Chapter

Cognitive Issues Experienced by Individuals Living with Neurofibromatosis

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Abstract

In this chapter, we will review cognitive issues faced by individuals living with neurofibromatosis. The chapter will discuss the complicated and sometimes inconsistent cognitive issues and adaptive functioning struggles associated with NF1, NF2, and schwannomatosis. We will review neurocognitive outcomes associated with each of these conditions across the lifespan while focusing on NF1. Specific neurocognitive domains we will review include: intellect, memory, language, nonverbal skills, attention, and executive functions. We will discuss the heterogeneity of the cognitive phenotype for each of these conditions. We will include how associated medical complications such as brain tumor, seizures, and hearing loss can impact neurocognitive outcomes. The chapter will also review the functional consequence of cognitive difficulties including academic struggles, learning disabilities, and decreased quality of life that are sometimes seen in this population.

Keywords: neurofibromatosis, schwannomatosis, cognitive, neurocognitive, learning, lifespan

1. Introduction

Neurofibromatosis is a collection of three distinct autosomal dominant genetic disorders including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. Each of these disorders has their own genetic variant, symptoms, and disease course [1]. These disorders are neurocutaneous syndromes, which represent a group of central nervous system (CNS) disorders with simultaneous lesions of other organs such as the skin or eye. One core common symptom among these conditions is that they cause tumors of nerve sheath [2].

In this chapter, we discuss cognitive, academic, and adaptive effects of neurofibromatosis over the course of the lifespan. Through review and synthesis of the extant literature, we summarize what is currently known regarding cognitive sequelae associated with neurofibromatosis and discuss the functional impact with regard to learning, academics, and overall quality of life (QoL). Neurofibromatosis is a multisystem disorder that can cause multiple nerve sheath tumors throughout the body [1]. Each of the three conditions present with their own distinct as well as overlapping symptoms that can have a negative impact on QoL (e.g., chronic pain, bone abnormalities, skin disorders, hearing problems, and learning disabilities) [3, 4]. The presence of benign and malignant tumors, depending on their presentation and treatment regimen, can impact cognitive and developmental functioning [1]. Understanding the functional

impact of this disorder is especially crucial in order to improve quality of life throughout the lifespan, as there is no known cure for neurofibromatosis [3]. NF1 is one of the most prevalent and researched genetic disorders. In contrast, prevalence rates of NF2 and Schwannomatosis are much lower, and related research is much more limited. As such, this chapter will focus on the most common of the genetic conditions, NF1.

NF1 is characterized by cutaneous symptoms, including café-au-lait spots, skin neurofibromas, bone abnormalities (e.g., scoliosis), and glial cell tumors (gliomas) [2]. It is associated with a range of developmental and cognitive issues that are present throughout the lifespan. Cognitive and learning problems are the most common complications associated with NF1 [5–7]. In contrast, we did not find any studies that directly investigate the cognitive impact and learning issues of NF2 or Schwannomatosis. This is likely in part because these conditions are less prevalent and believed not to be directly associated with learning issues or academic struggles. That said, these are multisystem conditions that can impact vision and hearing, which can have indirect impact on cognitive skills and learning. Thus, we will discuss the cognitive effects of NF2 and Schwannomatosis indirectly by looking at associated common symptoms of the disorders that can impact cognition. NF2 is defined by bilateral vestibular schwannomas (i.e., benign Schwann cell tumors on the vestibulocochlear nerve), which can cause hearing loss and balance issues [1]. Schwannomatosis is the newest recognized form of neurofibromatosis and is characterized by multiple schwannomas that typically occur in adulthood [1]. The degree of physical/medical phenotypical symptom presentation of each of these conditions is highly variable [1, 3]. Not surprisingly, the cognitive impact of these disorders has been found to be just as variable, which will be discussed more in detail below. At this time, the current literature does not demonstrate to what extent specific cognitive skills are related to each NF phenotype, and it is not yet known whether the presence of predisposing genetic factors for each variant of NF explain this heterogeneity of cognitive outcomes.

2. Neurofibromatosis type 1 (NF1)

Because the phenotypic expression of NF1 is so variable, some individuals living with NF1 are unaware they have the disorder while others are significantly impacted. Additionally, symptoms and signs of NF1 can be fluid and can change in presentation throughout a person's life [8]. In more severe presentations, NF1 can cause physical disfigurement and can be accompanied by significant neurological problems, such as brain tumor and seizures [2]. As noted above, NF1 is a disorder that affects multiple systems in the body, including the brain.

There have been many studies that have investigated the cognitive and learning issues associated with NF1 across age groups throughout the lifespan. One reason that the cognitive and learning struggles associated with NF1 have been well-researched is that NF1 is a single gene disorder (i.e., a mutation of the tumor suppressor gene on chromosome 17), and as such it presents an opportunity to investigate cognitive dysfunction at the molecular and cellular level [9]. The NF1 gene encodes the neurofibromin protein, which serves a vital role in regulating the development of the brain [10]. Brain abnormalities have been detected in magnetic resonance imaging (MRI) studies of those with NF1, such as increased white matter volume, increased subcortical gray matter volume in the thalamus right caudate, decreased cortical gray matter density, T2 hyperintensities (T2H), macrocephaly, and reduced integrity of white matter microstructure [11–13]. Research has also indicated that thalamic T2H as well as volume abnormalities in the corpus callosum, putamen, and amygdala are specifically associated with cognitive deficits in NF1

[11, 14]. Of note, studies looking into the number of T2 spots and how this relates to cognitive impairment have been inconsistently documented [15].

Medical complications that can co-occur with NF1 may lead to or compound cognitive deficits. For example, children with oncological complications of NF1 (e.g., brain tumors) are at risk for long-term cognitive issues as a result of treatment with chemotherapy and/or cranial irradiation [16]. Optic gliomas, tumors that arise from the nerve sheath of the optic nerve, are fairly common in children with NF1 and are sometimes associated with visual impairment, which can impact cognitive skills. The presence of a brain tumor also increases the risk of seizures or additional tumors arising in other areas of the brain [17], which can lead to specific cognitive deficits dependent on the area of the brain it is impacting. NF1 has also been associated with increased rates of other rarer neurological conditions that have known cognitive effects, including cortical dysplasia and hemimegalencephaly, as well as cerebrovascular diseases such as Moyamoya syndrome [17–19].

Just as the severity of phenotypic expression and incidences of medical symptoms are quite variable within those with NF1, the impact on the CNS and subsequent cognitive and academic functioning are significantly heterogeneous. Cognitive and academic weaknesses are some of the most common symptoms in NF1 [5–7]. Cognitive weaknesses can present challenges for the individual, and this has been shown to occur across the lifespan [7]. Findings from studies with very young children have noted that developmental delays and subsequent academic struggles and learning disabilities are pervasive [12, 20]. With regard to investigations with adults and elderly adults, cognitive weaknesses have been noted to be fairly stable over time from childhood [6, 21, 22]. Overall, the level and type of functional impairment may vary depending on what period in life an individual is in (e.g., preschool, school aged, college, working adult, elderly). Across age groups, cognitive issues associated with NF1 have significant associated morbidities, including weaker adaptive skills [15]. Additional consequences of cognitive difficulties associated with NF1 include poorer academic achievement and overall reduced QoL [3].

Below we will provide an in-depth discussion on the cognitive morbidities associated with NF1 as indicated by current research. **Table 1** summarizes specific cognitive domains and findings related to the NF1 population, including overall intellectual ability as well as underlying cognitive functions including language, nonverbal skills, memory, attention, executive functions, academic skills, and adaptive skills.

Studies investigating specific cognitive domains as they relate to NF1 have been wide ranging in their outcomes. Early on, it was believed that in childhood, NF1 was associated with a "nonverbal learning disability" (NLD) profile, a former term for what encompasses deficits in visual–spatial, fine motor, and handwriting abilities in the context of preserved verbal functioning [23]; however, later research challenged this notion with findings indicating that features of NLD are inconsistent among NF1 populations [24, 25]. Additionally, the comorbidity of learning difficulties with these deficits has been found to significantly vary [6, 24]. This is likely in part due to the heterogeneity of the clinical presentation of the condition as well as methodological issues used in research studies, including differences in approaches to cognitive measurement and how learning problems are operationally defined.

Additional studies examining the cognitive outcomes associated with NF1 have led to mixed findings and indicate varying degrees of prevalence of cognitive and academic problems. Hyman et al. [6] noted that these issues were likely due to research design factors, such low sample sizes, lack of controls, subject and control selection, as well as how learning problems are operationally defined. Individual cognitive test sensitivity and measures with overlapping cognitive domains have also been identified as leading to variability [26]. For example, performance on a

Domain	Definition	Common findings
Intellectual ability (IQ)	Summary score of overall cognitive/reasoning ability	Multiple studies suggest IQ to be mildly reduced (IQ ~ 90)
Language	How well a person expresses (including speech) and understands language	Studies have varied. Weaknesses with expressive language and speech are more common than receptive language issues Limited studies in adults.
Nonverbal skills	Visual spatial and fluid reasoning skills	Weaknesses are very common; however, recent studies suggest that findings are confounded by executive function demands inherent in nonverbal measures
Memory	Learning and retention of information	Studies on explicit memory have been variable. Weakness with working memory (short term memory) are common
Attention	Ability to focus, maintain focus on a task	Multiple studies have noted attention problems to be very common. Up to 70% of children demonstrate deficit(s) in one or more aspect of attention
Executive functioning	A collection of higher order skills that assist with complex goal directed behavior	Weaknesses are common. Specific weaknesses with planning/organization and working memory
Academic skills	Skills learned in school that include reading, writing, and mathematics	Weaknesses are very common. Studies vary in prevalence from 20 to 75%, which appears in part to how learning problems are defined
Adaptive skills	Basic skills needed for independent living	Mildly reduced, similar to IQ above

Table 1.
Cognitive domains affected in NF1.

commonly used visuospatial task in the assessment of nonverbal skills in children, the Rey-Osterrieth Complex Figure Test [27], can be undermined by weaknesses in attention and executive functions, as well as motor demands on the measure. Studies have varied in findings related to the prevalence of cognitive issues associated with NF1, though most note that cognitive issues are quite prevalent. Hyman et al. [6] noted that 81% of their sample had moderate to severe cognitive issues in one or more cognitive domains.

2.1 Intellectual ability

Intellectual ability is a cognitive construct that is commonly measured by an Intelligence Quotient (IQ), which represents an individual's performance on an intelligence test relative to similar-aged individuals and culminates performance across verbal and nonverbal problem-solving skills. [28] IQ represents what Charles Spearman (1904) proposed in the early 20th century as the *g* factor, which is thought to contribute to successful performance across various cognitive skills. As such, IQ tests utilize a collection of cognitive tasks to determine a person's overall intellectual functioning. Some of the most commonly used IQ tests are the Wechsler Intelligence Tests, which include various versions of assessments for individuals in preschool through adulthood. Most intelligence tests, like the Wechsler tests, are comprised of verbal and nonverbal reasoning tasks as well as cognitive efficiency tests, including working memory and processing speed. This is particularly the case with the older versions of the Wechsler tests, on which most of the published

literature on NF1 is based. IQ scores are typically standard scores with a mean of 100 and a standard deviation of 15.

Numerous studies have investigated IQ in NF1 populations. One of the more consistent cognitive findings in NF1 in children is that overall IQ is slightly lower than the normal population. That is, studies investigating IQ have placed the mean overall IQ approximately 10 points lower than normative sample [6, 29, 30]. This finding has been documented when compared to siblings controlling for environmental influences [30]. Hyman et al. [6] compared cognitive performance of 81 children with NF1 to 49 sibling controls. They found that the NF1 group demonstrated mildly reduced FSIQ with a mean of 90.6 compared to sibling mean of 102.6. Interestingly, this study found no associations between IQ and clinical severity, familial history of NF1, gender or age. Socioeconomic status was the only significant predictor of IQ in NF1 in their sample. Mild delays in IQ have also been noted with very young children, and given that difficulties have been found to be stable across the lifetime, this pattern has been noted in adults as well [14, 31]. In a combined adult and pediatric sample of 103 patients with NF1, Ferner et al. [32] noted an overall mean IQ score of 88.6 [32]. This finding appears to be consistent across cultures. Descheemaeker et al. found the overall IQ to be 89.96 in a Dutch-speaking sample [21]. With regard to elderly adults, there is very limited research investigating NF1; however, one small study noted mild delays in overall intellectual ability [22]. Taken together, these studies provide further support for the lack of progressive decline in IQ over time in NF1. In summary, it appears that NF1 is associated with average but mildly reduced overall IQ, which appears stable over the course of a lifespan.

Despite overall average intelligence, NF1 is associated with greater prevalence of intellectual disability. Intellectual Disability (ID), formerly known as Mental Retardation, is defined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) as an IQ approximately two standard deviations below the population mean with associated deficits in adaptive functioning [33]. Studies have varied on findings related to the actual prevalence of ID in NF1 populations. Early studies were believed to have significantly overestimated the prevalence of ID due to methodological issues as well as how ID was defined [5]. The rate of ID in NF1 is believed to be 6–7%, which is much less than what was previously believed, though still two to three times the normative expectation [6]. The prevalence of ID increases if neurological complications (brain tumor, seizures) are not excluded [34].

The overall composite score of the Full-Scale IQ likely masks the underlying subtle cognitive profile of NF1. Nearly 80% of people with NF1 have some cognitive deficit [14]. Thus, recent studies have focused on more discrete cognitive domains which we will discuss more below.

2.2 Language

Verbal skills are a collection of cognitive processes that involves language. Language is commonly divided into expressive and receptive language, which is how well a person uses language to relay their thoughts and ideas (including use of speech) and how a person understands language, respectively.

Weaknesses with aspects of language have been found in populations with NF1. Delays in early language development have been noted children as young as 10 months, which appear to persist [20, 35, 36]. NF1 has been associated with weaknesses with nearly all aspects of language; however, studies have not been consistent [37, 38]. Expressive language problems, especially with speech/articulation, have been more consistently found than deficits with receptive language. Additional speech issues include problems with prosody, overall voice qualify, and

aspects of speech sounds [37]. Hyman et al. [6] found that 44% of children with NF1 in their sample received speech-language therapy. Batista et al. [36] assessed central auditory temporal function in children with NF1 and correlated it with the results of language testing. They compared 25 NF1 patients to 22 healthy controls on audiometric and language tasks. They found no problems with peripheral acoustic hearing; however, the NF1 group performed more poorly on the temporal auditory processing task. Weaknesses with phonological skills in children have also been documented in several studies [38–40]. Phonological skills are not only associated with language delays but are also a core component of reading disability, which will be discussed further below. Studies on children have documented further weaknesses with verbal concept formation and comparisons as measured by the Similarities subtest from the Wechsler Intelligence Scales for Children (WISC). These findings were consistent compared to normal population and sibling control group [37, 41]. However, studies with childhood populations have not been consistent, as some studies noted that the differences in language disappear when IQ is controlled for [6, 38]. Verbal fluency has been found to be a relatively preserved cognitive function in children [42, 43]. Available literature on language in adult and elderly adult populations is relatively scarce as most studies in NF1 have been with pediatric populations.

2.3 Nonverbal skills

Nonverbal skills are a collection of visual perceptual, visual spatial, or visual-motor skills. They include visual perception, understanding spatial relations, and ability to integrate information from visual stimulus. Visuospatial (also referred to as visuoperceptual) skills have been found to be impaired in most studies involving children [5, 6, 12, 24, 26, 29, 34]. These studies have noted specific deficits in angulation, visual organization, and object recognition. The findings have been consistent when comparing children to normative sample or sibling control.

Early studies on children with NF1 noted a significant discrepancy between verbal and nonverbal reasoning abilities. Weaknesses were noted with nonverbal reasoning skills, while verbal skills were believed to be preserved [25, 44]. However, several follow-up studies did not find the same discrepancy between verbal IQ and perceptual (nonverbal) IQ [6, 25]. Hyman et al. [6] actually noted a pattern opposite of what was expected, with males with NF1 having weaker verbal than nonverbal reasoning compared to females with NF1. It is now clear that NF1 is condition that can impact a range of cognitive functions not limited to nonverbal reasoning.

In addition to nonverbal reasoning, studies with children and adults suggest weaknesses with many aspects of nonverbal skills including visual perception, visual-motor integration, form discrimination, visual organization [6, 21, 41, 42]. Indeed, weaknesses with aspects of visual spatial skills are common in NF1. However, several studies have not found significant differences between NF1 and controls regarding aspects of nonverbal skills [38, 45, 46]. Van Eylen et al. reviewed studies that directly assessed visuoperceptual and visual spatial functioning of children with NF1 [26]. They argue that the measures used to assess nonverbal skills are likely confounding findings. That is, many tasks that are purported to assess nonverbal skills also require other cognitive domains, most notably executive functions. In their sample, they found that when controlling for executive functions and IQ, performance on nonverbal tasks was not impaired. A similar pattern of weaknesses on nonverbal tasks has been documented in adults [21]. Overall, it appears that NF1 is associated with weaker visual/nonverbal skills; however, there are many confounds to previous studies which temper this conclusion.

2.4 Memory

Memory is our ability to encode, store, and retrieve previously learned information. Neuroscientists have identified many forms of memory, which at a basic level is divided into explicit and implicit memory. Cognitive tests of memory often only assess a small portion of memory functions. Cognitive tests typically focus on working memory and explicit memory. Working memory is our ability to actively hold information in mind for a short duration. It is commonly conceptualized as part of a collection of higher order executive functions.

Cognitive tests assess explicit memory with verbal and visual tests. Studies in both children and adults identifying memory weaknesses in NF1 have been variable, and several studies have not found a significant difference in memory performance than controls [6, 21, 37, 41]. Hyman et al. [6] did not find a significant difference in performance on verbal and visual explicit memory tests in children with NF1 compared to sibling controls. Similarly, Krab et al. [41] did not find a significant difference in NF1 children's performance on verbal or visual memory tasks when compared to children with no learning disabilities, children with specific learning disabilities, and children with general learning disabilities. In contrast, several studies have documented explicit memory weakness in children with NF1 [10, 14, 44, 47]. Bulgheroni et al. [47] assessed visual memory with the Rey Complex Figure Test (RCFT) [48]. They compared 18 children with NF1 to 17 siblings and 18 typically developing children. They found that the children with NF1 performed worse on recall memory, with no difference found regarding recognition memory. This pattern suggests that the NF1 had more difficulty with efficient retrieval rather coding and storing of the information, which is often due how the information was initially organized (an executive function). Overall, studies on explicit memory are mixed.

2.5 Attention

Attention involves of collection of processes that allows a person to engage in certain cognitive processing while ignoring others [51]. Attention is a complex system that has many subcomponents that includes focused attention, sustained attention, divided attention, and selective attention.

Cognitive weakness with attention is very common to children, adolescents, and adults with NF1 [7, 37]. Children with NF1 have frequently been reported to exhibit impaired performance on tasks measuring the ability to sustain and switch attention [6, 52]. These findings appear to be consistent across measures of both visual and auditory sustained attention, as well as divided auditory attention and response inhibition [53]. In a large cohort study of 199 children with NF1, approximately 54% were at risk for inattentive behavior based on parent and teacher ratings [43].

Up to 50% of individuals with NF1 meet diagnostic criteria for attention-deficit hyperactivity disorder (ADHD), [37, 54] and research has indicated that incidence rates of ADHD are much more common in children with NF1 than in immediate family members [55]. Neurocognitive deficits associated with NF1 have been found to be more severe in individuals with comorbid ADHD. While both groups have been found to demonstrate deficits in sustained attention, individuals with NF1 and comorbid ADHD have been indicated to be at higher risk [10]. Reduced attention skills in children with NF1 and ADHD have also been found to negatively impact the ability to process and respond to verbal instructions of increasing complexity, suggesting that receptive language skill development may also be vulnerable in this group as a result of attentional difficulties [10].

The behavioral phenotype of ADHD in NF1 also appears to differ from ADHD in the general population. In a large cohort study by Hyman et al. [6], ADHD co-occurrence in children with NF1 occurred equally in frequency among males and females, which differs from the 3:1 ratio of males to females in the general population [43]. Research suggests that ADHD in NF1 also differs from typical ADHD in that the combined subtype appears to occur at the highest frequency followed by the inattentive subtype, while the hyperactive/impulsive subtype is typically found at the highest rates in children with ADHD alone [56]. Additionally, while clinical symptoms of ADHD in children with NF1 and those diagnosed with ADHD are comparable, differences lie in performance deficits specific to each group such that response inhibition processes have been found to be compromised in ADHD, but not in NF1 when compared to healthy controls, suggesting that response inhibition deficits may be less strong compared to those occurring in ADHD [57]. It has also been suggested that NF1/ADHD is not associated with increased frequency of executive deficits related to behavioral inhibition as it is in the general ADHD population [6]. A study comparing individuals with NF1/ADHD with a group of participants with ADHD and no NF1 found that ADHD symptomatology in NF1 did not exacerbate attention deficits and suggested that ADHD cannot account for all attention impairments in NF1 [57].

Various brain-based characteristics associated with NF1 have been presumed to contribute to the neurocognitive deficits in NF1. For example, increased brain volume due to increased white matter and an enlarged corpus callosum appear to be characteristic of children with NF1 and may interfere with integration and processing of information [56]. Regarding attentional processes specifically, an fMRI study investigating ventral attention networks in the brain found that children with NF1 demonstrated hypoactivation in the temporoparietal junction and the anterior cingulate cortex when compared to typically developing children, which was associated with poorer selective attention and attentional control [58].

The presence of attentional deficits in children with NF1 is associated with even greater risk for poorer performance in other cognitive functions, learning, social skills, and academic achievement [12, 56]. Social outcomes in particular appear to be worse in this group than in children with NF1 only [56]. A study examining face perception in children with NF1 found that sustained attention to faces in a social context is reduced in this population, which may inhibit the processing of socially relevant information needed for successful reciprocal social interactions [59]. Research also suggests that the risk of developing a specific learning disorder is higher in children with NF1 who have a diagnosis of ADHD [6]. As with other domains, it is suggested that while the literature on attentional problems primarily investigates these issues in childhood, these difficulties likely persist into adulthood without treatment.

2.6 Executive functions

Executive functions include a wide range of higher-order cognitive processes that serve goal-directed behaviors, including working memory, planning, organization, inhibition, flexibility. Because executive functioning encompasses a wide range of processes, studies investigating executive functioning in individuals with NF1 vary greatly in terms of the areas of focus and measures used [37]. Of note, many neuropsychological measures of executive function have been found to lack correlation with functional/behavioral ratings of the same constructs when evaluating individuals with NF1, and it has been suggested that Behavior Rating Inventory of Executive Function (BRIEF) rating scale items are more predictive of performance in real-world tasks outside of the structured testing environment [43].

Children with NF1 demonstrate significant impairments across all composite scores on the BRIEF [43, 52]. Differences remained even after controlling for VIQ [43].

Despite this, executive dysfunction has been noted on performance measures as well. Beaussart et al. [50] conducted a meta-analysis of executive functioning in children with NF1. They included 19 studies in their analysis, with a total of 805 children with NF1 and 667 control subjects. They found a moderate effect with executive functions, indicating that children with NF1 had greater overall executive functioning impairments than controls. However, they noted variability in sub-domains of executive functions including cognitive flexibility, planning and problem solving, inhibitory control, and working memory. They found significant effect sizes for each sub-domain, with moderate effect sizes for working memory and planning/organization and small effect sizes for cognitive flexibility and inhibition. Significance remained even after controlling for moderating variables of executive functioning measures, control group composition, IQ, and ADHD.

Weaknesses with working memory in NF1 populations are much more consistent and prevalent than with explicit memory. Several studies have documented verbal and visual working memory weaknesses [10, 14, 49]. Beaussart et al. [50] found a moderate to large effect size for working memory problems. The effect size for verbal working memory was larger than nonverbal working memory. They note that differences in effect size may be due to the psychometric properties of the working memory tasks [50].

Executive function deficits have also been distinguished in NF1 adult populations. In particular, weaknesses in working memory and cognitive flexibility have been noted [21]. Very limited information is known with regard to executive functions in the elderly. Costa de et al. [22] noted working memory weaknesses in this population; however, this study was limited by a very small NF1 group.

2.7 Academic learning

Academic learning entails the use of basic educational skills to be successful in the classroom. This includes reading, writing, and mathematics. Academic learning struggles are one of the most common concerns of parents of children with NF1 [54]. Estimates of learning disabilities have significantly varied between studies. Research has found prevalence rates of learning difficulties to be 20–70% [5, 6, 41]. The variability is in part due to how each study operationalized the definition of "learning disability," as the definition of learning disability has changed over the years. Previously an IQ-academic discrepancy model in which an individual performing much more poorly in an academic skill as compared to his or her overall intelligence level was used to define learning disability; however, this limited definition of a specific learning disability has received increased scrutiny and is rarely used today [60]. Hyman et al. [6] found that 20% of their child sample met the strict definition (discrepancy model) of specific learning disability (SLD), which is double the rate found in the normal population. In contrast, Krab et al. [41] used a different definition that examined "learning efficacy" and found that 75% percent of their sample had learning difficulties based on this definition. This study also noted a connection between disease severity and increase in learning struggles; however, this pattern has not been consistent in other studies. They argue that this is due to the fact that other studies do not systematically measure severity and other methodological issues.

Despite the disagreement in overall prevalence rates of learning struggles, studies have been consistent in that NF1 is associated with significantly higher rate of learning disabilities in children when compared to normative sample and sibling controls [5, 6, 38, 41].

Specific learning disability in the area of reading has been noted in childhood NF1 populations. Weaknesses have been found regarding phonological awareness, word decoding, fluency, and reading comprehension [5, 38, 39, 54]. Cutting and Levine [38] compared four groups that included children without reading difficulties, a reading disability group, an NF1 group without reading disability, and an NF1 group with reading disability. They found that children with NF1 with reading struggles performed similarly as the reading disability group.

Learning struggles in mathematics and written expression in children with NF1 have also been noted. Math difficulties have been noted with computation and application of math concepts [6, 41, 49, 54]. Krab et al. [41] found that 23% of their NF1 sample met the criteria for a specific learning disability in mathematics and 77% demonstrated learning efficiency struggles with mathematics. However, another study did not find learning disability in mathematics [46]. Problems with writing including graphomotor control (penmanship) and spelling have noted as well [49, 61].

2.8 Adaptive skills

Adaptive skills are a collection of functional behaviors needed to effectively meet the demands of our environment. Adaptive functions are often divided into Conceptual skills, Practical skills, and Social skills. The DSM-V notes that adaptive deficits result in the failure to meet developmental and social standard for independent living without support.

Several studies have noted adaptive deficits in children with NF1 [15, 62]. In a cross sectional study of 104 children with NF1, Eby et al. [15] found that 46.5 percent of their sample demonstrated adaptive functioning impairment. They found mild reductions across Conceptual, Social and Practical skill domains. Less is known about the specific adaptive domains that are impacted in adults and elderly adults. While adaptive demands change as individuals develop across the lifespan, it is likely that because cognitive difficulties remain stable with age, adaptive deficits are associated with adults with NF1 as well.

3. NF2 and schwannomatosis

We were unable to locate any studies that directly investigate cognitive weaknesses in NF2 or Schwannomatosis populations. It is likely that this has not been investigated, as these disorders are rarer and typically have less brain involvement. As such, we will discuss the cognitive effects of NF2 and Schwannomatosis with regard to common symptoms associated with these disorders and how these symptoms may impact cognitive functions.

NF2 is defined in part by bilateral vestibular schwannomas [63]. Vestibular schwannomas are nonmalignant tumors that arise from eighth cranial nerve. The vestibular schwannomas can impact hearing, balance, at times vision, and facial weakness [65]. Hearing loss is progressive due to the presence of schwannomas and treatment, and it has been found in 60% of adults and 30% of children with NF2 [65]. Hearing loss can lead to decreased QoL [66] and can impact language development. Hearing loss has also been associated with decreased performance on intellectual and academic skills [67, 68]. Olivier et al. [69] investigated sensorineural hearing loss associated with intellectual and learning struggles in children with brain tumors. They found that children with severe hearing loss demonstrated greater difficulty with reading with weaker phonological skills, processing speed, and reading [69].

Schwannomatosis is clinically distinguished from NF2 by the lack of bilateral vestibular schwannomas and ependymomas [64]. All neurofibromatoses, including NF1, NF2, and schwannomatosis, have schwannomas. Depending on the size and location, schwannomas can also be associated with pain [3]. Chronic pain has been associated with cognitive weaknesses with memory, attention, processing speed, and executive functions [70]. More research is needed to determine the possible cognitive sequalae associated with NF2 and Schwannomatosis. Further research is also warranted to distinguish whether differences in these sequelae exist depending on the age of the individual.

4. Conclusions

Neurofibromatosis is associated with effects on cognitive domains that impact learning, adaptive functioning, and quality of life across the lifespan of individuals affected by these disorders. The three distinct genetic disorders that encompass neurofibromatosis have their own genetic variant, symptoms, and disease course that result in differences in phenotypic expression as well as impact on the brain. While patterns of neurocognitive outcomes vary among and within each disorder, relatively less research has been conducted on those with NF2 and Schwannomatosis as compared to NF1. In particular, more research is needed investigating cognitive sequalae associated with NF2 and Schwannomatosis as these conditions at least indirectly are associated with cognitive weaknesses which can impact overall quality of life, likely from diagnosis through late adulthood.

Within NF1, cognitive deficits are much more common yet highly variable within and between individuals. The heterogeneity of the cognitive outcomes is likely due to a combination of reasons, including genetic factors that have not been adequately elucidated yet, as well as methodological issues. Current research does not yet indicate to what extent differences among each NF phenotype are related to differences in typical cognitive deficits associated with each genetic variant. Common methodological issues in the literature include composition of control groups, evolving/varying definitions of cognitive domains and learning disorders, and limitations inherent in specific cognitive tests. Nonetheless, the current literature indicates that IQ, expressive language, visual spatial and fluid reasoning, and working memory are commonly impacted to some extent. Attention and executive functions appear to also be compromised in individuals with NF1, which are a factor in difficulties in receptive language, memory, academic skills, and adaptive skills. Most studies are focused on children, though existing adult studies suggest that cognitive deficits are present and similar to child studies, likely due to the stability of difficulties over time. Overall, evaluation of cognitive skills in those with neurofibromatosis is important in order to determine the functional impact that potential deficits may have on an individual, especially with regard to academic performance and adaptive functioning. This is especially significant due to the fact that neurofibromatosis is not a curable condition, which necessitates treatment that directly targets cognitive, academic, and adaptive problems directly. Regular monitoring of these individuals with respect to cognitive skills can aid in necessary intervention planning and should occur as early as possible to detect and treat issues that can arise early in development.

Conflict of interest

The authors have no conflict of interest.

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