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Pilot Study of a Novel Computerized Task to Assess Spatial Learning in Children and Adolescents With Neurofibromatosis Type 1

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Abstract

Difficulties with visual-spatial learning are frequently observed and often considered to be the hallmark of neurocognitive impairment in neurofibromatosis type 1. The computerized Arena Maze is a virtual environment task that has been developed as a human paradigm to the Morris Water Maze, which is used to evaluate spatial learning in animal models. The authors evaluated this task as a measure of spatial learning in children with neurofibromatosis type 1 compared with their unaffected siblings. Affected children were able to learn the task and navigate the virtual environment; however, they performed more poorly on standard measures of spatial learning and spatial working memory than their siblings. The group with neurofibromatosis type 1 demonstrated decreased proficiency in earlier target trials and had more difficulty in remembering target location. This study demonstrates the potential utility of a novel virtual task to assess spatial learning deficits in children with neurofibromatosis type 1.

Keywords

spatial learning, neurofibromatosis type 1, computerized task, arena maze

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Neurofibromatosis type 1 is one of the most common autosomal dominant disorders in humans, with a prevalence of approximately 1 in 3500.[1,2] Cognitive deficits and learning difficulties are among the most frequent problems that patients and their families face, with a prevalence of 35% to 65% in children with neurofibromatosis type 1 compared with 5% to 17.5% in the general population.[3,4] Visual-spatial deficits and difficulties with complex motor tasks are commonly seen in individuals with neurofibromatosis type 1 and can be considered hallmark features of neuropsychological impairment in children with neurofibromatosis type 1.[4-7]

At the cellular level, understanding of the underlying genetic defect in neurofibromatosis type 1 has become central to understanding the varied clinical spectrum of disease. The protein product of the neurofibromatosis type 1 gene, neurofibromin, is expressed in many tissues, including neurons, oligodendrocytes, and other nonneural cell types.[8] Neurofibromin inactivates *Ras* and interrupts *Ras*-mediated signal transduction.[9,10] Mutations of the neurofibromatosis type 1 gene may be responsible for decreased synaptic plasticity and decreased long-term potentiation and therefore may contribute to deficits in learning and memory.[11] Mice heterozygous for the neurofibromatosis type 1 mutation have deficits in visual-spatial learning and motor coordination that are thought to be analogous to the cognitive impairment observed in humans.[11] These spatial deficits, best characterized with the Morris Water Maze, can be reversed by restoring genetic and pharmacologic manipulations that decrease *Ras* function[12] or by blocking *Ras* activity with the drug lovastatin.[13]

Although testing of the *Nf1* +/– mice provides important information, it is difficult to make direct inferences from the murine model to neurocognitive functioning of children with neurofibromatosis type 1. Currently, no standardized tests of spatial learning in children or adults, comparable to the Morris Water Maze, evaluate the integrity of mechanisms of learning and memory that rely on intact hippocampal functioning. The Arena Maze is a virtual environment task that has been developed as a "human Morris Water Maze."[14,15] It has been used to assess spatial orientation strategies and sex differences in spatial abilities in young adults,[16] deficits associated with traumatic brain injury,[17] and changes in cognitive functioning associated with normal aging.[18] One study has examined the

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Table 1. Neurocognitive Functioning of Children With Neurofibromatosis Type 1 Compared With Unaffected Siblings

	Neurofibromatosis Type 1 (n = 10)	Siblings (n = 6)	*P*
Demographics			
Mean age, y (SD)	13.5 (2.3)	12.7 (1.7)	*NS*
Gender, % female	50	50	*NS*
Screening measures			
Wechsler Intelligence Scale for Children (fourth edition)			
Full-Scale IQ	93.8 (6.8)	NA	
Vocabulary subtest	10.3 (2.7)	12 (3.5)	*NS*
Block Design subtest	8.0 (1.8)	11.3 (2.3)	.01
California Verbal Learning Test for Children			
Total T score	53.3 (5.4)	47.8 (5.8)	*NS*
Behavioral Rating Scale of Executive Function			
Behavioral Regulation Index (T score)	56.6 (15.6)	48.7 (5.7)	*NS*
Metacognitive Index (T score)	68.9 (8.3)	43.8 (4.0)	.00
Global Executive Composite (T score)	65.4 (10.5)	45.3 (2.7)	.00
Conners Parent Rating Scale Revised			
Cognitive problems/inattention (T Score)	71.9 (6.2)	48.0 (5.6)	.00
Social problems (T score)	67.2 (15.5)	52.2 (6.6)	.04
Attention-deficit hyperactivity symptoms (T score)	70.4 (11.9)	50.3 (8.4)	.00

NA, not applicable.

maturation of spatial navigation strategies in a pediatric population. Laurance and colleagues[18] examined the maturation of spatial navigation strategies in children and found that by age 9 to 10 years, children were using relations among distal cues to guide their search, which are the same strategies used by adults.

The purpose of this study was to assess the utility of this novel computerized task as a measure of spatial learning in children with neurofibromatosis type 1.

Methods

Patient Selection and Recruitment

A total of 11 neurofibromatosis type 1 participants were recruited from the Multidisciplinary Neurofibromatosis Program at Children's Hospital Boston, where patients with neurofibromatosis type 1 are evaluated and receive ongoing care. All participants met National Institutes of Health Consensus Development Conference clinical criteria for neurofibromatosis type 1.[1] Children with neurofibromatosis type 1 and suspected learning or academic difficulties are routinely referred for a comprehensive neuropsychological evaluation to the Neuropsychology Program in the Department of Psychiatry at Children's Hospital Boston. Participants were excluded if they had a prior history of central nervous system injury, including seizures, brain tumor, hydrocephalus, developmental brain malformation, cerebral palsy, or other systemic cancer; a known symptomatic optic pathway glioma or visual field deficit that might affect performance on the computerized module; English as a second language; a major psychiatric or developmental disorder; or a Full Scale IQ standard score less than 80 following the initial assessment. One child was excluded using these criteria. Three participants met criteria for attention-deficit disorder but were not taking medications at the time of the testing with the Arena Maze.

A control group of 6 unaffected siblings of children with neurofibromatosis type 1 who were between the ages of 10 and 16 years was also recruited. Previous research with children with neurofibromatosis type 1 has included unaffected siblings as controls for potential confounding variables such as socioeconomic status and family context. In some areas of assessment, such as overall IQ, individuals with neurofibromatosis type 1 demonstrate more significant cognitive impairments when compared with familial/sibling performance than when compared with test population norms. We elected to use the sibling controls for the above reasons and for ease of recruitment. Unaffected siblings were included if they had a history of average school performance (per parent report) and excluded if they had a history of any central nervous system injury, a psychiatric or developmental disorder, or English as a second language; no children were excluded using these criteria.

At the time of evaluation, children and adolescents with neurofibromatosis type 1 who met inclusion and exclusion criteria were asked to participate in the optional add-on computerized tasks, performed at the completion of the routine neuropsychological evaluation. Unaffected siblings completed only the study evaluations. Mean age was 12.8 years (SD = 2.04) for children with neurofibromatosis type 1 compared with 12.7 years (SD = 1.7) for unaffected siblings. Both groups had equal numbers of boys and girls. Characteristics of the samples as well as results of screening assessments are provided in Table 1. This study was approved by the Institutional Review Board of Children's Hospital Boston. Informed consent was obtained from the parent/legal guardian for participants prior to any screening or evaluations performed.

Study Evaluations

The standard neuropsychological clinical assessment battery for children with neurofibromatosis type 1 includes several measures of visual-spatial functioning as well as parental reports of attention, executive functions, and social/emotional functioning. The Judgment of Line Orientation is a motor-free untimed measure of spatial perception and orientation that requires participants to match correctly the spatial directionality and size of angle of lines.[7,19] Participants' performance (number of items correct) was compared with published normative data.[20] In addition to the standard clinical battery, participants with neurofibromatosis type 1 also completed the experimental task (Arena

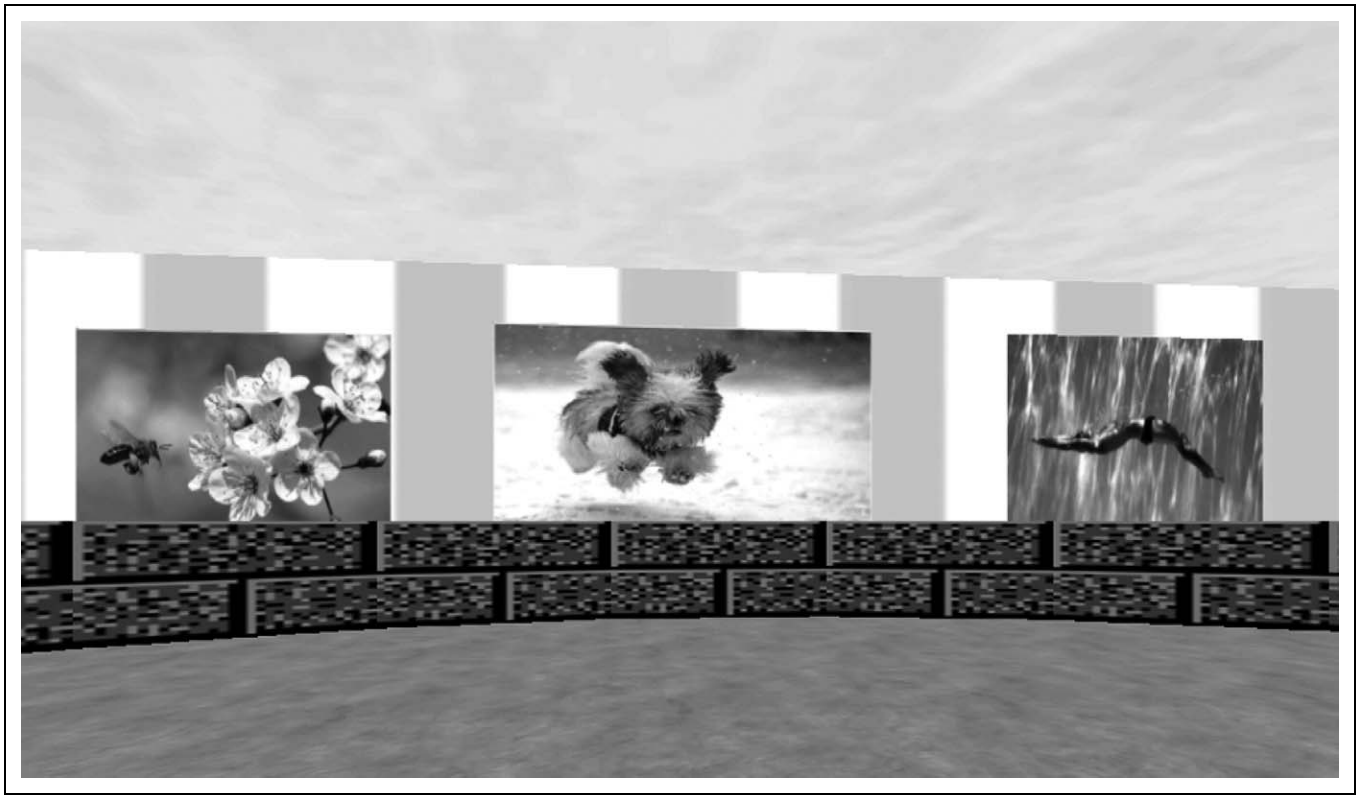

Figure 1. Background of the virtual Arena Maze. Sample black and white picture of the computerized virtual water maze/computerized Arena Maze with the virtual pool in the room. The actual graphics used during the experiments were in color.

Maze) as well as the Spatial Working Memory subtask of the Cambridge Neuropsychological Testing Automated Battery.[21,22] Unaffected sibling control participants performed the 2 computerized tasks, an intelligence screening using the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children (fourth edition),[23,24] the California Verbal Learning Test for Children,[25] and the Judgment of Line Orientation. The assessment of verbal learning uses an everyday memory task, in which the child is asked to recall a list of unrelated words. Parents completed questionnaires rating executive function (Behavior Rating Scale of Executive Function)[26,27] and attention (Conners Parent Rating Scale–Revised)[28] for both children with neurofibromatosis type 1 and their unaffected siblings.

The Cambridge Neuropsychological Testing Automated Battery is a computer-automated battery used to assess language, reaction time, working memory, automated memory, and several aspects of executive functioning. The spatial working memory task is a serial-order pointing task in which the participant is required to point to boxes on a touch-screen computer one at a time to discover which one contains a blue square. The task begins with 2 boxes for each trial and increases to a maximum of 8 boxes for the final trials. For all trials, each box location is used only once, and the children are instructed not to go back to the boxes in which they have previously found the blue squares. Primary performance measures for this task include the total number of errors within items and the total number of errors between items. We used between errors as the outcome variable and compared participant spatial working memory scores to normative data from the Cambridge Neuropsychological Testing Automated Battery.[21]

The Arena Maze is administered by computer and uses a video game controller to navigate around a circular ''arena'' within a square room to locate a target on the floor. The walls of the Arena Maze contain cues, such as windows, that remain in place through the test trials. A sample ''background'' is shown in Figure 1. Prior to beginning, participants are given directions and are introduced to the virtual room and allowed to familiarize themselves with the controller and to explore the environment. For the first 2 practice trials, the target is completely visible. For the 6 learning trials, the child is reminded that the target is no longer visible but is always hidden in the same place in the room. The child must then find the invisible target, starting from a new location in the periphery each time. When the child successfully navigates to the target, it becomes visible. On the final trial, the ''probe'' trial, the target is removed from the arena without the child's knowledge and does not appear when the child navigates to the target location. Participants are told to go to each target location as quickly and directly as possible for all trials.

Performance on the Arena Maze was assessed using several measures: (1) *path length*, the distance traveled from the start point to the target; (2) *latency*, the time required to find the target; and (3) *dwell time*, the time spent in each of the Arena Maze quadrants. During the final ''probe'' trial, dwell time in the quadrant where the target was located provides a measure of learning. The program also generates a separate data file that contains a pixel-by-pixel recording of the participant's path through the arena on each trial (*search path*). In addition, we evaluated the overall success in finding the target (*target crossings*).

Data Analysis

Data from the standard psychometric assessments and computerized Arena Maze were recorded, summarized, and graphed using Microsoft

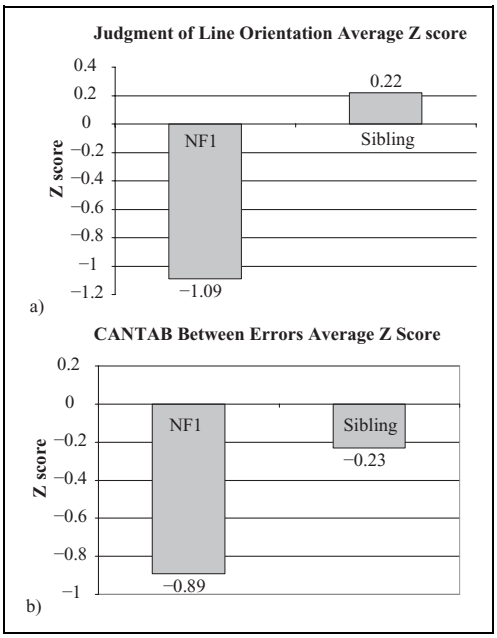

Figure 2. Spatial learning in children with and without neurofibromatosis type 1 on validated performance tasks. Performance of children with neurofibromatosis type 1 on (A) Judgment of Line Orientation and (B) Cambridge Neuropsychological Testing Automated Battery spatial working memory subtask compared with unaffected siblings.

Excel. Analyses were conducted using SPSS (Version 16; SPSS, an IBM Company[†]). We first compared performances of children with neurofibromatosis type 1 and their siblings on the screening measures and parent rating scales. We then examined the performance of children with neurofibromatosis type 1 on the Arena Maze and compared their performance with that of their unaffected siblings as a way to assess this novel measure of visual-spatial skills in the neurofibromatosis type 1 population. Finally, we examined the relationship between reported working memory problems and performance on the Arena Maze.

Results

Intellectual and Visual-Spatial Abilities Based on Standard Psychometric Assessments

Children and adolescents with neurofibromatosis type 1 were compared with unaffected siblings based on established measures of intellectual abilities, verbal learning and memory, visual-spatial perception, attention, and executive functioning. Comprehensive assessment of intelligence was available for the children with neurofibromatosis type 1. We compared the performance of the neurofibromatosis type 1 group with normative sample means on the intelligence screen using the Wechsler Intelligence Scale for Children (fourth edition).[29] Although the mean Full Scale IQ score for the neurofibromatosis type 1 group was in the average range, significant differences from the normative mean were found for Full Scale IQ (mean = 93.8, SD = 6.8; $t(9) = -2.86$, $P = .02$), Perceptual Reasoning Index (mean = 93.9, SD = 5.8; $t(9) = -3.34$, $P = .009$), and Processing Speed Index (mean = 85.0, SD = 16.7; $t(9) = -2.83$, $P = .02$). The Verbal Comprehension (mean = 103.1, SD = 10.6; $P = .38$) and Working Memory (mean = 94.9, SD = 8.8; $P = .10$) indices were not significantly different from the normative mean. We then compared performance on the screening intelligence subtests for both groups. Children with neurofibromatosis type 1 performed more poorly on the Block Design subtest ($P = .006$) than their unaffected siblings, but performance on the Vocabulary subtest was not significantly different ($P = .29$). Analysis of performance on the verbal memory test revealed no significant difference between the neurofibromatosis type 1 group and unaffected siblings (Table 1).

Impaired visual-spatial processing is commonly observed in individuals with neurofibromatosis type 1.[5,7] In our cohort, children with neurofibromatosis type 1 performed more poorly on the Judgment of Line Orientation and Cambridge Neuropsychological Testing Automated Battery Spatial Working Memory subtest compared with the sibling group (Figure 2). For the Judgment of Line Orientation, mean z score for the neurofibromatosis type 1 group was –1.09 compared with 0.22 for sibling controls ($P = .05$; 1-tailed test). On the Spatial Working Memory subtest, mean between-errors z score for the neurofibromatosis type 1 group was significantly different from expected normative data ($t(9) = -2.9$, z score = –.89, $P = .02$) but was not significantly different from the sibling controls ($P = .21$).

Parental ratings of attention and executive function were also compared. Children with neurofibromatosis type 1 had T scores in the clinically significant range on the Conners Parent Rating Scale for several relevant areas, including inattention, social problems, and attention-deficit hyperactivity disorder symptoms total. On the parental ratings of executive function, the Working Memory Scale was in the clinically significant range for children with neurofibromatosis type 1 and significantly different from that of the control group ($t(14) = 4.46$, $P = .001$). Children with neurofibromatosis type 1 were also more affected in the Global Executive Composite and Metacognitive Index (see Table 1).

Performance in the Computer-Generated Arena Maze

The computerized task required 10 minutes to complete using a video game controller device and was easily accomplished after completion of routine neuropsychological testing. All participants were able to use the game controller successfully and were able to follow the necessary instructions. A bird's-eye view of the typical path through the Arena Maze is shown in Figure 3a for a participant with neurofibromatosis type 1 for each of the 9 trials, including the first 2 trials, where the target is visible; the learning trials 3 through 8, where the target is invisible; and trial 9, where the target is removed. With a visible target, children with neurofibromatosis type 1 were able to navigate within the arena as quickly and as directly as the unaffected siblings. There was no significant difference in path length (trial 1 neurofibromatosis group mean = 67, SD = 21;

[†] SPSS was acquired by IBM in October 2009.

siblings mean = 57, SD = 10; $P = .22$) or latency (trial 1 neurofibromatosis group mean = 7.6, SD = 2.6; siblings mean = 9.4, SD = 3.0; $P = .27$) between the 2 groups on the trials with visible targets. Both groups were successful in finding all visible and hidden targets (6 of 6 target crossings for each participant). In addition, both cohorts demonstrated improvements in trial accuracy (path length) over time in the first and last learning trials, but some children with neurofibromatosis type 1 demonstrated more difficulty in earlier search trials compared with sibling controls, although this difference did not meet statistical significance (Figure 3b).

Children with and without neurofibromatosis type 1 demonstrated improvements in spatial learning during the learning trials (invisible target) of the Arena Maze; however, 2 different performance patterns emerged among the children with neurofibromatosis type 1. One group of patients appeared to search the arena and learn the task quickly and effectively with relatively short latencies from the initial trials. A second group demonstrated longer latencies on the first learning trial followed by reduced time to target over subsequent trials. Figure 4 demonstrates the time to target (target latency) for all participants with neurofibromatosis type 1. Although the number of participants is small, we did an exploratory analysis to evaluate performance using a 2-group t test to compare the group with longer latency (more than 7 seconds on the first learning trial) and shorter latency (less than 7 seconds). Based on this performance distinction, there is a significant difference between the 2 groups ($P = .004$). Unaffected siblings, by contrast, appeared to learn the target location on the first trial and were able to go to its location easily thereafter.

On the final probe trial, where the target is removed without the child's knowledge, children with neurofibromatosis type 1 were less able to focus their search for the target in the correct quadrant (dwell time; Figure 5). Unaffected siblings spent more time in the correct quadrant (80% vs 66%, $t(14) = -3.08$, $P = .008$), suggesting that they remembered where the target was and were confident in their knowledge. In addition, percentage dwell time in the correct quadrant correlated significantly with the Working Memory Scale of the parental assessment of executive function ($r = 0.61$, $P = .01$), suggesting that children with reported working memory difficulties spend less time in the quadrant where the target was originally found. Full Scale IQ was not available for sibling controls; however, for participants with neurofibromatosis type 1, there was no significant correlation between Full Scale IQ and dwell time ($P = .36$).

Discussion

Children with neurofibromatosis type 1 present with a variety of learning disorders similar to those seen in the general population; impairments in written language, reading comprehension, spelling, and mathematics have been identified.[3,30,31] Deficits in attention and executive functioning are common, and nearly half of all individuals with neurofibromatosis type 1 meet clinical criteria for attention-deficit/hyperactivity disorder.[7,32] Deficits with complex motor tasks and motor coordination are also frequently seen in neurofibromatosis type 1.[30,33]

Visual-spatial deficits are so common that some investigators have suggested that the presence of this deficit can be used to classify patients.[3,7] Studies demonstrate fairly consistently that children with neurofibromatosis type 1 have impaired performance on tasks of visual-spatial function such as the Judgment of Line Orientation Test, a task associated with activation of the parietal and occipital lobes.[5,7] As seen in our sample, children with neurofibromatosis type 1 also have difficulty with visual-constructional tasks, such as constructing patterns with blocks, assembling puzzles, and copying abstract drawings.[34-37] In a recent study using discriminant analysis, 92% of children were correctly identified using a multivariate combination of 4 visual-spatial tasks.[5,7]

Spatial learning deficits in the mouse model of neurofibromatosis type 1 are best characterized by the Morris Water Maze, a task that until recently had no comparable human equivalent. This study demonstrates the potential utility of a virtual task analogous to the Morris Water Maze task for assessing spatial learning deficits in a group of children with neurofibromatosis type 1. In our program, children with neurofibromatosis type 1 and suspected learning or academic difficulties are routinely referred for comprehensive neuropsychological evaluation. The Arena Maze was performed after completion of routine neuropsychological testing and was easily feasible, requiring only 10 minutes to complete. Participants reported that the task was fun and responded well to the video game aspect of the testing. All of the participants, with and without neurofibromatosis type 1, were able to easily understand the requirements of the task, and all participants were able to continue the task until completion.

As a measure of visual spatial learning, the computerized Arena Maze has several advantages and potential for novel applications. The task is portable and works with a desktop or laptop computer and allows for retesting in the same environment. The task also includes a training component and is safe for participants. Participants with neurofibromatosis type 1 were as capable as unaffected siblings in navigating in the presence of clear landmarks in the visible target trials and in ultimately finding the targets on the hidden target trials. In comparing patterns of performance on the learning trials, we found that affected and unaffected children both demonstrated improvements in trial accuracy (path length) over time, but the children with neurofibromatosis type 1 appeared to have more difficulty in earlier search trials compared with sibling controls. Performance of the neurofibromatosis type 1 group on the probe trial where the target was removed was significantly lower than for the control group, suggesting that ability to remember target location was less secure. Furthermore, participants with working memory problems (as rated by the parent) were more likely to spend less time in the correct quadrant.

The observed differences between the 2 groups were not likely the result of differences in the ability of the neurofibromatosis type 1 group children to manage the procedural aspects of the virtual task because all the children readily understood

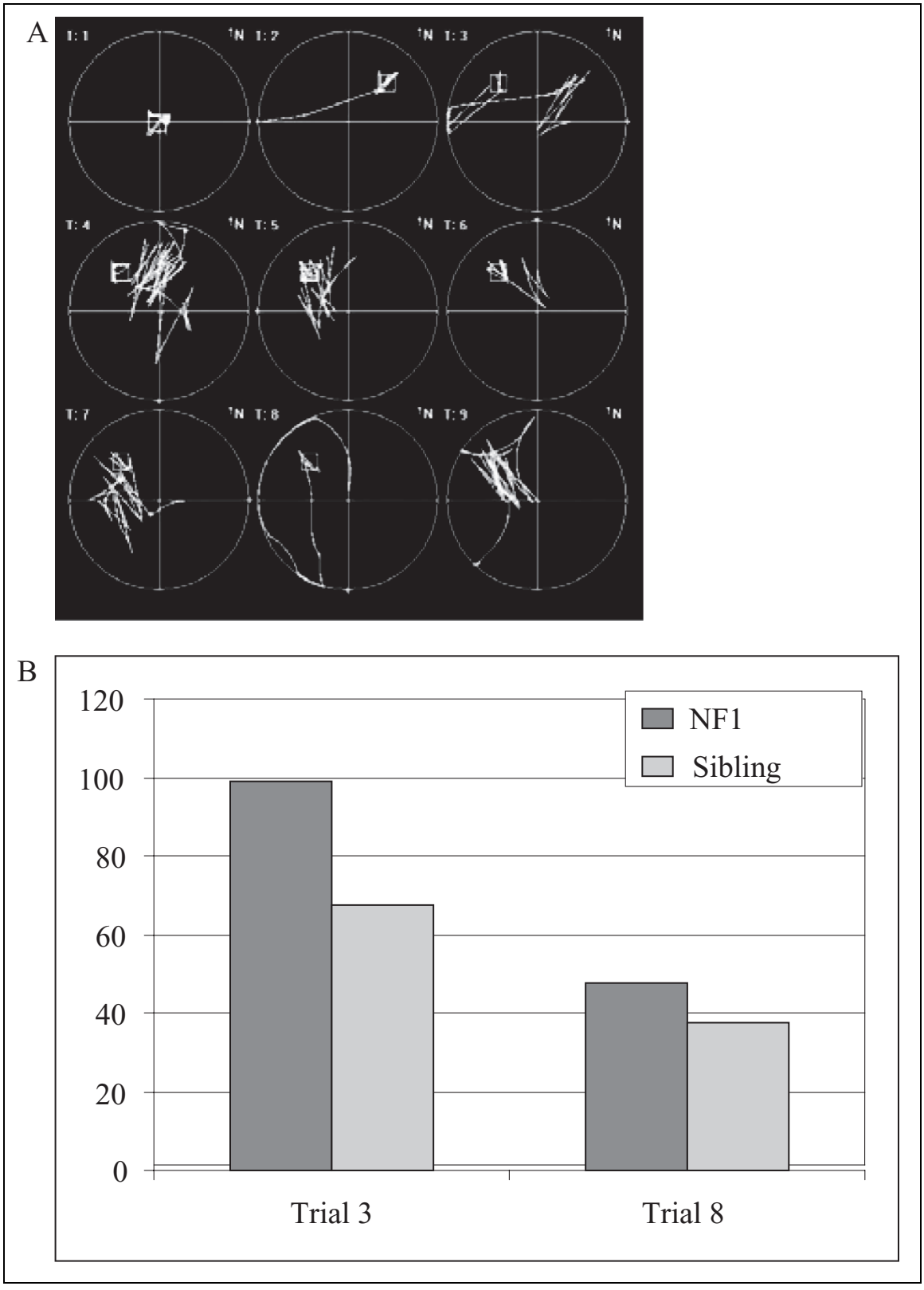

Figure 3. Performance on computerized arena. (A) Bird's-eye view based on pixel-by-pixel recording of the participant's path in the Arena Maze during the different trials, 1 to 9. Trials 1 and 2, the target is visible. Trials 3 through 8 are the learning trials with the invisible target. For trial 9, the target is removed. (B) Children with neurofibromatosis type 1 and their siblings both demonstrate improvements in trial accuracy (path length) over time between the first and last learning trials; however, affected children have more difficulty in earlier search trials compared with sibling controls.

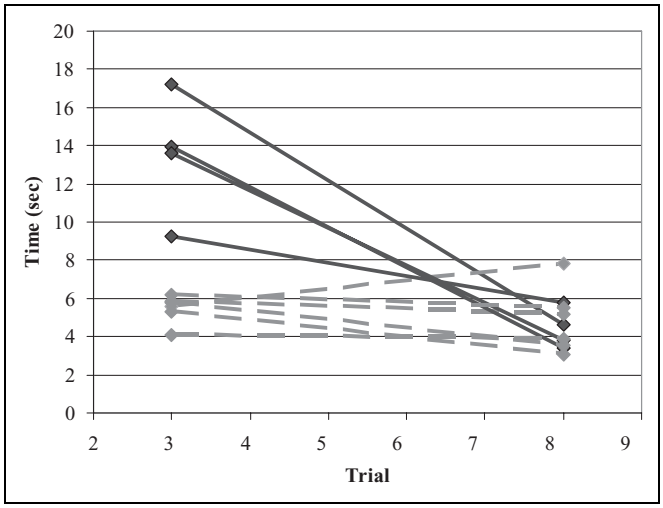

Figure 4. Children with neurofibromatosis type 1 demonstrate 2 different spatial learning patterns. Time to target (target latency) was determined for each participant over each trial of the Arena Maze. Each line represents the change in performance of individual patients between trial 3 (the first learning trial) and trial 8 (the last learning trial). Two patterns of performance were identified within the group of children with neurofibromatosis type 1: participants who had short latencies on all trials (seen in gray, dashed lines) and participants who demonstrated long latencies on the first learning trial followed by reduced time to target over subsequent trials.

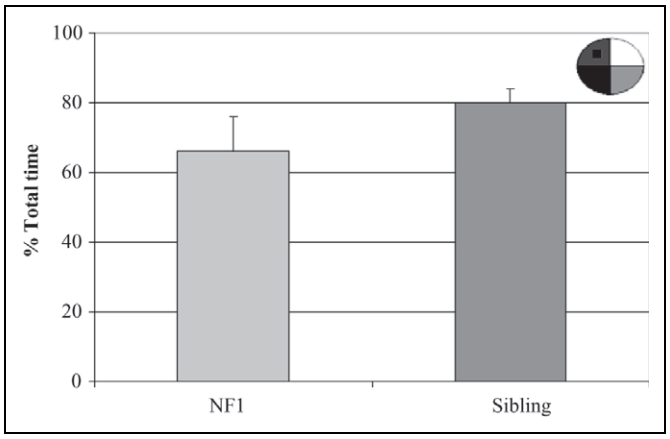

Figure 5. Spatial learning in children with neurofibromatosis type 1 and their unaffected siblings on the Arena Task. On the probe trial, trial 9, the target is removed from the arena without the participant's knowledge. Dwell time in the northwest quadrant where the target was located provides a measure of learning. Children with neurofibromatosis type 1 spend less time in the appropriate target compared with control siblings ($P = .008$).

the task. Performance on the first 2 visible target trials was also comparable between the 2 groups, suggesting that children with neurofibromatosis type 1 understood and remembered the instructions for the Arena Maze and were able to navigate easily in the virtual environment. Children with neurofibromatosis type 1 had difficulty locating the hidden target but always were able to successfully locate the target. Although this was a small pilot feasibility study, 2 patterns of performance emerged within the neurofibromatosis type 1 group: one group learned the task quickly at the beginning of the learning trials, whereas the other group had more difficulty initially but subsequently improved. These patterns of performance may be related to underlying differences in the presence and severity of visual-spatial impairments observed clinically in children with neurofibromatosis type 1. We hope that with further validation, we will identify subgroups within this population that define a clinically meaningful cutoff in terms of performance.

Spatial learning deficits may be an important target for interventions designed to ameliorate learning difficulties in children with neurofibromatosis type 1. Consequently, a paradigm to assess visual-spatial learning is needed. This pilot study represents the effort to bridge the gap between the mouse model and human clinical trials by testing a treatment endpoint that can be used in humans and employing a paradigm that evaluates functions analogous to those known to be impaired in the *Nf1* mouse model. Performance in virtual environments, such as the one used for this study, are thought to transfer readily to real-world contexts.[38] Ultimately, we hope to validate the Arena Task in a larger group of children and adolescents with neurofibromatosis type 1. This paradigm may also be useful in evaluating visual-spatial learning deficits in other clinical populations such as nonverbal learning disorder or traumatic brain injury. It is possible that modification of the Arena Task to make it more challenging will further potentiate the differences observed between children with and without neurofibromatosis type 1. The Arena Maze task will be assessed as a novel outcome parameter as an ancillary study to the upcoming, multicenter randomized placebo-controlled phase II study to determine the efficacy of lovastatin on visual-spatial learning and/or attention abilities of children with neurofibromatosis type 1.

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Declaration of Conflicting Interests

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

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