

# An executive functioning perspective in neurofibromatosis type 1: from ADHD and autism spectrum disorder to research domains

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## Abstract

**Purpose** Neurofibromatosis type 1 (NF1) is a rare monogenic disorder associated with executive function (EF) deficits and heightened risk for attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). The goal of this paper is to understand how EFs provide a common foundation to understand vulnerabilities for ADHD and ASD within NF1.

**Methods** A literature review and synthesis was conducted.

**Results** EF difficulties in working memory, inhibitory control, cognitive flexibility, and planning are evident in NF1, ADHD, and ASD. However, relatively little is known about the heterogeneity of EFs and ADHD and ASD outcomes in NF1. Assessment of ADHD and ASD in NF1 is based on behavioral symptoms without understanding neurobiological contributions. Recent efforts are promoting the use of dimensional and multidisciplinary methods to better understand normal and abnormal behavior, including integrating information from genetics to self-report measures.

**Conclusion** NF1 is a monogenic disease with well-developed molecular and phenotypic research as well as complementary animal models. NF1 presents an excellent opportunity to advance our understanding of the neurobiological impact of known pathogenic variation in normal and abnormal neural pathways implicated in human psychopathology. EFs are core features of NF1, ADHD, and ASD, and these neurodevelopmental outcomes are highly prevalent in NF1. We propose a multilevel approach for understanding EFs in patients with NF1. This is essential to advance targeted interventions for NF1 patients and to advance the exciting field of research in this condition.

**Keywords** Neurofibromatosis 1 · Executive functions · Attention-deficit/hyperactivity disorder · Autism spectrum disorder

## Introduction to neurofibromatosis 1 and related neurodevelopmental outcomes

Neurofibromatosis 1 (or NF1) is a neurocutaneous disorder affecting 1 in 2700 live births [1]. Diagnostic criteria for NF1 include at least two of the following: 6 or more café-au-lait macules, two or more neurofibromas or one plexiform

neurofibroma, freckling in axillary region, optic glioma, multiple lisch nodules, distinctive osseous lesion, or a first-degree relative with NF1 [2] (see [3] for a review of the clinical phenotype). NF1 is caused by a pathogenic *NF1* heterozygous variant. The *NF1* gene encodes for neurofibromin which negatively regulates the Ras pathway [3, 4].

NF1 research has grown exponentially in the last 20 years thanks to the common efforts of researchers, funding agencies, private philanthropy, and advocacy groups. The result is extensive new knowledge into the neurobiology of the disease and further characterization of the NF1 phenotype. The result, a recent FDA approved treatment [5] for plexiform neurofibroma, brings hope for many patients and families. In addition, new animal models [6, 7] complement existing well-established NF1 models to increase opportunities for research and development of interventions. Despite this progress, molecular- and disease-targeted interventions for cognitive deficits remain elusive.

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NF1 increases risk for cognitive deficits and neurodevelopmental disorders [8–11]. Research indicates a characteristic “downward shift” in intellectual functioning, where individuals with NF1 score approximately 1 standard deviation below the general population (e.g., [12]) as well as their unaffected siblings [13]. A minority of individuals with NF1 show more severe intellectual deficits, with about 4–8% of individuals with NF1 meeting criteria for an intellectual disability [10, 13]. Youth with NF1 are much more likely to develop attention deficit/hyperactivity disorder (ADHD) with rates ranging from 38 to 67% [13, 14] and autism spectrum disorder (ASD) with estimates ranging from 10.0 to 39.2% using a broader phenotype [15, 16]. Specific learning disorders, such as dyslexia, are observed in 19 to 61% youth with NF1 [13, 17]. Difficulties with motor coordination, planning, weakness, and fatigue are also evident in NF1 [18].

Taken together, NF1 increases risk for various cognitive and neurodevelopmental outcomes. These outcomes are closely related to behavioral and social functioning which are among the strongest predictors of quality of life in NF1 [19–22]. Therefore, it is important to understand factors that contribute to these difficulties. The purpose of this paper is to examine current research on executive function (EF) in the NF1 population and how EF deficits may contribute to general and specific vulnerability for neurodevelopmental difficulties within NF1, with a focus on the clinical diagnoses of ADHD and ASD. We will also review the limitations of this approach and propose recommendations to advance clinical and translational research to improve NF1 interventions.

## Executive function in youth with NF1

Executive function (EF) refers to a set of interrelated skills that are responsible for purposeful, goal-directed, problem-solving behavior [23]. EF includes initiating goal-directed behavior, inhibiting competing actions or stimuli, planning and selecting relevant task goals, organizing behavior to solve complex problems, flexible shifting of problem-solving strategies when necessary, and monitoring and evaluating problem-solving behavior ([23]; see Fig. 1c).

Extensive research has been done to try to understand the magnitude of EF deficits in NF1 and the impact such deficits have on cognition, behavior, and academic achievement. Children with NF1 have deficits in multiple EF domains when measured using daily life and laboratory measurement techniques [26]. Children and adults with NF1 exhibit extensive EF compromise in working memory capacity, inhibition, cognitive flexibility and planning [26], with effects similar to those found in ADHD and ASD samples (see Table 1). Fluency or generativity is also lower in NF1 samples [30], but it has received less attention in the NF1 literature. These EFs are thought to be primarily mediated by the prefrontal

**Fig. 1** A research domain approach to characterizing behavioral and social phenotypes in NF1 across multiple levels. **(a) Functional outcomes.** Individuals with NF1 exhibit increased functional impairment in behavioral, social, emotional, and academic domains and, relatedly, lower quality of life. **(b) Diagnosis.** NF1 greatly increases the likelihood for both ADHD and ASD [4]. In the general population, genetic and phenotypic correlations between ADHD and ASD are substantive [4]. Within NF1, ADHD and ASD diagnostic categories and symptom dimensions also overlap [16]. ADHD and ASD are predictive of functional outcomes in NF1 (e.g., [24, 25]). **(c) Executive functions.** Working memory, inhibitory control, cognitive flexibility, and planning are interrelated executive functions [23] and reduced in NF1 [26]. EF difficulties in these domains are also associated with ADHD and ASD (Table 1) and likely contribute to common and unique risk for diagnostic and functional outcomes. **(d) Neurobiology.** The neurobiological underpinnings of EF and ADHD and ASD diagnoses in NF1 are just beginning to be explored. The dorsolateral prefrontal cortex, ventromedial prefrontal cortex, and the dorsal/ventral anterior cingulate cortex are consistently associated with EFs across typically and atypically developing populations. The heterogeneity in functional connectivity in NF1 in frontoparietal, frontostriatal, and ventral attention networks may alter EF profiles in NF1. **(e) Genetic/Molecular/Cellular.** Pathogenic variants in *NF1* alter Ras signaling pathways with downstream effects on molecular and cellular phenotypes [3, 4]. Differences at this level provide a foundation for atypical neurodevelopmental trajectories

cortex (Fig. 1d; [13, 26, 31] and have been linked with academic, social and motor outcomes. The severity or variability of NF1 also needs to be considered when examining EFs in this population. For example, young patients with NF1 and an optic pathway glioma or other CNS tumors show increased EF difficulties compared to those without CNS tumors [32]. The most common EFs affected/studied in NF1 patients are discussed subsequently.

## NF1 and working memory

Working memory capacity plays a fundamental role in actively holding information in the service of problem solving [23]. Working memory difficulties are evident across the life span in NF1 samples [33–35], with effect sizes in the moderate range (Table 1). Differences between working memory skills of youth with NF1 compared to controls may increase over-time [26]. A recent meta-analysis shows that verbal and visual-spatial working memory are both negatively affected in NF1, but verbal working memory may be relatively more affected [26]. However, only two included studies examined visual-spatial working memory thus results should be interpreted cautiously. In NF1, working memory plays an important role in academic outcomes [36] and may allow some to experience more benefit from educational supports like phonics-based reading intervention [37].

Evidence from both NF1 ± mice and humans indicates hypoactivation in frontoparietal and frontostriatal networks, including the dorsolateral prefrontal cortex (dlPFC), which is associated with working memory deficits in humans [38]. In

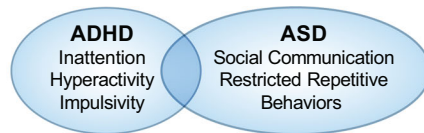
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### a Functional Outcomes

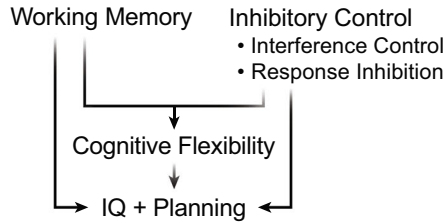
Behavioral + Social + Academic + Emotional Regulation + Quality of Life

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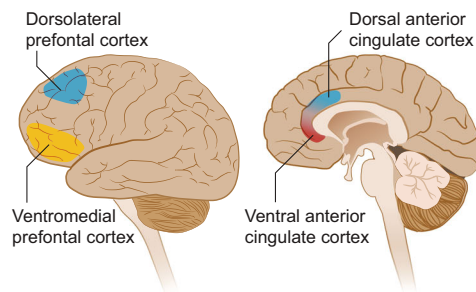
### b Diagnosis



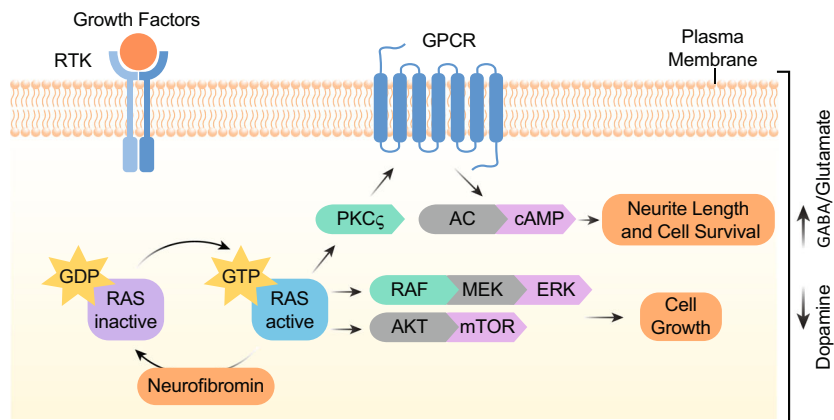
### c Executive Functions



### d Neurobiology



### e Genetic Molecular/Cellular



adults with NF1, there is reduced functional connectivity in the left dlPFC and the right parietal cortex [35], both implicated in the frontoparietal network. Adults with NF1 exhibit increased activation relative to controls in the posterior cingulate cortex and temporal regions [35]. Within NF1, increased connectivity between the posterior cingulate cortex and frontal

and parietal cortices is associated with increased working memory performance [35]. Additionally, a pilot study found that youth with NF1 demonstrated improved performance on tasks related to attention and spatial working memory following 6–10 weeks of Cogmed—a cognitive training program [39]. Improvements in cognitive outcomes were attributed to

**Table 1** Summary of published effect sizes of NFI, ADHD, and ASD on executive function domains

Clinical samples	Working memory		Inhibitory control		Cognitive flexibility		Planning/problem solving		Fluency/generativity	
	SMD	$k$	SMD	$k$	SMD	$k$	SMD	$k$	SMD	$k$
NFI <sup>a</sup>	-0.63 (-0.39, -0.87)	7	-0.37 (-0.17, -0.56)	6	-0.30 (-0.56, -0.05)	7	-0.72 (-1.06, -0.38)	10	-	-
ADHD <sup>b</sup>	-0.54 (-0.30, -0.78)	156	-0.52 (-0.24, -0.80)	438	-0.35 (-0.9, -0.61)	260	-0.51 (-0.16, -0.86)	37	-0.49 (-0.24, -0.74)	50
ASD <sup>c</sup>	-0.47 (-0.37, -0.57)	70	-0.46 (-0.38, -0.53)	103	-0.48 (-0.36, -0.60)	38	-0.55 (-0.44, -0.66)	51	-0.45 (-0.35, -0.55)	56
HF ASD <sup>d</sup>	Verbal -0.67 (-0.45, -0.88)	30	-0.41 (-0.31, -0.51)	42	-0.59 (-0.48, -0.71)	37	-0.62 (-0.42, -0.83)	21	-0.60 (-0.43, -0.78)	23
	Spatial -0.58 (-0.45, -0.71)	28		34						
HF ASD without ADHD <sup>d</sup>	Verbal -0.53 (-0.45, -0.50)	8	-0.32	11	-0.61	13	-0.24	5	-0.68	5
	Spatial -0.50	11		59						45

SMD, standardized mean difference (95% confidence interval) reported in the literature. Negative effect size indicates lower executive functioning skills in clinical sample.  $k$ , number of studies.  $I^2$ , percentage of the variability of effect size due to heterogeneity instead of measurement error. HF, high functioning, defined as IQ > 70. Fluency/generativity meta-analytic effect size not available for NFI. 95% CI not available for HF ASD without ADHD subgroup

<sup>a</sup>Beaussart et al. [26]

<sup>b</sup>Pievsky and McGrath [27]

<sup>c</sup>Demetriou et al. [28]

<sup>d</sup>Lai et al. [29]

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increased synchrony between the frontoparietal and visual cortex [39].

## NF1 and inhibitory control

Inhibitory control works in conjunction with working memory to maintain progress towards one's goal, by sustaining focused attention and inhibiting behavioral and cognitive responses that are inconsistent with one's goal [23]. Meta-analysis indicates that individuals with NF1 have small but significant reduction in inhibitory control, relative to controls [26]. The magnitude of effect of NF1 on types of inhibitory control is similar, including interference control/cognitive inhibition, selective/focused attention, and response inhibition [26]. Inhibitory control deficits in NF1 are found in those with and without ADHD comorbidity [40]. The developmental course of deficits in inhibitory control in NF1 is not well known.

Difficulty with inhibitory responses in NF1 is associated with decreased white matter integrity within the anterior thalamic radiations within the fronto-striatal circuit [41]. In addition, NF1-related inhibitory control difficulties are associated with decreased functioning in the pre-supplementary motor area, fusiform gyrus/posterior cerebellum, and the inferior occipital gyrus [42]. Additionally, in NF1, the ventral attention network is linked with attentional control and selective attention difficulties [43]. Elevated medial frontal GABA is also associated with increased response speed in NF1 and decreased response speed in controls [44]. Altered GABA/glutamate ratios have also been linked to NF1-related cognitive deficits [4, 45–47], and abnormal frontal GABA physiology in NF1 may be of particular importance to inhibitory control [44]. Hypofunctioning of mesolimbic dopaminergic pathways is associated with GABA/glutamate imbalance in NF1 [48]. This may contribute to differences in frontostriatal circuit function in NF1 and attentional difficulties within NF1 animal models [49, 50].

## NF1 and cognitive flexibility

Working memory and inhibitory control contribute to cognitive flexibility which promotes switching between tasks, perspective taking, and utilizing a range of problem-solving approaches [23]. Cognitive flexibility also provides a neurocognitive foundation for creativity and theory of mind [23]. In youth with NF1, cognitive flexibility skills are lower compared to controls and the effect size is small [26]. In particular, youth with NF1 demonstrate more difficulty with reactive flexibility—or adapting problem solving behavior in the context of inconsistent environmental responses [51]. These differences are related to ASD-associated behaviors [30]. Deficits in cognitive flexibility remain after controlling for IQ [51] and spatial working memory and inhibition [30],

indicating the deficits in cognitive flexibility in NF1 are not merely a function of other related EF weaknesses [30]. To our knowledge, no studies have investigated the neurobiological origins of cognitive flexibility specifically in NF1.

## NF1 and planning and problem solving

Higher-order EF processes, like planning and problem solving, are influenced by working memory, inhibitory control, and cognitive flexibility [23]. Planning is a complex construct and includes the ability to think ahead and consider consequences of actions or the sequencing of steps to accomplish a goal [52]. Planning and problem-solving skills are significantly lower in youth with NF1 relative to controls and in the moderate range (Table 1), but there is significant heterogeneity in effect sizes between studies [26]. It is currently unclear which sample or methodological factors are associated with variability in effect size. Differences in planning between NF1 and controls are not solely due to cognitive flexibility, visual-spatial reasoning, and/or ASD behavioral symptoms [30], suggesting deficits in planning skills are independent of other factors in NF1. Planning skills in NF1 youth may also be related to academic skills [36].

Youth with NF1 also experience difficulty with motor planning, motor coordination, and reduced muscle strength and fatigue [53–55]. EF planning deficits are associated with laboratory measures of motor planning [54], thus weaknesses in EF planning may contribute to motor difficulties observed in this population or vice versa. The impact of how motor deficits and cognitive skills influence one another on tasks that need a mediated motor output is not well understood in NF1. However, motor impact in NF development and cognition is beyond the scope of this paper.

Across a range of non-NF1 samples, planning appears to be a bilateral process involving the DIPFC, frontal eye fields, supplementary motor area, precuneus, caudate and anterior insula, and inferior parietal cortex [56], which have been implicated in other EFs within NF1 samples.

## Summary of executive functions in NF1

Taken together, specific EF deficits in NF1 are present across the lifespan. Deficits in working memory and planning/problem solving are in the moderate range, whereas deficits in inhibitory control and cognitive flexibility are slightly smaller (Table 1). Frontoparietal, frontostriatal, and ventral attention networks are implicated in the neural pathways mediating EF networks in NF1; however, research investigating the neural correlates of specific EFs in NF1 has been largely limited to the working memory [35, 38] and inhibitory control domains [41–43]. EF difficulties in NF1 are associated with decreased academic [36], motor [54], and social functioning

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[30]. Comparing EF outcomes between NF1, ADHD, and ASD samples may be the first step to increase our understanding of common and unique neurocognitive risk in NF1. However, to guide diagnosis and treatment, EFs should be integrated in a multi-level phenotypic characterization from genomics and circuits to behavior and self-reports, in order to explore basic dimensions of functioning.

## **Executive functions in ADHD and ASD in the general population**

Both ADHD and ASD are considered neurodevelopmental disorders with onset in childhood, and although causal links are currently unknown, both disorders are highly heritable with approximately 64–91% of both phenotypes being accounted for by genetics [57, 58]. ADHD and ASD symptom dimensions are correlated at both a phenotypic and genetic level [4]. Genetic correlations between ADHD and ASD symptom dimensions range from 0.33 to 0.56 [59, 60].

ADHD is characterized by elevated levels of inattention and/or hyperactivity/impulsivity in comparison to same-aged peers [61]. EF deficits largely contribute to the ADHD behavioral phenotype [62–64]. Relative to controls, individuals with ADHD demonstrate weaknesses in working memory, response inhibition, sustained attention, cognitive flexibility, planning, and fluency/generativity [27, 65]. However, the severity of EF deficits in ADHD varies by age and type of assessment [65, 66].

Alterations in the fronto-dorsal striatal network are related to disruptions in the mesocortical dopaminergic pathway [67, 68]. Additionally, altered reward circuitry, which is linked to the mesolimbic dopaminergic pathway, is associated with delay aversion contributing to impulsivity, inattention, or hyperactivity, depending on context [67, 68]. EF deficits in ADHD youth are related to hypoactivation in the frontoparietal and ventral attention networks, with increased activation also observed in the default, ventral attention, and somatomotor networks [69, 70].

ASD is characterized by social communication difficulties and restricted interests/repetitive behaviors. ASD is a highly heterogeneous disorder in symptom presentation and severity level. However, EF deficits in ASD are common and include weaknesses in working memory, inhibitory control, cognitive flexibility, planning, fluency, and concept formation [28], with effects in the moderate range across EF domains (Table 1). EF deficits in ASD appear to be largely stable across development [28], observed in individuals with ASD without intellectual disability [29, 71, 72], and are negatively associated with quality of life [73]. Additionally, variation in EF skills account for some phenotypic heterogeneity within ASD, including in social functioning [74], restricted interests/repetitive behaviors [75], disruptive behavior [71], and theory

of mind [76]. Approximately 28% of individuals with ASD also experience comorbid ADHD, among other comorbid disorders which are associated with EF impairments [77].

Data from a pooled resting-state fMRI analysis indicates that individuals with ASD exhibit corticocortical and inter-hemispheric functional hypoconnectivity, as well as hyperconnectivity in local subcortical circuits [78]. This indicates that during EF tasks individuals with ASD may prioritize the engagement of subcortical local circuits over long-range circuits [79]. Increased hyperconnectivity in ASD is associated with greater impairment [80]. Additionally, hypoconnectivity within frontoparietal and ventral attention networks is associated with ADHD symptoms in ASD [81].

## **ADHD and ASD in NF1: the role of executive function**

From a clinical perspective, it is clear that EF deficits are central to the comorbidity between NF1 and neurodevelopmental outcomes that affect quality of life. EF impact is not specific to academic performance but spans multiple domains of functioning (Fig. 1), from social interaction to economic independence. Traditional clinical assessments often measure EF functioning to inform diagnostic clarification, often related to ADHD, ASD or learning disabilities. While this categorical approach helps patients and families to access services and remediation interventions, it provides very little information about neuroscience and the neurobiological underpinnings of these manifestations. However, as this approach is the one that is currently used, we will summarize the findings from the limited studies examining EF deficits in patients with NF1 and ADHD and or ASD symptomatology.

### **NF1 and ADHD**

In the NF1 population, ADHD diagnosis has been reported to be between 38 and 67% [13, 14]. Those individuals are expected to have a more complex profile of EF and attention deficits than do the NF1 patients without an ADHD diagnosis. In addition, the presence of ADHD has been found to be a major risk factor for poor social functioning [11, 25, 82], as well as poor general intellectual functioning [14, 83]. Although there is evidence that cognitive control deficits are not limited to NF1 patients with comorbid ADHD [40, 84], children with both disorders are acknowledged as among the most severely affected in terms of academic performance, social interactions, and behavioral problems [11, 14, 25].

Children with NF1 with concomitant diagnosis of ADHD experience significant deficits in visual and verbal working memory [85]. Working memory is a particularly compelling target for intervention, given its critical role in the development of most cognitive and academic outcomes. In healthy

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children, it has been suggested that developmental increases in IQ are associated with age-related improvements in working memory and processing speed [86]. Because working memory capacity increases two- to three-fold from age 4 to 16 [87], disruption of the development of these processes can significantly curtail a wide range of the child's abilities over time. This may take the form of diminished IQ or difficulty with other aspects of EF and academic performance. For example, children with reading difficulties frequently have deficits in working memory that appear to contribute to problems with phonological memory [88, 89]. Math skills are also strongly linked to working memory capacity in typically developing children accounting for 20–57% of the variance in math performance [88, 90].

From a developmental perspective, it is reasonable to hypothesize that improving working memory in children with NF1 may help to offset problems with IQ, EF, and academic performance over time. Computerized working memory training interventions that have been tested on multiple neurological conditions to increase working memory are currently being tested on patients with NF1 [91]. If proven beneficial, these interventions may be used during the developmental periods to improve working memory, and have downstream effects on cognitive domains and functioning across domains. Assessment and interventions targeting improvements in EF should include patients from pre-school age to early adulthood given findings that EF deficits persist into adulthood in NF1 [25, 34, 82].

## NF1 and ASD

Parent and teacher report indicate that children with NF1 exhibit significant social functioning difficulties. They are perceived as socially isolated or sensitive as well as displaying less leadership behaviors [11, 16, 92]. Youth with NF1 show higher levels of autistic traits or meet full diagnostic criteria of ASD [15, 16]. For example, 44% of an NF1 sample demonstrated restricted and repetitive behaviors at least one standard deviation above the mean [11]. Additionally, problems with flexibility, transitions, and manifestations [92]. Impairment in social communication and lack of motivation in social interactions are reported in at least 30% of these children. From a neuropsychological perspective, these symptoms may be due to the complex dysfunction of frontal lobe pathways and EF alterations [93]. It is clear that ASD diagnosis in NF1 is not a homogenous profile and may differ significantly from ASD expression in non-NF1 samples.

The International NF1-ASD Consortium Team (INFACT) was created to further understand the significantly elevated rates of ASD symptomatology seen in NF1 samples. A multi-site analysis of 531 individuals with NF1 found that patients exhibited a significant burden of autistic traits and symptoms along a continuous distribution that encompassed

the full range of severity, from mild (subclinical) to severe (clinical) [16]. The consortium sample confirmed that more than 13.2% presented with severe symptoms of ASD and more than 43.2% were above the threshold scores for an ASD diagnosis. When NF1 was inherited, there was a high degree of within family association for the severity of autistic traits. Research into the biological mechanisms impacting these social deficits is currently on-going [47, 94].

The characterization of the behavioral and cognitive phenotype, genetic correlations and potential translation into therapeutics is an essential next step for the NF1 population. Of special interest is improving our understanding of cognitive flexibility—a key EF component. Difficulty with cognitive flexibility is also observed in NF1-related comorbidities, like ASD [95, 96] and anxiety [97, 98]. Difficulties with cognitive flexibility may contribute to increased externalizing and internalizing behavior [99, 100], especially in the context of parental inconsistency [101]. Thus, the interaction between cognitive flexibility and inconsistent contingency management in the environment may be one pathway to increased behavioral or emotional dysregulation in the NF1 population.

In summary, current advances in our understanding of increased rates of ASD symptomatology in patients with NF1 have demonstrated that the association between the syndromes is real and most likely associated at the genetic level. However, we have only taken the first steps into a completely novel field that has the potential to yield an abundance of research possibilities. By analyzing phenotypes and genetic correlations and weighing potential pharmacological and non-pharmacological interventions, we can continue to explore this relationship and the correlations with other genetic conditions as well.

## Discussion

The goal of this paper is to examine the impact that EFs have on the profile of neurodevelopmental outcomes in patients with NF1. At a group level, EF difficulties in NF1 are diffuse across EF domains, with moderate deficits in working memory and planning/problem solving domains and smaller deficits in inhibitory control and cognitive flexibility domains [26]. Evidence from NF1 human and animal studies implicates frontoparietal and frontostriatal circuitry working memory functioning [35, 38, 39] and frontostriatal and ventral attention circuits in inhibitory control functioning [41–43]. EFs serve as a putative mechanism underlying the relationship between NF1 and ADHD and NF1 and ASD and allow us to understand variability in ADHD and ASD within the NF1 population.

It is essential that we advance our understanding of the neurobiological variability of neural pathways, molecular and genetic factors that impact NF1. This will improve our

ability to develop targeted molecular interventions for cognitive deficits in this population. However, doing so requires a shift away from using a categorical framework for ASD and ADHD diagnosis and towards a detailed phenotypic evaluation (neuropsychological testing plus behavioral scales) in conjunction with objective neuro-biological assessments (i.e., fMRI, resting state fMRI, and genetic pathways; [102]).

**Limitations and future directions for research** First, differences in EF measurement between studies and limited reliability of single EF domain measures limit our ability to compare and replicate findings. The neurocognitive committee of the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration has provided guidance on measurement within the domain of attention [103] which should support measurement consistency between studies. Additionally, a latent factor approach with multiple indicators of EF domains will aid in the reduction of measurement error and improve replicability across studies [104]. Second, the majority of EF and cognitive research in NF1 is from case-control designs and analyses within NF1 samples are limited by sample size. These group-based EF differences may not apply to individual-level data, which limit their utility in understanding how to tailor intervention to individual NF1 cases. More analysis examining EF profiles or clusters within NF1 and linking these across multiple levels (e.g., neurofunctional and behavioral) are needed [24, 105]. Larger sample sizes and multidimensional and multidisciplinary research approaches need be strongly supported [8]. Third, neurobiological studies of EF in NF1 are limited to working memory and inhibitory control/attentional domains. The field would benefit from studies to extend our understanding of which neural circuits underpin EF cognitive flexibility, planning, and fluency/generativity domains. Important efforts are being made to improve our understanding of the neurobiological underpinnings of psychiatric and cognitive conditions [102, 106].

**Implications of multilevel phenotyping** A multi-level characterization of EF in NF1 (see Fig. 1) will help to provide an understanding of targets for interventions and ways to tailor intervention to individual cases. EFs may provide a general target to improve behavioral, social and academic functioning in the NF1 population. Given high prevalence rates of multiple neurodevelopmental disorders in NF1 and their comorbidity, EF provides a common or shared vulnerability target, which may help to maximize improvement across multiple domains of functioning.

Significant advances in the understanding of functional neural circuits implicated in brain function in patients with NF1 have been made. Using resting state fMRI, small studies have shown an overall decrease of the short and long-distance connectivity in the default network in patients with NF1

compared with typically developing controls [107]. In addition, changes in brain connectivity were observed after 12 weeks of treatment with lovastatin [107] and after computer training intervention for working memory [39]. A recent translational research study comparing brain functional connectivity in animal models of NF1 and patients with diagnosis of NF1 showed that decreased connectivity using resting state fMRI is a feature that is present in animals and patients carrying the NF1 mutations [108]. Additionally, the biological correlation between NF1 animal models and humans can be used to advance testing for medications and other interventions into clinical trials. However, correlations with high order cognitive function may require better phenotyping into complex models that allow understanding from the molecular pathway to the clinical manifestations.

Taken together, EF difficulties play an important role in the overall cognitive difficulties in NF1 and a core role in the social and behavioral profiles in this population; however, they are not fully understood [30]. We need to better understand the impact of EF deficits on these neurodevelopmental outcomes in individuals with NF1 beyond current DSM categorical diagnosis. As we better understand the neurobiology of EFs in individuals who are typically developing and those with developmental and neurodevelopmental disorders, we can better translate our knowledge to specific neurogenetic disorders like NF1.

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## Compliance with ethical standards

**Conflict of interest** Not applicable.

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