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Attention Skills in Children With Neurofibromatosis Type 1

Jill C. Isenberg, PhD[1], Alexandra Templer, BA[1], Feng Gao, PhD[2], Jeffrey B. Titus, PhD[3,4], and David H. Gutmann, MD, PhD[1]

Abstract

Children with neurofibromatosis type 1 are at increased risk for the development of attention problems relative to their unaffected peers. Previous studies have reported deficits in sustained auditory attention, but other aspects of attention, including sustained visual attention, divided attention, response inhibition, and selective attention, have not been consistently documented. In the present study, we specifically investigated attention skills in children with neurofibromatosis type 1 using measures of visual and sustained auditory attention, divided attention, selective attention, and response inhibition. Consistent with previous reports, we confirmed the presence of deficits in sustained visual and auditory attention in children with neurofibromatosis type 1 but also identified deficits in divided attention and response inhibition. Based on the high frequency and wide spectrum of attention system impairments in this at-risk population, we advocate screening children with neurofibromatosis type 1 for attention problems and providing appropriate interventions that address all aspects of their executive functioning.

Keywords

attention deficit, executive function, inherited cancer syndrome, learning disabilities, NF1, neurofibromatosis

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Neurofibromatosis type 1 (NF1) is a common autosomal dominant condition affecting approximately 1 in 3000 individuals worldwide.[1] Children and adults with neurofibromatosis type 1 may come to medical attention based on the presence of pigmentary abnormalities (café-au-lait macules, freckling in the axillary or inguinal regions, and Lisch nodules), distinct bony lesions (tibial pseudarthrosis, sphenoid dysplasia, and dystrophic scoliosis), or tumors (neurofibromas, optic gliomas, and malignant peripheral nerve sheath tumors).[2] Although benign and malignant tumor development represents a major concern, a large proportion of children with neurofibromatosis type 1 have significant cognitive and learning deficits.[3-6] Mental retardation is uncommon, but several studies have documented a "left shift" in the distribution of intelligence scores in individuals with neurofibromatosis type 1.[7,8]

Neurofibromatosis type 1 negatively affects several specific domains of cognitive functioning beyond general intellectual ability. In this regard, 30% to 65% of children with neurofibromatosis type 1 have specific learning disabilities and lower performance across all domains of learning, including written language, reading accuracy, reading comprehension, spelling, and math.[3,5,9] Moreover, individuals with neurofibromatosis type 1 demonstrate deficits in a wide range of neurocognitive skills beyond academic achievement, including visual-spatial, visual-constructional (eg, copying complex drawings, arranging puzzles), language, executive functioning, gross-motor, and fine-motor skills.[3-5]

In addition, 30% to 50% of children with neurofibromatosis type 1 also exhibit deficits in attention compared with 3% to 7% of school-age children in the general population.[3,10,11] Children with neurofibromatosis type 1 and attention-deficit hyperactivity disorder (ADHD) have poorer social outcomes than children with neurofibromatosis type 1 only as well as children with neurofibromatosis type 1 and learning deficits.[12] This result suggests that the social skills deficits commonly observed among children with neurofibromatosis type 1 may not be due to neurofibromatosis type 1 itself but to the presence of ADHD as a comorbid condition, consistent with the notion that ADHD, in general, is a risk factor for poor social outcomes.[12]

[1] Department of Neurology, Washington University School of Medicine, St Louis, MO, USA
[2] Division of Biostatistics, Washington University School of Medicine, St Louis, MO, USA
[3] Pediatric Neuropsychology, Dell Children's Medical Center, Austin, TX, USA
[4] Department of Psychology, University of Texas at Austin, Austin, TX, USA

Corresponding Author:
David H. Gutmann, MD, PhD, Department of Neurology, Washington University School of Medicine, Box 8111, 660 South Euclid Avenue, Washington University School of Medicine, St Louis, MO 63110
Email: gutmannd@neuro.wustl.edu

Although many studies have documented the presence of attention problems in children with neurofibromatosis type 1, less research speaks to the specific attention domains that are problematic for children with neurofibromatosis type 1. Identifying which specific aspects of attention are difficult for children with neurofibromatosis type 1 would facilitate the development of more targeted interventions designed to compensate for specific attention weaknesses. The purpose of the present study was to define the spectrum of attention system deficits in children with neurofibromatosis type 1 by examining their performance on specific measures of attention, including measures of sustained visual and auditory attention, selective visual attention, and divided auditory attention.

Methods

Participants

Children and adolescents between the ages of 6 and 14 years of age with a diagnosis of neurofibromatosis type 1 established using National Institutes of Health Consensus Development Conference criteria were eligible for participation in this study under an approved Human Studies Protocol at the Washington University School of Medicine.[13] All individuals were active patients in the Neurofibromatosis Clinical Program at St Louis Children's Hospital and examined by a single neurologist (DHG). Potential participants were recruited during routine clinic visits or by telephone. Two hundred eighty-five potential participants were identified. Of these participants, 86 initially appeared eligible and were able to be contacted via telephone or at clinic appointments (30%). Of these 86 potential participants, 70 participants expressed interest in participating. Fifteen of the 70 patients were excluded based on the exclusionary criteria, which included previous exposure to chemotherapy or radiation, a prior neurosurgical procedure, a previous diagnosis of a Pervasive Developmental Disorder, a previous diagnosis of another neurodevelopmental condition (eg, Noonan syndrome), a history of in utero exposure to illicit substances, or a previous diagnosis of epilepsy. A total of 55 patients comprised the cross-sectional cohort for this study (19% of the originally identified patient group). Participants had a mean age of 9.71 years (standard deviation [SD] = 2.63 years), and the population was predominantly white (78.18%), with both African Americans (12.73%) and Asians (9.09%) represented.

Materials

As part of our analysis of the descriptive characteristics of our population, all participants were administered the Peabody Picture Vocabulary Test, Fourth Edition, to serve as an estimate of intellectual ability.[14] In addition, given the known prevalence of visual-spatial deficits in the neurofibromatosis type 1 population, participants were administered the Judgment of Line Orientation, which requires individuals to make judgments about angular relationships between lines.[15]

All study participants were evaluated using subtests from the Test of Everyday Attention for Children.[16] The Sky Search subtest served as a measure of selective visual attention. Participants were presented with a large display of pairs of spaceships arranged in columns and were instructed to circle each pair of spaceships in which the spaceships were identical. The dependent variable yielded by this subtest reflects time spent per target while controlling for the influence of motor speed (Sky Search Attention Score). The Score! subtest served as a measure of sustained auditory attention and required participants to count the number of beeps heard on a tape during each of 10 trials. The primary outcome measure from this subtest is the number of correct trials (Score!). The Score DT subtest was used as a measure of divided auditory attention. The examinee again counted beeps heard on a tape while simultaneously listening for the name of an animal presented in a news story for each of 10 trials. The dependent variable for this task was the total number of correctly identified count targets plus the total number of correctly identified animal targets (Score DT).

Participants also completed the Conners Continuous Performance Test–Second Edition.[17] The Conners Continuous Performance Test–Second Edition is a computerized task that presents the examinee with letters of the alphabet. The examinee is instructed to press the space bar each time a letter appears (targets) with the exception of the letter X (nontarget). When the letter X appears, the examinee is to not respond. The letters are presented for 250 milliseconds and the interstimulus interval varies between 1, 2, and 4 seconds. Stimuli are presented for 14 minutes, with the trials being divided into 6 blocks across the administration. Dependent variables of interest comprised several measures of vigilance, including *T* scores for omissions (number of targets to which the examinee did not respond), hit reaction time block change, and hit standard error block change. Hit reaction time block change indicates the slope of change in reaction time over the 6 blocks. High *T* scores on this measure reflect a slowing of reaction time across the blocks and a loss of vigilance. Hit standard error block change reflects the slope of change in reaction time standard errors over the 6 blocks. High *T* scores on this measure reflect less consistent reaction times as the task progressed as well as a loss of vigilance. *T* scores for commissions (number of nontargets to which the examinee responded) were determined, which served as a measure of impulsivity.

Parents of participants also completed the Conners Third Edition–Parent.[18] This measure uses 110 items to assess a parent's perception of a child's functioning in a variety of domains, including symptoms of inattention, hyperactivity/impulsivity, learning problems/executive functioning, aggression, anxiety, depression, peer relationships, and family relationships. Specifically, the parents' report was used to determine if participants met criteria for ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders–4th Edition, Text Revision*.[11]

Procedures

Consent was obtained from parents of the participants, and participants provided their assent. The total time for completion of the neuropsychological measures was slightly more than 1 hour. Participants completed testing in a quiet, distraction-free testing room within a Pediatric Psychology clinic setting. Tests were administered by a trained research assistant (AT) with supervision by a licensed psychologist (JBT and JCI). Testing was completed in individual sessions with each participant. Parents completed the Conners Third Edition–Parent while waiting in an adjoining room.

Statistical Analysis

All the scores were summarized using means SD. One-sample *t* tests were used to compare the mean scores of participants in the study to the corresponding population levels, whereas Mann-Whitney nonparametric rank-sum tests were used to compare the average scores between subgroups of participants (ie, children on attention

Table 1. Conners Third Edition–Parent Ratings for Children On and Off Stimulant Medication (Mean ± SD)

Index	Participants on Medications (N = 12)	Participants Not on Medications (N = 43)	*P*
Inattention *T* score	74.67 ± 10.39	60.74 ± 14.06	.003
Hyperactivity/impulsivity *T* score	69.67 ± 15.49	65.63 ± 16.54	.391
Conduct problems *T* score	51.81 ± 13.35	51.25 ± 11.88	.573
Oppositional-defiant *T* score	60.08 ± 16.13	52.51 ± 10.25	.089

medications vs children not on attention medications, children with neurofibromatosis type 1 and ADHD versus those with neurofibromatosis type 1 without ADHD, etc). All analyses were 2-sided and significance was set as $P < .05$. Statistical analyses were performed using statistical package SAS (SAS Institute, Cary, North Carolina).

Results

Participants in our study demonstrated generally average intellectual ability, as determined by their performance on the Peabody Picture Vocabulary Test, Fourth Edition (with mean ± SD of 102 ± 13.1). In addition, these children, as a whole, exhibited visual-spatial processing that was approximately 1 standard deviation below the age-based normative data (84.0 ± 22.3), with a relatively wide standard deviation that suggested variability in performance across the study group. This group weakness in visual-spatial processing is consistent with previous published reports, suggesting that the children in this study exhibit a cognitive profile typical for children with neurofibromatosis type 1.

To facilitate unencumbered participation in the study, participants who were taking stimulant medication at the time of their testing appointment (n = 12) were not required to refrain from taking the medication. The 12 participants taking stimulant medication were compared with the 43 participants without stimulant medication on the dependent variables of interest in this study. No significant differences were identified on the primary outcome measures. Notably, parental responding to the Conners Third Edition–Parent indicated that children on stimulant medication were more inattentive (74.7 vs 60.7, $P = .003$) and oppositional (60.1 vs 52.5, $P = .089$) than children not on medication (Table 1).

Next, we examined the performance of children with neurofibromatosis type 1 on specific tests of executive function (Table 2). The mean score for participants on each of the dependent Test of Everyday Attention for Children subtest variables was compared with the population mean for these subtests (mean ± SD of 10 ± 3). Children with a diagnosis of neurofibromatosis type 1 did not differ significantly from the population mean on measures of selective visual attention (Test of Everyday Attention for Children Sky Search Attention Score); however, significant differences were identified for sustained auditory attention and divided auditory attention (with $P < .0001$ and $P = .009$ for Score! and Score DT, respectively, of the Test of Everyday Attention for Children). Using the Conners Continuous Performance Test–Second Edition test, individuals with neurofibromatosis type 1 had greater omissions ($P = .017$) and commissions ($P < .0001$) compared with the population mean (mean ± SD of 50 ± 10). In contrast, no significant differences were found for hit reaction time block change or hit standard error block change.

Table 2. Performance of Children With Neurofibromatosis Type 1 on Tests of Executive Function

Subtest	N	Mean (SD)	*P*
Sky Search Attention Score	55	9.33 (2.74)	.074
Score!	53	7.75 (3.63)	<.0001
Score DT	52	8.81 (3.15)	.009
CPT-II Omissions	55	53.93 (11.86)	.017
CPT-II Commissions	55	55.70 (8.49)	<.0001
CPT-II Hit Reaction Time Block Change	55	51.10 (8.47)	.341
CPT-II Hit Standard Error Block Change	55	50.45 (11.06)	.765

Abbreviation: CPT-II, Conners Continuous Performance Test–Second Edition.

Based on parental responses to the Conners Third Ed ition–Parent, 23 of the 55 participants met *Diagnostic and Statistical Manual of Mental Disorders–4th Edition, Text Revision*/criteria for ADHD (5 predominantly inattentive type, 9 predominantly hyperactive/impulsive type, and 9 combined type).[11] Participants with neurofibromatosis type 1 and ADHD were compared with participants with neurofibromatosis type 1 without ADHD on the dependent variables described above. No significant differences were observed. Importantly, there were no significant correlations between the parental report of inattention/hyperactivity and the outcome measures used in this study.

Discussion

Previous studies examining the behavior of children with neurofibromatosis type 1 have shown that this population has a high proportion of executive function deficits, notably in the realm of attention. Although each of these reports demonstrates that children with neurofibromatosis type 1 have significantly more difficulties with sustained attention, performance on tests that specifically measure attentional switching, selective and divided attention, and response inhibition has been less well characterized. In the current study, we used a combination of evaluation tools to assess these understudied aspects of attention function in children with neurofibromatosis type 1.

Overall, our study demonstrated that children with neurofibromatosis type 1 displayed significant deficits in multiple aspects of attention compared with age-expected performance. In particular, children with neurofibromatosis type 1 demonstrated deficits in sustained and divided auditory attention, sustained visual attention, and response inhibition.

These results make several contributions to the existing literature. First, they replicate previous research documenting deficits in sustained auditory and visual attention as well as divided auditory attention.[4,6,19,20] Second, the findings confirm that children with neurofibromatosis type 1 demonstrate attention deficits across sensory modalities, suggesting that these deficits are not secondary to difficulty manipulating particular types of stimuli (eg, deficits in visual attention secondary to problems with visual-spatial processing). Third, our findings suggest that children with neurofibromatosis type 1 can be more prone to deficits in skills associated with the anterior attention system rather than the posterior attention system, as previously reported for children with ADHD, but not other neurologic conditions such as hydrocephalus.[21] The anterior attention system is implicated by the notion that only when the children with neurofibromatosis type 1 in our study were required to sustain attention over time and/or attend to multiple types of stimuli simultaneously did they perform significantly below their unaffected peers. Fourth, deficits in response inhibition have been identified as a common problem in children with ADHD in the general population,[22] but they have received less study in children with neurofibromatosis type 1. Our study and a recent study using a virtual reality format to present a classroom scene to children with neurofibromatosis type 1 and age- and sex-matched controls found that children with neurofibromatosis type 1 made more response inhibition and sustained attention errors than control participants.[10]

Our study also has implications about the applicability of ADHD criteria and common medication approaches for children with neurofibromatosis type 1. In particular, we demonstrated that a large portion of our sample met *Diagnostic and Statistical Manual of Mental Disorders–4th Edition, Text Revision*, criteria for ADHD, but children with neurofibromatosis type 1 and ADHD did not differ significantly from children without ADHD on measures of attention. This finding suggests that ADHD features as defined by the *Diagnostic and Statistical Manual of Mental Disorders–4th Edition, Text Revision*, do not fully capture all of the attention problems experienced by children with neurofibromatosis type 1. Further, these findings indicate that parental identification of attention performance deficits underestimates the true prevalence of executive functioning abnormalities in this at-risk population, which likely results in a failure to identify children with neurofibromatosis type 1 who would benefit most from appropriate intervention. Moreover, no significant differences were apparent on measures of attention between children who did and did not meet diagnostic criteria for ADHD. This observation raises the intriguing possibility that children with deficits in some areas of executive function are not responding to current stimulant medication regimens. This concern is underscored by the finding that the children on medication were described by their parents as continuing to demonstrate clinically significant attention problems in their daily lives.

Several important recommendations regarding the management of children with neurofibromatosis type 1 flow from these findings. First, children with neurofibromatosis type 1 will benefit from a multimodal assessment of attention skills that includes both parent report and formal, clinical measures of attention ability. Second, children with neurofibromatosis type 1 taking stimulant medication for the treatment of ADHD symptoms should be monitored closely for medication responsiveness to ensure that clinically significant symptoms do not persist. Third, there are several environmental modifications that may be helpful for children with neurofibromatosis type 1 and attention problems, including support from an adult throughout tasks that require sustained attention and an emphasis on environments that do not make simultaneous demands on attention.

The present study is not without limitations. First, the study did not use a control group and compared participants to a population mean. This may have obscured differences between the participants with neurofibromatosis type 1 and same age, typically developing peers. Second, the study used a relatively small sample size and there was a low rate of participation among potential participants. These factors decrease the ability to generalize the study's findings to the population of children with neurofibromatosis type 1. Third, the diagnosis of ADHD was based on parent report on one behavior rating scale. Thus, there may have been bias in the manner in which participants were grouped as having or not having ADHD. Finally, children with neurofibromatosis type 1 who were taking stimulant medications were not required to discontinue taking them as part of their participation in this study. Thus, the children who may have presented with the most severe attention difficulties may not have been able to demonstrate their deficits on formal testing, which could have impeded us from identifying deficits.

Despite these limitations, the current study contributes to the existing literature on ADHD in children with neurofibromatosis type 1 by further documenting deficits in sustained attention in both visual and auditory formats. The study also highlights the difficulties that children with neurofibromatosis type 1 have with dividing their attention between stimuli and spotlights deficits in response inhibition among children with neurofibromatosis type 1. The results from the current study underscore the need for a careful assessment of a variety of attention skills in children with neurofibromatosis type 1. Future research should validate the effectiveness of both pharmacological and environmental interventions designed to address specific attention skills that are difficult for children with neurofibromatosis type 1.

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Author Contributions

JCI completed the first draft of the manuscript. AT, JBT, and DHG contributed to conception and design of the study. JCI, AT, and JBT took part in data acquisition. FG completed the data analysis. All authors took part in the revision and final approval of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This research was completed according to a protocol approved by the Human Research Protection Office at Washington University School of Medicine.

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