were conducted in the R language (version 4.1.1; The R Core Team, 2021) with the *metafor* package (version 3.0-2; Viechtbauer, 2010).

2.5 | Publication bias

A combination of graphical and statistical methods was carried out to evaluate publication bias. A funnel plot was appraised for a symmetric distribution of effects. In addition, a normal quantile-quantile plot was examined to evaluate whether effects were normally distributed. Begg and Mazumdar's (1994) rank correlation test, Egger et al.'s (1997) linear regression approach, and Orwin's (1983) fail-safe N for effect size were employed to test for publication bias. Egger's regression test was performed with included studies' standard errors as the predictor while Orwin's fail safe N was estimated based on a target average effect size of $g = -0.1$, an average effect of limited significance. Random-effects models were adjusted for publication bias following Duval and Tweedie (2000) where appropriate. Sensitivity analyses of publication year, country of origin, control group type, and effect size type were also undertaken with Cochran's Q tests and linear mixed effect approaches.

3 | RESULTS

3.1 | Study selection and characteristics

A total of 109 articles were identified through database searches and 50 articles published between 1989 and 2021 were deemed eligible for meta-analysis (Figure 1). A comprehensive list of articles excluded from the meta-analysis is available in Appendix B. Studies yielded 52 independent samples comprising patients with NF1 ($n = 1522$) and healthy comparison subjects ($n = 1576$). Characteristics of included studies are in Table 1.

The mean age of patients with NF1 across studies was 15.70 years ($Mdn = 11$, range = 0.52–69.60). The average proportion of the patient samples which were male was 51.85% ($Mdn = 51.02\%$, range = 25.00–94.44%). The levels of education of the patients with NF1 and their parents were largely unreported within studies, however the mean level of education of NF1 probands across studies was 6.92 years ($Mdn = 8$, range = 0–12.82) and their parents attained an average of 12.16 years of education ($Mdn = 12.1$, range = 11.50–12.91). A range of intelligence, neuropsychological, and academic achievement tests were reported in the literature (Table S1).

Studies contributed an average of 8.85 effects ($Mdn = 6$, range = 1–42). Effect size data reported across studies was primarily means, standard deviations, and sample sizes ($k = 394$) followed by p-values ($k = 25$), z statistics ($k = 19$), independent samples t statistics ($k = 17$), and univariate F statistics ($k = 5$).

3.2 | Meta-analysis

Meta-analysis revealed a deficit in overall cognitive functioning between patients with NF1 and healthy controls within the moderate range [$k = 460$, $g = -0.643$ ($SE = 0.023$), $Z = -28.607$, $p < 0.0001$, 95% CI = (−0.687, −0.599)], which was heterogeneous (Q [459] = 1441.703, $p < 0.0001$). Between-study variance was moderate ($I^2 = 68.46\%$). Notwithstanding, observed effect sizes were normally distributed (Figure S1).

3.3 | Publication bias

Analysis for the presence of possible publication bias revealed an asymmetric funnel plot (Figure 2) and significant Begg ($\tau = -0.117$, $p = 0.0002$) and Egger ($Z = -4.168$, $p < 0.0001$) tests, intimating publication bias in this literature. Calculation of a fail-safe N revealed that 2573 effects would need to be found and incorporated in the analysis to reduce the overall effect to a trivial result, suggesting the present findings are unlikely to have been affected by missing contradictory studies. To address possible publication bias, we imputed potentially missing studies following Duval and Tweedie (2000) and informed by results of the aforementioned Begg's rank correlation test. This procedure imputed two effects ($SE = 2.450$, $p = 0.125$) to the right of mean estimate and marginally adjusted the overall model [Figure S2; $k = 462$, $g = -0.634$ ($SE = 0.023$), $Z = -28.001$, $p < 0.0001$, 95% CI = (−0.683, −0.593)].

3.4 | Sensitivity analyses

3.4.1 | Year of publication

A linear mixed effect model indicated year of publication did not significantly predict effect size outcomes ($Q_M[1] = 0.884$, $Z = 0.940$ $p = 0.347$).

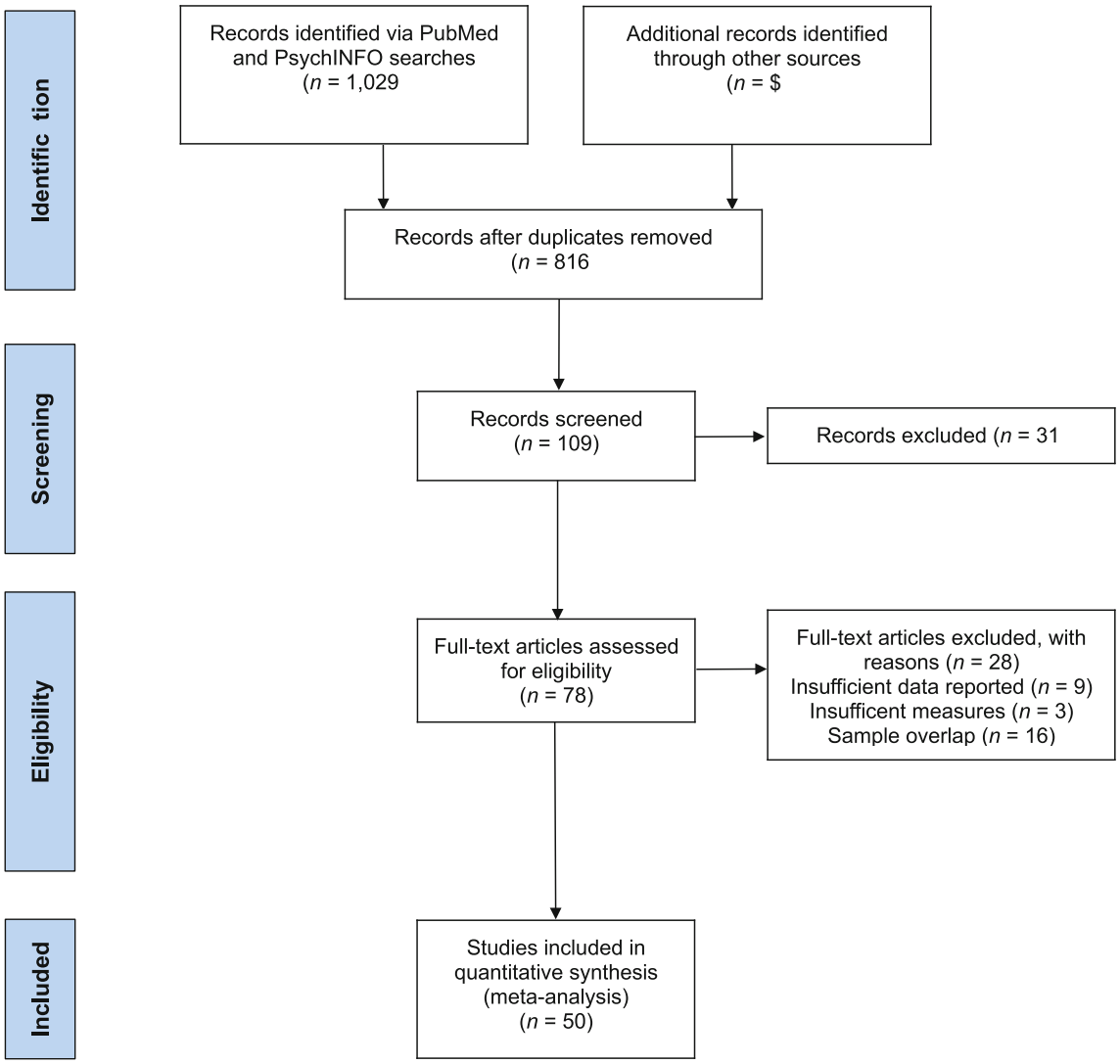

FIGURE 1 Flowchart of literature search

3.4.2 | Country of origin

By contrast, a linear mixed model demonstrated effect sizes varied as a function of country of origin ($Q_M[14] = 897.536$, $p < 0.0001$). Post hoc pairwise contrasts revealed effect size outcomes varied between each country of origin ($Q_M[2] \geq 21.490$, $p \leq 0.0001$). However, significant residual heterogeneity was also observed ($Q_E[446] = 1312.244$, $p < 0.0001$), indicating other factors are influencing heterogeneity among effect size outcomes.

3.4.3 | Control group type

Control group type was also found to significantly moderate effect size outcomes ($Q_M[3] = 819.134$, $p < 0.0001$). Post hoc pairwise contrasts demonstrated effect size outcomes varied between each control group type ($Q_M[2] \geq 193.616$, $p \leq 0.0001$). Post hoc pairwise contrasts indicated studies utilizing both typically developing and unaffected siblings controls demonstrated mean differences that were larger in magnitude [$g = -0.674$ ($SE = 0.087$), $Z = -7.715$, $p < 0.0001$, 95% CI = (−0.845, −0.503)] than studies incorporating solely typically developing controls [$g = -0.662$ ($SE = 0.026$), $Z = -25.010$, $p < 0.0001$, 95% CI = (−0.713, 0.610)] or unaffected sibling controls [$g = -0.570$ ($SE = 0.049$), $Z = -11.580$, $p < 0.0001$, 95% CI = (−0.667, −0.474)]. Although, significant residual heterogeneity was revealed within this analysis, as well ($Q_E[457] = 1441.284$, $p < 0.0001$).

3.4.4 | Effect size type

A linear mixed effects analysis with mean differences set as the reference level found effect size outcomes were significantly moderated by reported effect size ($Q_M[4] = 12.465$, $p = 0.014$). Post hoc pairwise contrasts indicated mean differences were larger in magnitude [$g = -0.658$ ($SE = 0.024$), $Z = -27.582$, $p < 0.0001$, 95%

TABLE 1 Characteristics of included studies

Study	Country	NF1 (*n*)	Control (*n*)	Age group	Patient selection	Control type	Outcome measure
Eldridge et al. (1989)	USA	13	13	Pediatric	Clinic	Unaffected sibling	Wechsler Intelligence Scale for Children-Revised
Mazzocco et al. (1995)	USA	19	19	Pediatric	Clinic; Patient organizations	Unaffected sibling	Wechsler Intelligence Scale for Children-Revised; Woodcock–Johnson Psychoeducational Battery-Revised; Test of Variables of Attention; Wisconsin Card Sorting Test; Judgment of Line Orientation; Dot Localization; Rey–Osterrieth Complex Figure Test; Rapid Automatized Naming; Category Fluency; Boston Naming Test; Phoneme Segmentation; Phonological Memory Test; Grammaticality Judgment Test; Token Test for Children; Test of Written Language-Second Edition
Zöller et al. (1997)	Sweden	23	23	Adult	Clinic	Typically developing	Dureman Sälde Battery; Halstead–Reitan Test Battery; Benton Visual Retention Test
Moore III et al. (2000)	USA	52	19	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Third Edition/ McCarthy Scales of Children's Abilities; Judgment of Line Orientation; Florida Kindergarten Screening Battery Recognition–Discrimination; Halstead–Reitan Test Battery
Billingsley et al. (2003)	USA	38	38	Pediatric	Clinic	Mixed	Wechsler Intelligence Scale for Children-Third Edition
Billingsley et al. (2004)	USA	15	15	Pediatric	Clinic	Mixed	Woodcock–Johnson Psychoeducational Battery-Revised
Feldmann et al. (2003)	Germany	100	100	Lifespan	Clinic	Typically developing	Wecshler Intelligence Scale for Children-Revised; Motorische Leistunds-Serie
Hyman et al. (2005)	Australia	81	49	Pediatric	Clinic	Unaffected sibling	Wechsler Intelligence Scale for Children-Third Edition; Children's Category Test; Controlled Oral Word Association Test; Judgment of Line Orientation; Woodcock–Johnson Psychoeducational Battery-Revised; California Verbal Learning Test for Children; Wechsler Individual Achievement Test; Grooved Pegboard Test; Test of Variables of Attention; Test of Everyday Attention for Children; Tower of London
Greenwood et al. (2005)	USA	36	39	Pediatric	Clinic	Mixed	Wechsler Intelligence Scale for Children-Third Edition
Pavol et al. (2006)	USA	20	25	Adult	Clinic	Typically developing	Beery–Buktenica Developmental Test of Visual-Motor Integration; Judgment of Line Orientation; Visual Form Discrimination Test; Figure Cancellation; Booklet Category Test; Peabody Picture Vocabulary Test-Revised; Controlled Oral Word Association Test; Neurosensory Center Comprehensive Examination for Aphasia
Clements-Stephens et al. (2008)	USA	13	13	Pediatric	Clinic; Patient organizations	Typically developing	Hooper Visual Organization Test; Developmental Test of Visual Perception-Second Edition; Wechsler Individual Achievement Test; Woodcock–Johnson Psychoeducational Battery-Revised

(Continues)

TABLE 1 (Continued)

Study	Country	NF1 (*n*)	Control (*n*)	Age group	Patient selection	Control type	Outcome measure
Rowbotham et al. (2009)	United Kingdom	16	16	Pediatric	Patient organizations	Typically developing	Amsterdam Neuropsychological Tasks
Erdoğan-Bakar et al. (2009)	Turkey	27	20	Pediatric	*Unspecified*	Unaffected sibling	Wechsler Intelligence Scale for Children-Revised; Bender Visual-Motor Gestalt Test; Judgment of Line Orientation
			40			Typically developing	
Ullrich et al. (2010)	USA	10	6	Pediatric	Clinic	Unaffected sibling	Wechsler Intelligence Scale for Children-Fourth Edition; California Verbal Learning Test for Children; Arena Maze
Sangster et al. (2011)	Australia	24	21	Pediatric	Clinic	Mixed	Wechsler Preschool and Primary Scale of Intelligence-Third Edition; Connors Kiddie Continuous Performance Test
Cutting and Levine (2010)	United States	12	36	Pediatric	Patient organizations	Typically developing	Wechsler Intelligence Scale for Children; Gray Oral-Word Reading Test-Third Edition; Comprehensive Test of Phonological Processing; Gates–MacGinitie Reading Tests-Fourth Edition; Clinical Evaluation of Language Fundamentals-Third Edition; Test of Language Competence-Expanded; Peabody Picture Vocabulary Test-Third Edition
Roy et al. (2010)	France	36	36	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Third Edition; Developmental Neuropsychological Assessment; Rey–Osterrieth Complex Figure Test
Huijbregts et al. (2010)	Netherlands	30	30	Pediatric	Patient organizations	Typically developing	Amsterdam Neuropsychological Tasks
Payne et al. (2012)	Australia	49	30	Pediatric	Clinic	Typically developing	Cambridge Neuropsychological Test Automated Battery
Duarte et al. (2014)	Portugal	21	24	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Third Edition; Judgment of Line Orientation
		18	22	Adult	Clinic	Typically developing	Raven's Advanced Progressive Matrices; Judgment of Line Orientation
Descheemaeker et al. (2013)	Belgium	20	20	Adult	Clinic	Typically developing	Rey-Osterrieth Complex Figure Test; Trail Making Test; Tower of London; Wisconsin Card Sorting Test; Wechsler Adult Intelligence Scale-Third Edition; Rey Auditory Verbal Learning Test; Bourdon–Wiersma Test; Stroop Color Word Test; Controlled Oral Word Association Test
Roy et al. (2014)	France	30	60	Pediatric	Clinic	Typically developing	Developmental Neuropsychological Assessment; Modified Card Sorting Test; Brixton Spatial Anticipation Test
Pride et al. (2014)	Australia	29	30	Adult	Clinic	Typically developing	Wechsler Adult Intelligence Scale-Third Edition; The Awareness of Social Inference Test

TABLE 1 (Continued)

Study	Country	NF1 (*n*)	Control (*n*)	Age group	Patient selection	Control type	Outcome measure
Lorenzo et al. (2013)	Australia	43	43	Pediatric	Clinic	Mixed	Expressive One-Word Picture Vocabulary Test; Woodcock–Johnson Psychoeducational Battery-Revised; Developmental Neuropsychological Assessment; Beery–Buktenica Developmental Test of Visual-Motor Integration-Fifth Edition; Tower of Hanoi; Shape School; Delayed Alteration
Klein-Tasman et al. (2014)	USA	40	37	Pediatric	Clinic	Mixed	Differential Ability Scales-Second Edition
Batista et al. (2014)	Brazil	25	22	Pediatric	Clinic	Typically developing	Sequential Verbal Memory Test; Sequential Non-Verbal Memory Test; Phonological Awareness Test
Galasso et al. (2014)	Italy	18	18	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Third Edition; Tower of London
de Souza Costa et al. (2014)	Brazil	5	49	Adult	Clinic	Typically developing	Five Digits Test; Frontal Assessment Battery; Mini-Mental State Examination; Stick Design Test; Clock Drawing Test; Category Fluency Test; Token Test; Neuropsychological Investigations Laboratory Naming Test; Rey Auditory Verbal Learning Test
Gilboa et al. (2014)	Israel	29	27	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Revised; Behavioral Assessment of the Dysexecutive Syndrome in Children
Ribeiro et al. (2015)	Portugal	16	16	Pediatric	Clinic	Typically developing	Go/No-Go
Lehtonen et al. (2015)	United Kingdom	49	19 29	Pediatric	Clinic	Unaffected sibling Typically developing	Wechsler Abbreviated Scale of Intelligence; Wechsler Individual Achievement Test-Second Edition; Test of Everyday Attention; Judgment of Line Orientation; Cambridge Neuropsychological Test Automated Battery; Diagnostic Analysis of Nonverbal Accuracy
Loitfelder et al. (2015)	Netherlands	14	30	Pediatric	*Unspecified*	Typically developing	Wechsler Intelligence Scale for Children-Fourth Edition
Plasschaert et al. (2016)	Belgium	42	52	Pediatric	Clinic	Typically developing	Go/No-Go; Cambridge Neuropsychological Test Automated Battery; Flanker Task; Wisconsin Card Sorting Test; Switch Task; Use of Objects Task; Delis-Kaplan Executive Function System; Wechsler Nonverbal Scale of Ability; Wechsler Intelligence Scale for Children-Third Edition
Allen et al. (2016)	USA	23	23	Pediatric	Clinic	Typically developing	Diagnostic Analysis of Nonverbal Accuracy-Revised
Koini et al. (2017)	Netherlands	13	9	Pediatric	*Unspecified*	Typically developing	Amsterdam Neuropsychological Tasks

(Continues)

TABLE 1 (Continued)

Study	Country	NF1 (*n*)	Control (*n*)	Age group	Patient selection	Control type	Outcome measure
Riva et al. (2017)	Italy	16	16 16	Pediatric	Clinic	Unaffected sibling Typically developing	Wechsler Intelligence Scale for Children-Third Edition; Behavioral Assessment of the Dysexecutive Syndrome in Children
Remigereau et al. (2017)	France	18	20	Pediatric	Clinic	Typically developing	Finger Sequence of Movements; Developmental Neuropsychological Assessment; Pantomime Production; Imitation of Meaningless Postures; Matching Pantomime-Object; Stroop Color Word Test; Rey-Osterrieth Complex Figure Test
Lewis et al. (2017)	Australia	29	29	Pediatric	Clinic	Typically developing	Benton Facial Recognition Test-Long Form
Chaix et al. (2018)	France	75	75	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Fourth Edition; Peabody Picture Vocabulary Test-Revised; Thurstone Test of Mental Awareness; Judgment of Line Orientation; Corsi Block-Tapping Test; Connors Continuous Performance Test-Second Edition; Outil de Dépistage des Dyslexies-Version 2 [Dyslexia Screening Tool]; Lire avec epreuves pour evaluer la capacite de lecture [Tests to assess reading ability]
Loin-François et al. (2020)	France	32	40	Pediatric	Clinic	Typically developing	Test of Attentional Performance for Children
Bulgheroni et al. (2019)	Italy	18	17 18	Pediatric	Clinic	Unaffected sibling Typically developing	Rey–Osterrieth Complex Figure Test
Wang et al. (2019)	China	20	20	Adult	*Unspecified*	Typically developing	Attention Network Test-Revised
Baudou et al. (2020)	France	38	42	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Fourth Edition; D2 Test of Attention
Castricum et al. (2020)	Netherlands	30	30	Adult	Clinic	Typically developing	Wechsler Adult Intelligence Scale-Fourth Edition
Arnold et al. (2021)	Australia	60	36	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Fourth Edition; Wechsler Abbreviated Scale of Intelligence-Second Edition; Judgment of Line Orientation; Test of Everyday Attention for Children; Castles and Coltheart Word/Nonword Test-Second Edition; Test of Word Reading Efficiency; Test of Everyday Reading Comprehension; Letter-Sound Test; Grapheme–Phoneme Correspondence Test; Test of Orthographic Choice; Rain/Hane Task; Peabody Picture Vocabulary Test-Fourth Edition; Cross-Case Copying; Letter Orientation

TABLE 1 (Continued)

Study	Country	NF1 (*n*)	Control (*n*)	Age group	Patient selection	Control type	Outcome measure
							Task; Developmental Neuropsychological Assessment-Second Edition; Blending Nonwords Test
Biotteau et al. (2021)	France	75	75	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Fourth Edition; Connors Continuous Performance Test-Second Edition; Peabody Picture Vocabulary Test-Revised
Beaussart-Corbat et al. (2021)	France	33	52	Pediatric	Clinic	Typically developing	Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition; Sun-Moon Stroop Task; Hand Game; Dimensional Change Card Sort; Brixton Preschool; Wechsler Intelligence Scale for Children-Fourth Edition; Wechsler Nonverbal Scale of Ability; Children's Gambling Task
Porbic et al. (2021)	United Kingdom	16	16	Pediatric	Clinic	Typically developing	Wechsler Intelligence Scale for Children-Fourth Edition; Test of Everyday Attention for Children; Visuospatial Adaptive N-Back
Castricum et al. (2022)	Netherlands	32	32	Adult	Clinic	Typically developing	Amsterdam Neuropsychological Tasks
Begum-Ali et al. (2021)	United Kingdom	11	34	Pediatric	Clinic	Typically developing	Mullen Scales of Early Learning
		19	40	Pediatric	Clinic	Typically developing	

CI = (−0.704, −0.611)] than independent samples t statistics [g = 0.138 (SE = 0.114), Z = 1.213, p = 0.225, 95% CI = (−0.085, 0.361)], univariate F statistics [g = −0.576 (SE = 0.245), Z = −2.350, p = 0.019, 95% CI = (−1.056, −0.096)], z statistics [g = 0.270 (SE = 0.140), Z = 1.928, p = 0.054, 95% CI = (−0.005, 0.545)], and p values [g = 0.145 (SE = 0.106), Z = 1.358, p = 0.174, 95% CI = (−0.064, 0.353)]. No other post hoc contrasts were significant. In addition, significant residual heterogeneity remained (Q_E[455] = 1419.649, p < 0.0001).

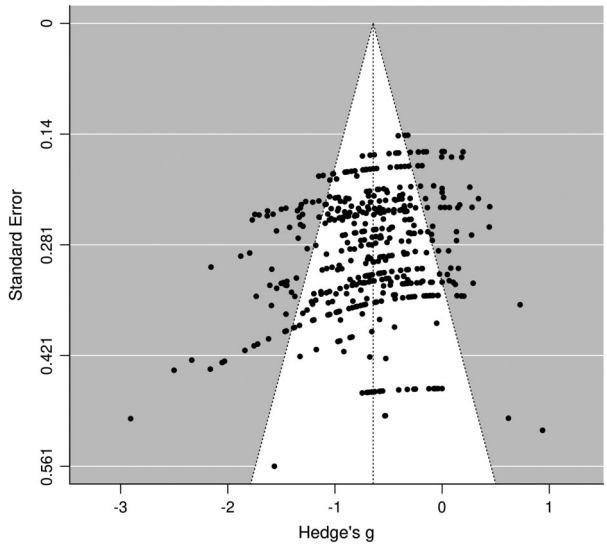

FIGURE 2 Funnel plot of individual effect sizes (Hedge's g) by their standard error

3.5 | Moderator analysis

3.5.1 | Cognitive domain

Moderation analysis of the 27 cognitive domains revealed significant heterogeneity (Figure 3; Q_M[27] = 1003.965, p < 0.0001). Large deficits were seen among the domains of general intelligence, performance intelligence, visuospatial abilities, verbal intelligence, math, and writing. Moderate deficits were seen among nonverbal long-term memory, nonverbal short-term memory, verbal working memory, receptive language, processing speed, nonverbal fluency, reading, planning, motor function, expressive language, interference control, and attention. Small deficits were found among set-shifting, nonverbal working memory, response inhibition, and emotion. Differences were not significant among the domains of phonemic

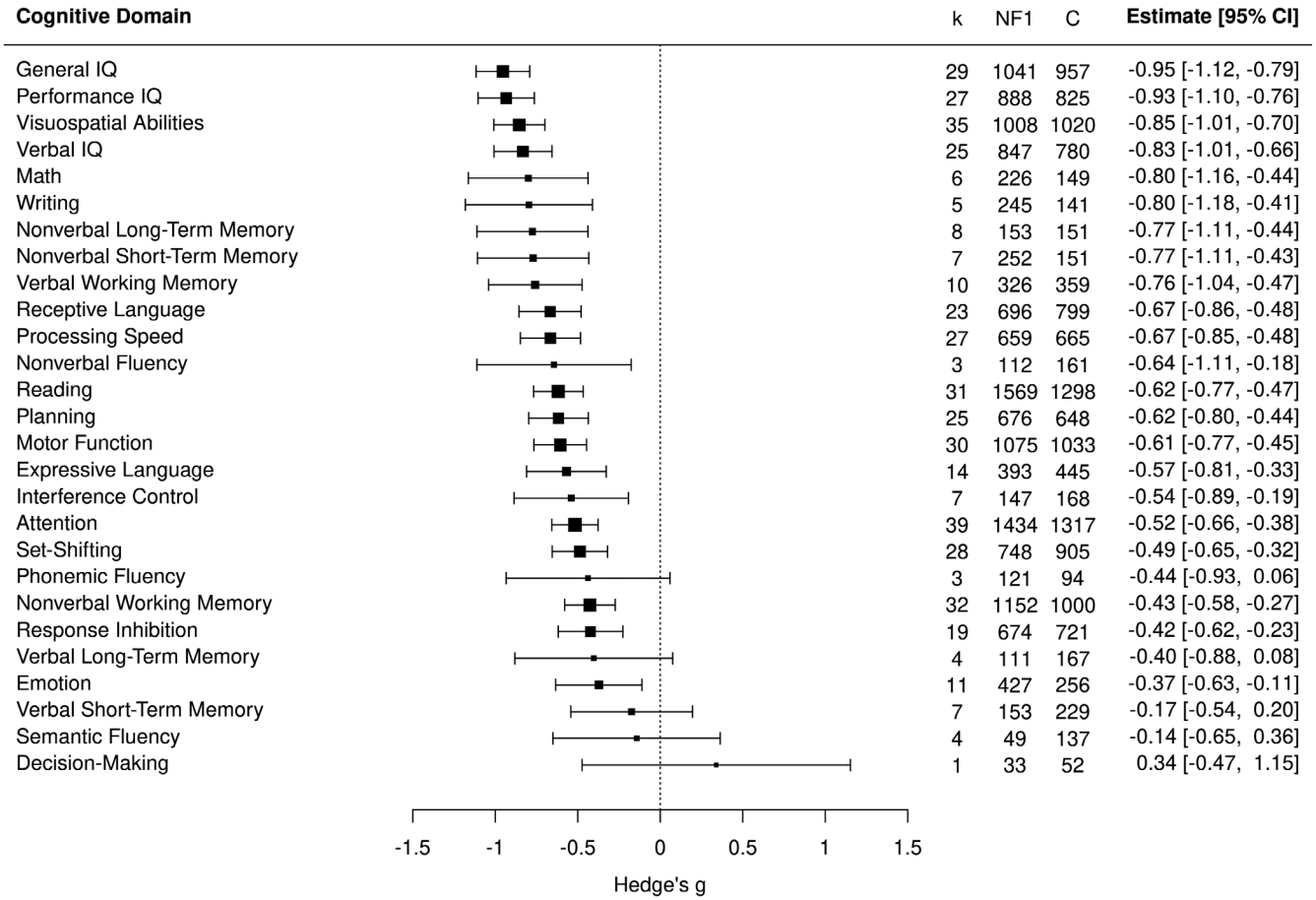

FIGURE 3 Forest plot of average effect sizes (Hedge's g) by cognitive domain. Error bars represent 95% confidence intervals. C, total sample size of control groups; K, total number of effects; NF1, total sample size of patient groups

fluency, verbal long-term memory, verbal short-term memory, semantic fluency, and decision-making. Significant residual heterogeneity was demonstrated in this moderation analysis ($Q_E[433] = 1178.034$, $p < 0.0001$), suggesting additional factors are influencing effect size variances.

3.6 | Meta-regression

3.6.1 | Age

Analysis revealed that mean patient age did not significantly explain variances in effect size outcome ($k = 379$, $Q_M[1] = 1.855$, $Z = 1.362$, $p = 0.173$), indicating that the observed deficits in cognitive function among patients with NF1 remain relatively static throughout the lifespan.

3.6.2 | Sex

Analysis with the proportion of the patient sample being male as the predictor did not significantly explain effect size outcomes ($k = 376$, $Q_M[1] = 1.421$, $Z = -1.192$, $p = 0.233$). This result suggests sex distribution does not influence cognitive outcomes in patients with NF1.

3.6.3 | Proband level of education

With mean years of education among patients as the predictor, analysis did not demonstrate an association between educational attainment and effect size outcomes ($k = 43$, $Q_M[1] = 0.104$, $Z = -0.322$, $p = 0.748$). This finding should be interpreted with caution given the low level of reporting within studies with respect to proband level of education.

3.6.4 | Parental level of education

Similarly, analysis predicting effect size outcomes from parental years of education among patients was not significant ($k = 51$, $Q_M[1] = 0.857$, $Z = 0.926$, $p = 0.355$). Likewise, this finding should be interpreted with caution as few studies reported parental level of education.

4 | DISCUSSION

The present meta-analysis revealed moderate impairments in overall cognitive performance in patients with NF1 relative to healthy comparison subjects. These deficits were broad, affecting a range of cognitive domains. Importantly, differences in cognitive outcome were largely uninfluenced by sociodemographic moderators such as age, sex, educational attainment, or parental level of education.

4.1 | Neuropsychological domain

The largest deficits in cognitive functioning in NF1 were seen on tests of intellectual functioning, visuospatial ability, and academic achievement with smaller differences seen in other domains, consistent with a previous systematic review (Lehtonen et al., 2013). These findings likely reflect the mild reductions in performance on intelligence tests, LD, and common optic nerve neuropathology described previously (Ferner, 2007). Consistent with this general finding, our data suggests patients with NF1 generally present with an IQ approximately one standard deviation below the mean.

In addition to mild reductions in intelligence, notable deficits were also observed in studies of primarily nonverbal, visuospatial functions (e.g., nonverbal long-term and short-term memory, nonverbal working memory, nonverbal fluency, processing speed, attention, response inhibition) which contrast with certain verbally mediated functions (e.g., verbal long-term and short-term memory and phonemic and semantic verbal fluency), which were not significantly reduced. However, studies of verbal working memory, expressive and receptive language, reading, and writing demonstrated significant impairment, as well. Consequently, these findings intimate a cognitive profile that goes beyond deficits in nonverbal abilities.

This heterogeneity has been the focus of much research (Lehtonen et al., 2013) and hypothesized to be related to a system of weaknesses in visuospatial ability, executive function, and learning (Cutting et al., 2004). As Cutting et al. (2004) have suggested, the more pervasive deficits in visually mediated functions does not necessarily indicate a form of nonverbal learning disability (NVLD) but a more heterogeneous profile of LD that includes a key impairment in visuospatial functioning. However, executive function deficits may effectuate visuospatial dysfunction among patients who do not have a primary visual impairment (Van Eylen et al., 2017). As such, visuospatial deficits may be dependent on executive dysfunction among a subgroup of patients. The breadth of deficits seen may also be associated with the high disease burden that includes comorbid LD, ADHD, and other neurological and developmental disorders. With this understanding, it is conceivable patients with NF1 may present with heterogeneous deficits and lower than average performance on intelligence tests.

4.2 | Age effects

Our findings suggest a limited role of age-related influences on cognitive outcomes in NF1. Specifically, meta-regression analysis demonstrated that age did not significantly moderate cognitive performance. These findings run counter to findings in a recent meta-analysis showing adolescents with NF1 had greater executive function deficits, though this meta-analysis included only executive function domains, was restricted to children and adolescents, and this age effect seemed to be specific to working memory (Beaussart et al., 2018). Overall, these results may echo the high penetrance (DeBella et al., 2000) and

early emergence of cognitive impairments in the disease course of NF1 (Williams et al., 2009).

4.3 | Neurobiological basis

In general, the cognitive deficits seen in NF1 may reflect the diffuse neurodevelopmental consequences of reduced neurofibromin expression in the brain (Gutmann, 2002; Gutmann et al., 2012). Particularly, it has been proposed that the Ras-pathway dysfunction resulting from the typical course of NF1 may be more directly responsible for these deficits as previously illustrated in early mouse studies (Costa & Silva, 2002). Animal studies have shown Ras/ERK signaling indirectly modulates γ-aminobutric acid (GABA) neurotransmission via its role in the phosphorylation of synapsin 1, a regulator of neurotransmitter release (Gutmann et al., 2012). Both human and animal studies have implicated NF1 in increased GABA-mediated inhibition in regions critical to learning, memory, and executive function (Shilyansky et al., 2010). These findings are consistent with literature demonstrating lesser cortical GABA abundance in NF1 (Violante et al., 2013; Violante et al., 2016). Given statin drugs are known to modulate Ras activity, recent randomized control trails using statin drugs have been conducted though have shown limited efficacy with respect to improving cognitive and psychosocial outcomes in this population (e.g., Krab et al., 2008; van der Vaart et al., 2013).

In addition to the Ras pathway, neurofibromin indirectly moderates cyclic adenosine monophosphate (cAMP) signaling via *rut* activation (Diggs-Andrews & Gutmann, 2013). In model *NF1* knockout *Drosophila*, learning and memory impairments have been observed which were ameliorated by the correction of neurofibromin and cAMP deficiencies (Buchanan & Davis, 2010; Guo et al., 2000). In prior studies of knockout mice, abnormal cortical morphology has been found and attributed to decreased neuronal arborization in addition to dysfunctional apoptotic processes stemming from reduced cAMP synthesis (Brown et al., 2012; Hegedus et al., 2007; Hegedus et al., 2009).

With the considerable executive function and attention deficits and the high prevalence of ADHD documented in NF1, researchers have finally implicated aberrant dopaminergic neurotransmission in NF1 (Diggs-Andrews & Gutmann, 2013). Methylphenidate, a common stimulant medication for ADHD, has consistently shown positive efficacy in treating cognitive deficits and ADHD-related symptomology in NF1 (Lidzba et al., 2014; Loin-François et al., 2014; Mautner et al., 2002). These outcomes are consistent with the finding that *NF1* knockout mice have reduced striatal dopamine (Brown et al., 2010; Brown et al., 2011) which has been implicated in learning and memory deficits in these mouse models (Diggs-Andrews et al., 2013).

Taken together, these findings intimate a disruption of typical neurodevelopmental processes in NF1 and underscore the importance of neurofibromin in normal brain development. Despite this growing literature on the neurobiological bases of NF1, the available knowledge is still limited. Further study is required in order to elucidate the molecular and cellular bases that cause cognitive deficits in this population.

4.4 | Limitations

The findings of the current meta-analysis should be taken in light of the following limitations. First, our analysis was comprised of studies that had to include typically developing peers, unaffected siblings, or a combination of these. Studies were excluded if the comparison group was not adequately matched. While this allowed for comparisons of effect sizes between patients with NF1 and age-matched healthy comparison and sibling comparison groups, it excluded studies that relied on normative data to calculate differences as variance of effect size would increase when calculated on disparate and unrelated normative samples. Second, moderator analyses were limited by a paucity of reporting of variables of interest such as education level and other neurological or psychiatric symptomatology (e.g., depression, anxiety, ADHD, or quality of life) in the included articles. Thus, our analyses cannot clarify the effects of these likely influential factors on cognitive outcomes in NF1. Third, we were unable to examine the role of genotype and transmission pattern as these variables were similarly underreported. Recent studies have noted that these variables may influence cognitive deficits in NF1 (e.g., Biotteau et al., 2020; Ottenhoff et al., 2020). While few genotype–phenotype correlations have been demonstrated in NF1 (Bettegowda et al., 2021), future studies should examine the contribution of genotype and transmission pattern to cognitive variability in NF1. Lastly, we did not evaluate study bias at the individual study level as studies did not differ considerably regarding the selection and matching of patient and control groups and outcome (independent) measures. However, the use of quality assessment scales may have allowed for the identification of possible study bias beyond the graphical and statistical approaches used.

5 | CONCLUSIONS

The current meta-analytic review sought to summarize the magnitude, scope, and differential impairments in cognitive functioning in patients with NF1 in the current literature. Here, we have revealed moderate effects in overall cognitive performance to which the largest deficits are observed in intellectual domains, visuospatial ability, and academic achievement. Decrements in other cognitive domains, notably in executive function, motor function, attention, visual memory, and working memory among others, are also considerable. These impairments seem to be uninfluenced by several sociodemographic moderators. In summary, our data further evidences NF1 is associated with significant cognitive impairments across several functional domains which should be taken into consideration holistically in patients suspected of having this disease.

AUTHOR CONTRIBUTIONS

Andrew J. D. Crow co-led the project, identified and reviewed articles for inclusion, planned and conducted statistical analysis, and drafted and revised the article. Jennica M. Janssen co-led the project, identified and reviewed articles for inclusion, planned and conducted

statistical analysis, and drafted the article. Carolina Marshall identified and reviewed articles for inclusion and assisted with article preparation. Anne Moffit identified and reviewed articles for inclusion and assisted with article preparation. Laura Brennan critically reviewed the study methods, statistical analyses, and article. Christian G. Kohler critically reviewed the article. David R. Roalf critically reviewed the article. Paul J. Moberg conceived and supervised the project.

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CONFLICT OF INTEREST

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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