A Neuropsychological Perspective on Attention Problems in Neurofibromatosis Type 1

Alexandra K. Templer1, Jeffrey B. Titus2,3, and David H. Gutmann1

Abstract
Cognitive problems are common in children with neurofibromatosis type 1 and they can often complicate treatment. The current literature review examines cognitive functioning in neurofibromatosis type 1, with a specific focus on executive functioning. This includes exploration of how deficits in executive functioning are expressed in children with neurofibromatosis type 1 and how these deficits contrast with ADHD. The value of investigating subcomponents of executive functioning is discussed, as are implications for effective treatment and future research. (J. of Att. Dis. 2012; XX(X) 1-XX)

Keywords
neurofibromatosis, ADHD, cognitive functioning, NF1, ADD/ADHD

Introduction
Neurofibromatosis Type 1 (NF1) is one of the most common genetic disorders affecting the nervous system. It is an autosomal dominant disease that affects between 1 in 2,500 and 1 in 3,000 individuals regardless of gender, race, or ethnicity (Ferner & Gutmann, 2002; Huson, Compston, Clark, & Harper, 1989). Early research focused on classifying and studying the physical complications of the disorder such as café-au-lait spots, neurofibromas (peripheral nerve sheath tumors), brain tumors, bone deformities, Lisch nodules, and other malignancies. In the 1990s, research on the cognitive and learning difficulties experienced by individuals with NF1 became more prominent, and further investigations suggested that cognitive problems in NF1 were among the most common variables to negatively affect quality of life (Gutmann et al., 1997; Hyman, Shores, & North, 2005; Moore, Ater, Needle, Slopis, & Copeland, 1994). Because children with NF1 as a group have generally lower IQ scores, the prevalence of mental retardation tends to be somewhat higher than the general population. However, the majority of research has confirmed that children with NF1 score in the average range of intelligence, demonstrating generally lower rates of mental retardation than what is found in other genetic disorders, such as Turner syndrome and Fragile X (Hyman et al., 2005).

Clinically, the cognitive problems in NF1 are often described in terms of global developmental delay and intellectual delay, with limited appreciation for variations in the development of various components of cognitive functioning. However, certainly, the negative impact of the cognitive difficulties on everyday functioning can be pervasive, affecting school performance, social development, and emotional adjustment. Specifically, children with NF1 are twice as likely as their peers to repeat a grade in school (Coude, Mignot, Lyonnet, & Munnich, 2007), and they have been found to be at greater risk for problems with peer acceptance, leadership skills, and general social competence (Noll et al., 2007). Many studies have sought to define a distinct cognitive profile of NF1 with varying success. Children with NF1 have been found to exhibit a wide variety of cognitive concerns, including language problems, math and reading disabilities, motor deficits, visual–motor impairment, memory problems, and visual–spatial deficits. In addition, children with NF1 are frequently described in the neuropsychological literature as having problems with attention and executive functioning (EF). This is often discussed in the context of the high comorbidity between NF1 and ADHD (e.g., Brewer, Moore, & Hiscock, 1997; Denckla, 1996; Hofman, Harris, Bryan, & Denckla, 1994; Sonuga-Barke, Bisikatou, & Thompson, 2010). In the current literature review, we

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present a review of the published literature on executive function in NF1. We consider the overlap and distinctive aspects of NF1 and ADHD, and we highlight the various subtypes of attention as they relate to the NF1 pediatric population.

**ADHD as a Measure of Attention in NF1**

The literature to date has consistently demonstrated that attention problems affect 33% to 50% of children in the NF1 clinical population, representing a hallmark of the cognitive impairment in NF1 (Chapman, Waber, Bassett, Urion, & Korf, 1996; Eliason, 1986; Hofman et al., 1994; Hyman, Shores, and North, 2005; Hyman et al., 2005; H. Johnson, Wiggs, Stores, & Huson, 2005; N. S. Johnson, Saal, Lovell, & Schorry, 1999; Kayl, Moore, Slopis, Jackson, & Leeds, 2000; Koth, Cutting, & Denckla, 2000; Mautner, Kluwe, Thakker, & Leark, 2002; B. D. Moore et al., 1994; North et al., 1994). Children with NF1 are about 3 times more likely than their unaffected siblings to have ADHD (Hyman et al., 2005, 2006). Because ADHD is a condition diagnosed solely by behavioral features, this high incidence of ADHD is more descriptive of the behavioral presentation of children with NF1, rather than the cognitive phenotype. To date, most NF1 studies reference the high rate of ADHD in the NF1 population as a marker of the presence of attention problems, with little to no use of direct neurocognitive measures of attention. As such, these studies operationally define cognitive constructs with behavioral features. While this can be effective at describing the behavioral presentation in a subset of the NF1 population, the lack of diagnostic specificity in behavioral ratings does not lend itself well to studying the subtypes of attention problems with NF1.

ADHD is the most commonly diagnosed psychological/behavioral disorder of childhood (Diamond, 2005; Stefanatos & Baron, 2007) and, in 2003, affected 4.4 million children between 4 and 17 years old in the United States (cited in Stefanatos & Baron, 2007). It represents a complex constellation of behavioral and neurological attributes, and it involves "a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development" (American Psychiatric Association [APA], 2000, p. 85). In its current version, the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* differentiates between two main subtypes of ADHD (primarily hyperactive/impulsive [ADHD-PHI] and primarily inattentive [ADHD-PIA]) and a third combination subtype (combined type [ADHD-C]). Patients must meet at least six criteria for either the ADHD-PIA or ADHD-PHI or both for the ADHD-C.

In recent years, evidence has been growing on the distinction between ADHD-PHI and ADHD-PIA, with some contending the merits of making these subtypes wholly distinct disorders (Diamond, 2005; Hinshaw, 2006). The distinction between these two subtypes of ADHD is based on factor analytic studies of parent and teacher symptom ratings (Biederman et al., 2002; Stefanatos & Baron, 2007). Each has its own developmental trajectory, type of behavioral impairment, comorbidities, response to medication, and underlying neurobiology (Biederman et al., 2002; Diamond 2005; Hale et al., 2009). Hale et al. (2009) concluded that although there is disagreement about whether the subtypes are distinct disorders or different endophenotypes, they require differentiation in diagnosis and treatment.

However, in the NF1 literature, only one study makes a diagnostic distinction between ADHD-PIA and ADHD-PHI (Table 1). Hyman et al. (2005) found a 2:1 ratio of ADHD-C to ADHD-PIA subtypes (24.7%;12.3%). They also found in their sample ($N = 81$) that only 0.01% of children with NF1 had ADHD-PHI. While this low rate may have been partially due to the high age range of their sample (8-16 years), ADHD-PHI is also noted to occur at lower frequency in the general population (Stefanatos & Baron, 2007).

### Table 1. Subtypes of ADHD in NF1 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Broadly defined (%)</th>
<th>PIA (%)</th>
<th>PHI (%)</th>
<th>Combined (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyman, Shores, and North (2005)</td>
<td>38</td>
<td>12.3</td>
<td>1.23</td>
<td>24.7</td>
</tr>
<tr>
<td>Hofman et al., (1994)</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kayl, Moore, Slopis, Jackson, and Leeds (2000)</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Koth, Cutting, and Denckla (2000)</td>
<td>42</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mautner, Kluwe, Thakker, and Leark (2002)</td>
<td>49.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: NF1 = neurofibromatosis Type 1; PIA = predominantly inattentive type; PHI = predominantly hyperactive/impulsive type.

*Rate rises to 46% in children with a general learning problem and 50% in children with a specific learning problem.*
Relying on the diagnosis of ADHD, or ADHD subtypes, for the identification of cognitive phenotypes remains problematic. Many studies use behavioral rating questionnaires, like the Child Behavior Checklist (CBCL) or the Connors’ Parent Rating Scale (CPRS), to obtain information from parents or teachers about children’s behavior. Such scales provide information about the severity and/or frequency of the behaviors, especially in line with diagnostic criteria from the DSM. Unfortunately, as indicated, such behavior rating scales have been found to have limited discriminant validity for ADHD subtypes and other disorders (Hale et al., 2009), with some studies suggesting a lack of consistency in ratings (Stefanatos & Baron, 2007). Such limitations in NF1 studies on attention are further compounded by the lack of detailed developmental screening when investigating the diagnosis of ADHD (Stefanatos & Baron, 2007).

Certainly, relying on a DSM definition of attention problems introduces some bias into the research on EF in NF1. As contended by Diamond (2005), children and adults are sometimes given the diagnosis of PIA because they might not be as hyperactive as young boys. Girls and older children might not meet full criteria for PHI, resulting in a diagnosis of PIA. However, these children may still have more hyperactivity or impulsivity than is appropriate for their age. Similarly, children with NF1 may be more likely to be diagnosed as PIA rather than PHI because of their tendency to demonstrate more internalizing symptoms.

**Behavioral differences between ADHD and NF1.** According to the DSM, the defining feature of ADHD is attention problems, and the majority of research about the cognitive profiles of children with NF1 suggests the presence of attention problems. So describing the EF problems of children with NF1 in terms of ADHD is understandable. However, it is important to consider whether individuals with ADHD and NF1 experience the same type of attention problems. The limited research in this area suggests some similarities and differences. On the Test of Variables of Attention (TOVA), a neuropsychological measure of sustained attention, the performance of children with both NF1 and ADHD were comparable with children who had NF1 alone (Mautner et al., 2002; Preston, Fennell, & Bussing, 2005). This suggests that children with NF1 can experience attention problems even though they do not meet diagnostic criteria for ADHD. Similarly, children with NF1 alone and those with NF1 and ADHD both appear to have problems with planning (Hyman et al., 2005), even when controlling for IQ or visual–spatial skills (Roy et al., 2010). This would suggest that children with NF1 experience problems with EF that are not wholly accounted for by the behavioral features of ADHD. Indeed, both populations appear to have problems with sustained attention and planning, but the conditions begin to diverge when tasks require a greater degree of cognitive control.

**Neuroanatomic differences between ADHD and NF1.** Huijbregts, Swaab, and de Sonneville (2010) suggested that the behavioral differences between ADHD and NF1 may reflect variability in the neural processes that are affected in NF1 versus those that are traditionally implicated in the behavioral features of ADHD. For example, Schrimsher, Billingsley, Jackson, and Moore (2002) found that the degree of caudate asymmetry significantly predicted severity in inattentive behaviors in ADHD. In terms of whole brain volume, NF1 is typically associated with macrocephaly (Moore, Slopis, Jackson, De Winter, & Leels, 2000), whereas ADHD is noted for small total brain volume, smaller right hemisphere prefrontal volumes, abnormal caudate (basal ganglia volumes), and smaller cerebellar volumes (Huijbregts et al., 2010). While no correlations have been identified between cognitive or behavioral abnormalities, children and adults with NF1 exhibit increased corpus callosum size (Wignall et al., 2010). Other studies report significant differences in total brain volume and specific differences in the corpus callosum, cerebellar asymmetries, and differences in gray and white matter in children with NF1 when compared with their unaffected counterparts (Payne, Moharir, Webster, & North, 2010). The enlarged corpus callosum size in NF1 may correlate with lower IQ, reduced abstract concept formation, reduced verbal memory, and diminished academic ability in reading and math (Pride et al., 2010).

In a few published studies to date, individuals with NF1 have been found to rely more on posterior cortex when performing visual–spatial tasks, which positively correlates with reading scores (Billingsley et al., 2004), and they exhibit decreased volume of activation in the primary visual cortex, recruiting right hemispheric regions for visuospatial processing (Clements-Stephens, Rimrodt, Gaur, & Cutting, 2008). In addition, abnormalities in the inferior frontal gyrus and Heschl’s gyrus have been associated with performance across language and neuropsychological measures in individuals with NF1 (Billingsley et al., 2003).

Furthermore, the most prevalent neuroimaging finding in children with NF1 is the presence of T2-hyperintensities, known as unidentified bright objects (UBOs), found in 50% to 60% of patients (Brewer et al., 1997). Diffusion-based imaging has demonstrated that these T2-bright objects have higher apparent diffusion coefficient (ADC) values without any changes in fractional anisotropy (van Engelen et al., 2008). However, there are also higher ADC values throughout the brains of individuals with NF1 compared with unaffected controls, specifically in the cerebellum, basal ganglia, and thalamus, independent of the presence of UBOs (Chabernaud et al., 2009; Ferraz-Filho et al., 2011; Goh, Khong, Leung, & Wong, 2004; Hyman, Gill, Shores, Ste-ingburg, & North, 2007). UBOs are not specifically associated with ADHD, but have been correlated with poor
differences in children with NF1 as compared with ADHD. Because there are known white and gray matter levels of attention and impulsivity in individuals with diffusion tensor imaging (DTI), Konrad et al. (2010) found cerebellar networks (Konrad et al., 2010). Moreover, using is specifically indicated in the fronto-striatal and fronto-

decreases in short-range connections and increases in long-
development of resting-state networks involves both disruption of EF in NF1 (Huijbregts et al., 2010). Healthy controls. Deficits in sustained attention are also prevalent in poor on the selective attention task than unaffected con-

domain of EF, attention has been the most consistently stud-

difficulties, these studies remain contradictory (e.g., Hofman et al., 1994; Huijbregts et al., 2010; Moore & Slopis, 1995; North et al., 1994).

Functional connectivity is an emerging area of research that has expanded significantly over the past few years, particularly in the field of ADHD research. Many of these investigations, thus far, suggest common neuroanatomic findings shared between children with ADHD and those with NF1. Because of the extensive communication required between brain regions during EF tasks, functional connectivity may prove to be a valuable tool for understanding the disruption of EF in NF1 (Huijbregts et al., 2010). Healthy development of resting-state networks involves both decreases in short-range connections and increases in long-range connections between associated resting-state networks. Delays in this developmental process may be associated with a range of developmental disorders, including ADHD (Fair et al., 2007). Early resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) studies have shown that adults with ADHD have decreased coherence in the resting-state default network as compared with adults without ADHD (Fair et al., 2007, 2010). This is specifically indicated in the fronto-striatal and fronto-cerebellar networks (Konrad et al., 2010). Moreover, using diffusion tensor imaging (DTI), Konrad et al. (2010) found that white matter integrity was directly correlated with levels of attention and impulsivity in individuals with ADHD. Because there are known white and gray matter differences in children with NF1 as compared with typically developing children (Payne et al., 2010), future functional connectivity studies of NF1 are warranted. Such studies could be particularly useful for studying task-controlled networks in children with NF1 (Dosenbach et al., 2007). In addition, functional connectivity holds the promise of helping us better understand the neural plasticity observed in NF1, providing a potential model for determining whether attention problems are mediated more by changes in connectivity or morphology in the brain (Costa et al., 2002; Johnston, 2004).

Evidence for Executive Function Deficits in Children With NF1

Despite a paucity of studies on EF, there is strong evidence that EF is a core deficit in NF1 and that multiple areas of EF are affected (see Table 2; Huijbregts et al., 2010; Hyman et al., 2005; Ozonoff, 1999; Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009; Roy et al., 2010). EF is generally believed to be made up of three primary constructs: inhibition, working memory (or updating), and cognitive flexibility (or shifting). These three primary constructs then give rise to planning, problem solving, abstract formation, and reasoning (Diamond, Barnett, Thomas, & Munro, 2007). While all but one of these areas is implicated in NF1, further research is necessary to confirm the pattern(s) of impairment.

Inhibition is the most frequently demonstrated EF deficit in individuals with NF1 (Descheemaeker, Ghesquiere, Symons, Fryns, & Legius, 2005; Ferner, Hughes, & Weinman, 1996; Mazzocco et al., 1995; Rowbotham et al., 2009). Inhibition refers to the ability to keep a particular response from happening. Difficulties with inhibition are present in children with NF1 with and without ADHD (Huijbregts et al., 2010). A subcomponent of inhibition is attention. Within the domain of EF, attention has been the most consistently studied construct in children with NF1. While attention problems are cited frequently as an important feature of this condition, information about the types of attention problems in individuals with NF1 is limited (see Table 3). Multiple types of attention have been identified, and all have been found to be impaired in children affected with NF1. This includes selective, focused, and sustained attention.

Selective attention is the ability to attend to one type of stimuli while resisting the inclination to attend to other types of stimuli (Diamond et al., 2007). This type of attention has been found to be impaired in subsets of children with NF1 (Hyman et al., 2006). Although Hyman et al. (2006) found that selective attention, as measured by the Test of Everyday Attention for Children (TEA-Ch), was intact for children with NF1 as a whole, children with NF1 who had a specific learning problem performed more poorly on the selective attention task than unaffected controls. Deficits in sustained attention are also prevalent in

Table 2. Evidence for Executive Function Problems in NF1

<table>
<thead>
<tr>
<th>Area of impairment</th>
<th>Supporting studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive flexibility</td>
<td>Rowbotham et al. (2009)</td>
</tr>
<tr>
<td>Abstract formation</td>
<td>Hyman et al. (2005)</td>
</tr>
<tr>
<td>Organization</td>
<td>Eliason (1986)</td>
</tr>
</tbody>
</table>

NF1 = neurofibromatosis Type 1.
Table 3. Types of Attention Problems in NF1

<table>
<thead>
<tr>
<th>Attention subtypes</th>
<th>Supporting studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>General or unspecified</td>
<td>Chapman, Waber, Bassett, Unrion, and Korf (1996)</td>
</tr>
<tr>
<td></td>
<td>Kayl, Moore, Slopis, Jackson, and Leeds (2000)</td>
</tr>
<tr>
<td></td>
<td>Koth, Cutting, and Denckla (2000)</td>
</tr>
<tr>
<td></td>
<td>Mautner et al. (2002)</td>
</tr>
<tr>
<td>Sustained</td>
<td>Hyman et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>Hyman et al. (2006)</td>
</tr>
<tr>
<td></td>
<td>Mautner et al. (2002)</td>
</tr>
<tr>
<td>Selective</td>
<td>Hyman et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>Hyman et al. (2005)</td>
</tr>
<tr>
<td>Switching</td>
<td>Hyman et al. (2005)</td>
</tr>
<tr>
<td></td>
<td>Hyman et al. (2005)</td>
</tr>
<tr>
<td>Divided</td>
<td>Hyman et al. (2005)</td>
</tr>
</tbody>
</table>

Note: NF1 = neurofibromatosis Type 1.

*Identified by behavioral checklists.

bEvidence of deficits identified in subsets of the NF1 population.

Additional studies suggest that other areas of EF are also impaired in the NF1 population. For example, Rowbotham et al. (2009) reported that cognitive flexibility, the ability to shift focus from one activity to another, was impaired when compared with age-matched controls, particularly when higher levels of cognitive control were required. Children with NF1 also have deficits in planning and abstract concept formation (Hyman et al., 2005), and their problems with planning are independent of deficits in either IQ or visuospatial skills (Roy et al., 2010).

While children with NF1 consistently exhibit problems with EF, little is known about the persistence of these problems into adulthood. Huijbregts et al. (2010) found that children with NF1 did not show improvements in working memory, response inhibition, or motor control as they matured, and they did not overcome deficits in these specific areas as teenagers. Because the study did not include adults, it is unclear whether children with NF1 eventually improve on these skills later in life.

Currently, our understanding of EF in children with NF1 is limited, and a full picture of how deficits in EF affect everyday functioning in individuals with NF1 has yet to emerge (Roy et al., 2010).

### Treatment of EF Deficits in NF1

At present, there is little consensus regarding the treatment of executive function deficits in children with NF1. North, Joy, Yuille, Cocks, and Hutchins (1995) found that four children were prescribed stimulant medication (type and amount not specified), and had a “good response from parents and teachers at a 6 month follow-up.” In a larger study, participants had improved performance on the TOVA and improved ratings on the CBCL (Mautner et al., 2002). Specifically, on the TOVA, children’s performances improved significantly on commissions, omissions, and response time, which are measures of inhibition, attention, and speed of information processing. In addition, on the CBCL and Teacher Report Form (TRF), children’s total rating scores improved but remained unchanged for social problems, somatization, and acting-out behavior. Diamond (2005) described differences in how children with subtypes of ADHD respond to stimulant medications. Specifically, she explained that children with ADHD PHI/C often respond well to stimulants at moderately high doses, whereas many children with ADHD-PIA do not respond to stimulant medications and, if they do, it is likely at low doses. This may help explain the differential efficacy of medications in the NF1 population as well.

Current work is focused on the use of stimulant medication for children with NF1. Recent basic science research revealed that Nf1 mutant mice exhibit reduced exploratory behaviors, which may be suggestive of attention system dysfunction (Brown et al., 2010). These exploratory behaviors returned to

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Individuals with NF1. Using the TEA-Ch and the parent and teacher forms of the Conner’s ADHD Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; APA, 1994) Scales (CADS) as measures of sustained attention, Hyman et al. (2005) found that 63% of children scored at least one standard deviation below the mean and 54% scored at least one standard deviation below their sibling. In 2006, Hyman et al. found that children with NF1, regardless of the presence of a learning difficulty, had some level of impaired sustained attention compared with unaffected controls. The presence of a learning difficulty was correlated with greater difficulties with sustained attention.

The second most commonly studied area of EF in NF1 is working memory (Huijbregts et al., 2010, Rowbotham et al., 2009). Working memory refers to the ability to hold and manipulate information or rules in mind. A classic example of this is mental arithmetic. Inhibition has been proposed to be a significant component of working memory, due to the necessity to inhibit competing information or rules while focusing on one or two specific elements of a task (Diamond, 2005). Children with NF1 (with and without ADHD) have been found to have deficits in working memory. For example, Huijbregts et al. (2010) revealed that children with NF1 tend to make more mistakes on tasks as the demands on working memory increase (i.e., when required to hold and manipulate more pieces of information in mind at one time; Huijbregts et al., 2010).
baseline following treatment with methylphenidate or l-dopa, which may implicate a mechanism for treatment in children with NF1 and attention problems. The correction of attentional deficits in these mice by increasing dopamine levels was underscored by biochemical studies in which Nf1 mutant mice were found to have reduced dopamine levels in the striatum. Future studies will be required to determine whether a subset of children with NF1 and attention problems have dysregulated brain dopamine homeostasis.

In addition, more recent preclinical work using Nf1 mutant mice also demonstrated that spatial learning deficits could be reversed by treatment with an HMG-CoA reductase inhibitor, lovastatin (a medication often prescribed to lower cholesterol; Li et al., 2005). Based on these findings, the investigators suggested that lovastatin inhibited p21Ras hyperactivation and resulted in normalization of the impairments in long-term potentiation. These preclinical observations prompted human clinical trials using a related statin drug, simvastatin (Zocor); however, no efficacy was observed (Krab et al., 2008). With the availability of several mouse models of learning and behavioral deficits in NF1, additional biologically targeted therapies may be identified.

Summary

Our understanding of attention and executive function in children with NF1 is still emerging. ADHD has been often used in the literature to describe the EF deficits experienced by children with NF1; however, emerging research suggests that children with NF1 may exhibit deficits in EF that are distinct from those traditionally demonstrated in ADHD. Moreover, it remains unclear whether the diagnosis of ADHD-PIA accurately captures the majority of attention problems displayed in NF1. The state of the literature in NF1 supports the fact that poor EF, particularly in the areas of attention and organization, might underlie poor performance in other cognitive domains (e.g., Ozonoff, 1999). Ozonoff (1999) suggested that the subtle nature of the executive function problems in children with NF1 may cause them to escape the notice of educators, which, in turn, compounds their negative impact on learning. Through continued exploration of EF in children with NF1, these subtle deficits in cognitive functioning may help to identify children for intervention at a younger age, thus allowing for more effective management and treatment.

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