

Neurobehavioral Consequences of a Genetic Metabolic Disorder: Visual Processing Deficits in Infantile Nephropathic Cystinosis

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Objective: The purpose of the current study was to further characterize the nature of the visual processing deficit in infantile nephropathic cystinosis. It was hypothesized that children with cystinosis would demonstrate a dissociation between visuospatial and visuoperceptual abilities, with impaired spatial functioning and intact perceptual functioning. Hypotheses were based on cognitive studies to date as well as on a review of the visual processing literature. **Background:** Infantile nephropathic cystinosis is a genetic metabolic disorder in which the amino acid cystine accumulates in various organs, including the kidney, cornea, thyroid, and brain. The existing neurocognitive literature suggests the presence of a visual processing deficit against a background of generally normal intellectual capacity. The nature of the deficit, however, is still somewhat ambiguous. **Method:** Study participants were 141 children (33 with cystinosis and 108 controls), ages 5 through 14 years. Tests of visuospatial and visuoperceptual functioning were administered. **Results:** Data were analyzed using hierarchical regression analyses and MANCOVA. After covarying for relevant demographic variables, the cystinosis group consistently demonstrated impairments in spatial processing, whereas perceptual processing was largely intact. **Conclusions:** Results support the hypothesis of a dissociation in visual processing. Findings suggest that cystinosis has a differential effect on the two cortical visual processing streams, with spatial functions affected to a greater extent than perceptual functions. The present study has implications for brain-behavior relationships in other genetic disorders as well. (NNBN 2000;13:254-263)

Infantile nephropathic cystinosis is a genetic metabolic disorder with an autosomal recessive inheritance. In this condition, the amino acid cystine accumulates in lysosomes as a result of defective transport (1-3). The disease is characterized by normal appearance at birth and apparently normal development during approximately the first 6 to 18 months of life. It typically makes its clinical presentation with failure to thrive and renal tubular dysfunction (Fanconi syndrome) (4). The incidence of infantile nephropathic cystinosis is approximately 1 per 100,000 to 200,000 live births (5). In 1995, the gene for cystinosis was mapped by linkage analysis to chromosome 17p13 (6,7). The gene, *CTNS*, codes an amino acid protein, cys-

tinosis, which has a function in lysosomal membrane transport (8-10).

Deposition of cystine crystals has been noted in various organs of the body, including the kidney, cornea, thyroid, liver, bone marrow, and brain. Cystine has been found to accumulate in utero (11) and likely has a prenatal influence on renal (and possibly central nervous system [CNS]) functioning. The accumulation of cystine crystals can eventually lead to destruction of tissue and problems such as progressive renal and thyroid dysfunction. Kidney dialysis and renal transplantation have served to extend survival beyond the first decade of life and to the second and third decades (12), although the disease does progress in nonrenal tissues even after successful renal transplantation (13). In addition, cystine-depleting drugs (cysteamine and phosphocysteamine) now further extend the life span of individuals with cystinosis (14-17). As patients are surviving longer, the long-term effects of cystinosis on various nonrenal organs can be assessed.

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Cystinosis was originally thought to spare the CNS (11, 18–20), although recent evidence has indicated otherwise. For example, cystine accumulation in the brain has been documented in several postmortem studies (21–24). In particular, deposition of cystine crystals and abnormally high cystine levels have been reported in the cerebral cortex, choroid plexus, pituitary, basal ganglia, thalamus, cerebellum, and internal capsule (21–25). Neuroimaging studies (e.g., computed tomography, magnetic resonance imaging) have found evidence of subcortical or cortical atrophy (24, 26–31) and hydrocephalus (26,32,33). Abnormal electroencephalograms have also been obtained in individuals with cystinosis (24,26,29,32). Some studies document neurologic impairments such as poor fine and gross motor skills, hypotonia, or tremor (27,32,34). Other studies note pyramidal or extrapyramidal symptoms, particularly in older individuals with cystinosis (24,27,28). In contrast, others have found few frank neurologic abnormalities (19,29,33).

Recent studies of cognitive functioning have indicated that as a group, individuals with cystinosis have overall intelligence within the normal range (29,33–36). Despite normal intellect, however, individuals with cystinosis may have specific impairments in the processing of visual information, particularly when the processing demands are complex and the stimuli do not readily lend themselves to linguistic mediation (30,34,35). Individuals with cystinosis have been found to have difficulty in tasks requiring visual short-term memory (34,35,37,38), spatial relations (35), visuomotor integration (39), and tactile recognition of common objects (40). In contrast, these individuals demonstrate intact object perception as well as intact general intellectual ability, language, auditory processing, and auditory attention and memory (30,34–36,40). Although studies to date provide evidence for a visual processing deficit, the nature of the deficit is still somewhat ambiguous. The present study was designed to further characterize the nature of the visual processing deficit in children with cystinosis by analyzing their performance in the visuospatial and visuoperceptual domains.

Visuospatial and visuoperceptual skills may be mediated by different neuroanatomic pathways, and deficits may be found in one visual processing area but not the other (41). There is strong evidence from both animal and human research of the existence of two major cortical visual processing systems or “pathways,” with both originating in the occipital cortex. The occipitoparietal system follows a dorsal path to the parietal lobe, whereas the occipitotemporal system follows a ventral path to the temporal lobe (42–44). Parallel to this anatomic divergence, functional dissociations have been identified. One model is that of “where” versus “what” as proposed by Ungerleider and Mishkin (42). In that model, the occipitoparietal pathway is thought to be specialized for spatial perception

(i.e., visuospatial skills, including analysis of spatial relations or location), with lesions of the posterior parietal cortex associated with spatial deficits (42,44,45–47). The occipitotemporal pathway is thought to be specialized for object perception (i.e., visuoperceptual skills, including object identification, recognition, or discrimination), with lesions of the inferior temporal cortex associated with visuoperceptual deficits (42,44,48,49). In more recent work, Goodale and Milner (50, 51) offer an alternative view of the two visual processing streams proposed by Ungerleider and Mishkin (42). Whereas the previous model focuses on input to the system, Goodale and Milner (50,51) formulate the two streams in terms of output demand. They propose a “how” versus “what” model in that the posterior parietal system (dorsal stream) engages in viewer-based coding and provides action-relevant information in terms of visuomotor control of the eyes, limbs, and/or body. The occipitotemporal system (ventral stream) is involved in perceptual coding independent of a particular viewpoint. Goodale and Milner (50,51) argue that spatial processing can occur in either stream, depending on the output characteristics. Parietal cells are associated with saccadic eye movements and egocentric spatial coding, used for goal-directed actions. They do acknowledge that tasks such as mental rotation, the manipulation of visual and tactual images, and map reading would involve parietal regions (dorsal stream) because of the requisite and extensive scanning and visual guidance and/or viewer-based characteristics (50,51). In contrast, inferotemporal neurons are associated with more object-centered characteristics. They are sensitive to form, pattern, and color, and they are suited for the recognition of objects, scenes, and individuals independent of viewpoint (50,51).

In terms of neurobehavioral assessment, visuospatial functioning includes abilities such as topographic orientation and judgment of direction and distance (41). In addition, measures involving mental rotation and spatial memory are thought to involve spatial processing (52,53). Measures of topographic orientation, mental rotation, and spatial memory were included in the current study. There is ample evidence linking specific task performance to parietal lobe integrity (41,45,46,50–61).

Visuoperceptual functioning includes such abilities as object and color recognition, facial recognition or discrimination, and analysis and synthesis (41). Evidence indicates that individuals with cystinosis do not have deficits in basic areas such as object or color recognition or in the area of facial recognition or discrimination (35,40). Instead, the area of analysis and synthesis merited investigation. This area may involve skills such as visual closure, figure-ground differentiation, or fine visual discrimination; measures of such were incorporated within the current study. Tasks involving these skills have been used to

detect disturbances of perceptual processing (41,56,62-71) and have been associated with ventral stream or temporal lobe functions (42,44,48-51,56,58,66).

In addition, a visual scanning task was included in the current study to evaluate visual attention and visual search. Visual scanning impairments may be associated with inattentiveness, difficulty with shifting attention (e.g., involving engagement or disengagement), response slowing, or unilateral spatial neglect (72). Such information was deemed potentially useful for the interpretation of other findings.

HYPOTHESES AND IMPLICATIONS

Based on prior cognitive studies of cystinosis patients as well as on a review of the visual processing literature, it was hypothesized that children with cystinosis would demonstrate a dissociation between visuospatial and visuosperceptual abilities, with impaired spatial functioning and intact perceptual functioning. The present study has implications for our understanding of the neurocognitive effects of cystinosis and for remediation of specific cognitive deficits that may be problematic for the individual. This investigation also has broader implications for brain-behavior relationships in other genetic disorders.

METHOD

Participants

Study participants were 141 children ranging in age from 5 through 14 years. Thirty-three of these children were diagnosed with infantile nephropathic cystinosis, and 108 were control subjects. The diagnosis of cystinosis was based on elevated leukocyte cystine levels (73,74) and clinical history. None of the individuals in the cystinosis group was experiencing renal failure at the time of testing, all were euthyroid, and all were free from uncorrected visual difficulties. The control subjects had normal developmental and medical histories and were free from motor and uncorrected visual difficulties.

Tests

Tests of visuospatial and visuosperceptual functioning, as well as a measure of visual scanning, were administered. Tests were chosen on the basis of prior research and/or clinical usage and findings.

Spatial Measures

Locomotor Maze (54). This is a task of extrapersonal orientation suitable for children aged 6 years and older. Subjects were required to walk through a series of paths presented on five separate maps. On each map were nine dots or "landmarks," a path, and "North"; in the test room, there were nine landmarks on the floor, and "North" was marked on the wall. The subject had to walk through a

path on the floor that corresponded to the path on each map. Detailed instructions and two practice items preceded the actual test items. The subject was not able to turn the map while walking; therefore, the map was not always in proper orientation with respect to extrapersonal space, and a series of translations of its coordinate system to true directional coordinates had to be effected by the subject. The total score was the number of "landmarks" correctly visited in order. The maximum score was 49 (perfect performance).

Luria-Nebraska Visual-Spatial Subtest (75). This is a mental rotation task suitable for children through 11 years of age. Subjects were shown a rotated stimulus figure, which was a square with a heavy dark line along one side and a circle in one corner. Subjects then had to choose the one target figure (from four choices in which the circle was located in a different position relative to the dark line) that was identical to the rotated stimulus figure. Two practice items preceded the test items. The score was the number of correct items out of eight total items.

K-ABC Spatial Memory (76). This test is used to assess short-term spatial recall of simultaneously visually presented material. The subject was shown a page with familiar pictures for 5 seconds and was then shown an empty grid and asked to point to those boxes on the grid that corresponded to the exact positions of the previously shown pictures. One practice item preceded the test items. The score was the total number of correct items out of 21 total items. To examine possible error patterns, the numbers of addition, omission, and misplacement errors were tabulated.

Perceptual Measures

Gollin Incomplete Figures (77). This is an object recognition task in which the stimuli are incomplete and the subject must mentally "fill in" missing visual information. Subjects were administered 21 test items, which were preceded by 1 practice item. Each item consisted of a line drawing of a familiar object presented in five gradations of completeness. Subjects were shown the most incomplete picture for 3 seconds and asked to guess what it might be. Subjects were shown more pictures in subsequent gradations of completeness until they had enough visual information to correctly identify the object. The total number of pictures needed to identify all the items was tabulated. The possible range of scores was 21 to 105, with a higher score representing poorer performance.

Children's Embedded Figures Test (78). This is a test of complex visual perception in which the stimuli are complicated by distracting embellishments. The standardized version of the test, which is composed of caricatured drawings of familiar objects for complex figures, was administered. It is appropriate for children ages 5 through 11

years. Subjects were asked to find one of two different simpler forms (shaped like a "tent" and a "house") within a larger complex figure. A series of practice items preceded the tent and house test items. There were 11 tent and 14 house test items. The score was the number of items correct out of 25 total items.

Visual Form Discrimination (69). This is a visuoperceptual test that evaluates the subject's ability to discriminate between complex visual configurations that differ by distortion or rotation of a major figure or by misplacement or rotation of a peripheral figure. Subjects were administered the standardized 16-item test in which a stimulus card and a multiple choice response card are simultaneously presented, and the subject must identify the one design that is exactly the same as the stimulus. Each design consists of two major figures and one peripheral figure. Two practice items preceded the test items. According to the scoring guidelines (69), two points were awarded for each correct response, one point was awarded for each incorrect response involving a peripheral error, and no points were awarded for errors of major rotation or major distortion. The total score was the number of points awarded out of a maximum of 32 points. To examine possible error patterns, the numbers of peripheral errors (which represent either simple misplacement or rotation of the peripheral figure), major distortion errors, and major rotation errors were tabulated.

Visual Scanning

A visual scanning test was given to screen for impairments in visual attention and visual search because such information was deemed potentially useful for the interpretation of other findings.

Cancellation (79). This is a test of visual scanning that can be used for evaluating hemispatial neglect, scanning efficiency, and attention to visual details. The subject was shown a target form (a shape or a letter) and asked to

cross out all the targets he or she could find on a page displaying a random array of forms (shapes or letters, respectively). Each page contained 60 targets, with 15 in each quadrant. Subjects were given four different colored marking pens at 15-second intervals (for a total scanning time of 1 minute) to cross out target forms. For the purposes of our study, the 1-minute time limit was imposed to avoid ceiling effects and only random stimuli were used (rather than structured) because the randomly distributed stimuli are somewhat more difficult (72). The score was the number of stimuli identified out of 120 total stimuli. To evaluate left-right differences in scanning, the number identified in left or right hemispace was also tabulated.

Procedure

Given the rare nature of cystinosis and the availability of subjects, not every subject was administered each test. Table 1 shows the number of cystinosis and control participants who received each test and the mean ages of the cystinosis and control groups on each measure. The total group sizes (N) shown in Table 1 are comprised of approximately equal numbers of male and female subjects. In addition to the measures shown, all subjects were administered the Stanford-Binet Intelligence Scale, 4th edition (80), and a composite score was derived from the following subtests: Vocabulary, Quantitative, Pattern Analysis, and Memory for Sentences. Subjects were tested as part of a larger study of cognitive functioning in families affected by cystinosis. The Stanford-Binet was chosen because it is normed on a wide age range (2-23 years) and was thus suitable for all subjects in the larger study. For patients and controls who were enrolled in our studies longitudinally and who received the same test on more than one occasion, we used data from the first administration of the test so as to avoid confounds caused by familiarity with particular tests and practice effect.

Informed consent was obtained before testing each

TABLE 1. Number of subjects in, and mean ages of, the cystinosis and control groups on each measure

| Measure | Cystinosis | | | Control | | |
|-------------------------------|------------|----------|------|---------|----------|------|
| | N | Mean age | SD | N | Mean age | SD |
| Spatial | | | | | | |
| Locomotor Maze | 19 | 9.72 | 2.48 | 57 | 9.83 | 2.13 |
| Luria-Nebraska Visual-Spatial | 25 | 8.47 | 1.60 | 70 | 8.73 | 1.77 |
| Spatial Memory | 30 | 8.29 | 2.43 | 108 | 9.22 | 2.55 |
| Perceptual | | | | | | |
| Gollin Incomplete Figures | 33 | 7.80 | 2.58 | 107 | 9.22 | 2.57 |
| Children's Embedded Figures | 25 | 7.38 | 1.56 | 76 | 8.06 | 1.79 |
| Visual Form Discrimination | 31 | 8.12 | 2.50 | 106 | 9.25 | 2.55 |
| Visual scanning | | | | | | |
| Cancellation | 24 | 8.35 | 2.73 | 91 | 9.26 | 2.61 |

Age is used as a covariate in data analyses.

subject in accordance with the guidelines of the Institutional Review Board at the University of California at San Diego.

RESULTS

Analyses of Group Differences

Hierarchical regression analyses were conducted to test the hypothesized relationships between each of the seven dependent variables (visual processing test scores) and the independent variable of group membership (cystinosis vs control) after statistically controlling for relevant demographic variables. Because not all subjects were administered all tests, each dependent variable was examined separately.

Initial data screening included examination of the data for missing values, outliers and unusual cases, normality, and linearity. Before full regression models were tested, it was confirmed that assumptions were met. The covariates (age and IQ) accounted for a significant proportion of variance for each dependent variable, and in all cases except one, the covariates did not interact with the independent variable of group membership (for that single case, the interaction was included as an independent variable rather than a covariate). Sex was also evaluated as a potential covariate but was found not to account for a significant proportion of variance for any of the seven measures. Consequently, sex was not included as a variable.

Variables were entered by blocks, with covariates (age and IQ) entered in the first block and the primary independent variable (group membership) entered in the second block. Table 2 presents the mean raw scores and adjusted raw scores for the cystinosis and control groups

on each measure. The mean IQs for the cystinosis and control groups on each test ranged from 101.38 ± 14.32 to 103.92 ± 14.15 for the cystinosis group and from 112.02 ± 10.34 to 113.23 ± 10.50 for the control group. For each of the seven measures, Table 3 presents the proportion of variance accounted for after entry of the covariates, and after entry of the primary independent variable of group membership in the regression model.

Spatial Measures

It is clear from Table 3 that the covariates of age and IQ accounted for a significant proportion of variance in score for each of the three spatial tests. Group membership accounted for a significant proportion of additional variance in score for each of the three measures, with the cystinosis group consistently performing more poorly than the control group.

Perceptual Measures and Visual Scanning

The covariates of age and IQ accounted for a significant proportion of variance in score for all perceptual and visual scanning measures. In contrast to the spatial measures, however, group membership did *not* account for a significant proportion of variance on three of the four measures (see Table 3). Only for Visual Form Discrimination did group membership account for a significant proportion of variance. In addition, the full model for this dependent variable included a significant $IQ \times Group$ interaction. Examination of the data revealed that the interaction was the result of a ceiling effect in those controls with higher IQs, whereas there was no ceiling effect within the cystinosis group; hence, the slopes of the regression lines for each group differed.

TABLE 2. Mean raw scores and adjusted raw scores for the cystinosis and control groups on each measure

| Measure | Cystinosis | | | Control | | |
|-------------------------------|---------------|-------|---------------|---------------|-------|---------------|
| | Observed mean | SD | Adjusted mean | Observed mean | SD | Adjusted mean |
| Spatial | | | | | | |
| Locomotor Maze | 18.21 | 13.67 | 20.18 | 33.79 | 12.67 | 31.82 |
| Luria-Nebraska Visual-Spatial | 3.28 | 2.15 | 3.76 | 5.49 | 2.24 | 5.00 |
| Spatial Memory | 11.20 | 4.29 | 11.94 | 14.23 | 2.91 | 13.49 |
| Perceptual | | | | | | |
| Gollin Incomplete Figures | 48.42 | 11.55 | 46.12 | 41.73 | 8.35 | 44.02 |
| Children's Embedded Figures | 9.72 | 5.53 | 11.32 | 13.76 | 5.73 | 12.16 |
| Visual Form Discrimination | 23.16 | 5.46 | 24.26 | 27.28 | 4.17 | 26.19 |
| Visual scanning | | | | | | |
| Cancellation | 53.33 | 30.72 | 59.87 | 73.02 | 26.40 | 66.49 |

Sample sizes and ages for the cystinosis and control groups on each test are shown in Table 1. The significance levels for the regression models and coefficients are shown in Tables 3 and 4, respectively. Observed and adjusted means reflect adjustment for the covariates of age and IQ. For Gollin Incomplete Figures, a higher score represents poorer performance.

TABLE 3. Proportions of variance accounted for by covariates (age, IQ) and independent variable of group membership

| Measure | R ² with covariates | R ² with covariates and group | Group significance |
|-------------------------------|--------------------------------|--|--------------------|
| Spatial | | | |
| Locomotor Maze | 0.40‡ | 0.51‡ | Yes |
| Luria-Nebraska Visual-Spatial | 0.47‡ | 0.52‡ | Yes |
| Spatial Memory | 0.57‡ | 0.60‡ | Yes |
| Perceptual | | | |
| Gollin Incomplete Figures | 0.51‡ | 0.51 | No |
| Children's Embedded Figures | 0.48‡ | 0.49 | No |
| Visual Form Discrimination | 0.38‡ | 0.40* | Yes |
| Visual scanning | | | |
| Cancellation | 0.77‡ | 0.78 | No |

* $p < 0.05$. † $p < 0.01$. ‡ $p < 0.001$.

The p -values noted for "R² with covariates and group" reflect the significance of the increment in R² after entry of group membership.

Impact of Age, IQ, and Group Membership on Each Measure

To assess the impact of the covariates and independent variable (group membership) across measures, standardized regression coefficients are displayed in Table 4. The standardized rather than unstandardized regression coefficients are appropriate for comparing the effects of different variables within the same population (81). As can be seen in Table 4, the covariates had a considerable impact on all measures. The impact of group membership was examined only after variance attributable to the covariates was removed. It can be seen that group membership had the greatest impact on the spatial measures as opposed to the perceptual and scanning measures. Among the spatial

TABLE 4. Standardized regression coefficients of covariates (age, IQ) and independent variable of group membership

| Measure | Standardized regression coefficients | | |
|-------------------------------|--------------------------------------|-------|------------|
| | Age | IQ | Group |
| Spatial | | | |
| Locomotor Maze | 0.46 | 0.44 | 0.35 |
| Luria-Nebraska Visual-Spatial | 0.39 | 0.52 | 0.23 |
| Spatial Memory | 0.68 | 0.30 | 0.18 |
| Perceptual | | | |
| Gollin Incomplete Figures | -0.67 | -0.18 | -0.09 (NS) |
| Children's Embedded Figures | 0.53 | 0.44 | 0.06 (NS) |
| Visual Form Discrimination | 0.46 | 0.37 | 0.17 |
| Visual scanning | | | |
| Cancellation | 0.83 | 0.24 | 0.09 (NS) |

NS, not significant.

The values are significant unless noted. For Gollin Incomplete Figures, the negative coefficients reflect the fact that a higher score represents poorer performance (whereas for all other tests, a higher score represents better performance).

measures, Locomotor Maze was most influenced by group membership, followed by the Luria-Nebraska Visual-Spatial subtest and K-ABC Spatial Memory, respectively.

Analysis of Hemispatial Differences

Although the cystinosis and control groups performed similarly for total score on Cancellation (i.e., visual scanning), it was of a priori interest to determine whether the two groups had differential performance in terms of left-sided or right-sided stimuli identified. Therefore, a 2×2 (Group [cystinosis, control] \times Side [left, right]) MANCOVA was conducted, with the covariates again being age and IQ. Results indicated that the cystinosis and control groups did not differ in terms of left-sided or right-sided score.

Error Analyses

Two of the measures, Spatial Memory and Visual Form Discrimination, were scored in such a way that error analyses were possible. Analyses were conducted with age and IQ as covariates.

For Spatial Memory, a 2×3 (Group [cystinosis, control] \times Error Type [addition, omission, misplacement]) MANCOVA indicated that there was a significant main effect for group ($F[3,132] = 5.12, p < 0.01$). Univariate tests revealed that the cystinosis group made significantly more misplacement errors ($F[1,134] = 14.82, p < 0.001$) than did the control group, whereas their scores did not significantly differ for addition or omission errors. The cystinosis and control unadjusted means, respectively, were 10.70 and 5.87 for misplacement errors, 1.63 and 0.70 for addition errors, and 3.23 and 2.55 for omission errors.

For Visual Form Discrimination, a 2×3 (Group [cystinosis, control] \times Error Type [major rotation, major distortion, peripheral error]) MANCOVA indicated that there was a significant main effect for group ($F[3,130] = 2.98, p < 0.05$). Univariate tests indicated that the cystinosis group made significantly more errors of major rotation ($F[1,132] = 4.40, p < 0.05$) and major distortion ($F[1,132] = 5.07, p < 0.05$) than did the control group. Peripheral errors were not significantly different between the two groups. The cystinosis and control unadjusted means, respectively, were 1.55 and 0.74 for major rotation errors, 1.55 and 0.88 for major distortion errors, and 2.58 and 1.49 for peripheral errors.

DISCUSSION

Results of the current study support the hypothesis that children with cystinosis exhibit a dissociation in visual

processing. Spatial processing impairments were present, whereas perceptual processing seemed to be largely intact. Compared with control subjects, cystinosis subjects showed impairment on each of the spatial measures used in this study. These tests involved extrapersonal orientation, mental rotation, and short-term memory of spatial location. Interestingly, an analysis of error types on the spatial memory task revealed that the cystinosis subjects accurately recalled information about the number of visual stimuli shown (i.e., there were no between-group differences for omission or addition error types) but were significantly impaired at recalling the spatial location of the stimuli and thus tended to misplace the stimuli on recall. This finding lends further support to the hypothesis of a spatial deficit in children with cystinosis and helps to rule out a memory deficit as the primary basis of the defective performance on this task.

In addition, on a task that was used as a measure of perceptual functioning (Visual Form Discrimination), it seems that a small spatial component may have made it more difficult for cystinosis subjects. Analysis of error types revealed that the cystinosis subjects made more major rotation and major distortion errors than did control subjects, whereas there was no difference in peripheral errors between the groups. Peripheral errors can represent either a misplacement or rotation of a peripheral figure. Although there are no known studies on the different error types, perhaps major rotation and major distortion errors have a greater spatial component, whereas peripheral errors, in contrast, have a greater perceptual component. This is supported by the fact that only a portion of peripheral errors are rotations; the others are simple misplacements, which seem to require perceptual skills to a greater extent than spatial skills.

The spatial processing defects in cystinosis seem to represent a rather specific impairment and are not due solely to global intellectual decrements. The children with cystinosis in this study had a mean IQ within the normal range (which is consistent with previous findings), and spatial difficulties were found even after partialling out the effect of IQ on spatial test scores. The visual processing differences found between the two groups were also unlikely to be due to differences in visual scanning efficiency or to spatial neglect because there were no between-group differences in visual scanning.

The present study builds on previous research and indicates that the visual processing deficits in cystinosis are specific to the spatial domain and involve the analysis of spatial relations or location. Basic encoding and retrieval of visual information seem to be intact in cystinosis because perceptual measures that make demands on these aspects of processing do not differentiate cystinosis from control subjects. This functionally based pattern of impaired spatial processing and largely spared perceptual

processing has implications for our understanding of the effect of cystinosis on the brain.

The neurologic basis of the observed visuospatial deficit in cystinosis is unknown, although several possibilities exist. First, it is possible that the primary genetic defect (and concomitant accumulation of cystine in the brain) is responsible for the spatial deficits. The genetic defect involves a gene that encodes for a transport protein that allows cystine to cross the lysosomal membrane (1,9,82). It is well documented that cystine accumulates in various areas of the brain in individuals with cystinosis (21-25). Particular neuronal populations or areas of the brain may be more vulnerable than others to the effects of cystine accumulation over time.

If cystine accumulation were the cause of the observed deficits, we might expect to see decrements in functioning with age, although this was not the case. Performance on all measures improved with age, and both the cystinosis and control groups improved at the same rate. An important consideration, however, is that most of the cystinosis participants were receiving treatment with cysteamine (or phosphocysteamine), which is an intracellular cystine-depleting drug (17,83) that helps to protect renal function. It is possible that cystine accumulation in brain tissue is also attenuated by this treatment, thereby eradicating decrements in functioning across the age range studied. Future studies are needed to address the effect of (phospho)cysteamine treatment on brain tissue and to clarify how this treatment influences the neurocognitive manifestations of cystinosis.

If cognitive differences are due to the effects of cystine accumulation, studies of individuals not treated may show a different pattern of performance from that seen here. Such studies are underway. Also, similar studies of older adults with cystinosis could further elucidate any relationship between spatial performance and age.

Alternatively, it is possible that a subtle neurodevelopmental anomaly may account for the observed cognitive deficits in cystinosis. This is plausible given that the metabolic defect is present during brain development. Cystine accumulates in utero and affects renal functioning (11); thus, it is possible that the CNS is also affected prenatally by cystine accumulation or by other indirect metabolic influences. This could result in differences (from the norm) in neural or cerebral organization for particular structures and/or functions. Detailed neuroanatomic and neurophysiologic studies, particularly of very young cystinosis patients, could help to determine whether atypical neural or cerebral organization is present.

Finally, the observed deficits could be related to some other effect of the gene either direct or indirect. For example, the gene for cystinosis may be closely linked to a gene that influences visuospatial processing, or the absence of the cystine transporter may result in as yet

undefined metabolic consequences such as changes in neurotransmitter function or other CNS alterations.

Although the mechanism(s) of impairment are currently unknown, the pattern of results in the current study suggests that cystinosis may have a differential effect on the two cortical visual processing streams, with the "where" system more affected and the "what" system less affected. Impairments on spatial tasks such as those used in the current study are frequently related to parietal lobe compromise in adults. Because there is a paucity of similar studies in children, we cannot say with certainty that the same neuroanatomic localizations apply to children. However, if the same neuroanatomic localizations do hold up, perhaps the posterior parietal lobe is more vulnerable than other areas of the brain to the direct and/or indirect effects of the disease. Recent findings of arithmetic difficulties (84) in individuals with cystinosis lend further support to the involvement of parietal lobe function because spatial and arithmetic difficulties tend to co-occur and are associated in a number of syndromes (e.g., Turner syndrome, Gerstmann syndrome, right-hemisphere deficit syndrome) (85-89).

These findings may have implications for the daily functioning of children with cystinosis. Their spatial problems may cause difficulty in school with, for example, learning arithmetic or geography, or finding their way from one class to another. These individuals may have difficulty with tasks such as putting together puzzles, assembling household items, map reading, or navigating around unfamiliar surroundings. It would be important to identify such problems early so that these children could receive the appropriate therapeutic intervention through the school or in occupational therapy.

Several methodological issues must be considered when interpreting the results of this study. Measures were classified as belonging to the visuoperceptual or visuospatial domain on the basis of previous research and clinical findings. The measures used in the current study were deemed appropriate for use with children of the ages studied. As would be expected, there were significant positive correlations between the demographic variables of age and each test score as well as between IQ and each test score. Sex was not significantly associated with score on any of the measures. Although this may seem surprising at first glance, it is less so when we consider the age of these subjects, who were predominantly preadolescents. Sex differences generally become apparent in adolescence (53) and are more salient in adulthood than in childhood. Ceiling and floor effects were not present, with the exception of perfect performance on Visual Form Discrimination by higher IQ controls; this test was designed, however, to yield (near) perfect scores in "normal" adults.

Results of this study could potentially be related to differential task difficulty for the perceptual and spatial mea-

asures, although this is unlikely. For each measure, the performance of the cystinosis subjects was compared with that of control subjects, and the measures were not directly compared within the groups. In addition, a recent study (90) used a framework and measures similar to those used in the current study to assess perceptual and spatial abilities in Alzheimer disease. Interestingly, the Alzheimer disease patients had predominantly perceptual impairments and were less impaired in the spatial domain. This would argue against the perceptual set of measures simply being "easier" psychometrically than the spatial set. Examination of the distribution of scores among subjects in the current study also supports the contention that the sets of measures were generally comparable and contained no systematic psychometric flaws.

Due to the paucity of published normative data for children's performances on many of the tests, the current study used a large control group that was similar to the cystinosis group in terms of the age and sex distribution of participants, and all comparisons were based on raw scores. Analyses were conducted so as to account for potentially confounding demographic variables (age, IQ, sex). Moreover, analyses were appropriately focused on between-group differences (i.e., for each test, comparing the performance of cystinosis subjects with that of controls) rather than within-group differences (i.e., comparing performance on the different tests within the cystinosis or control groups) because the measures were all scaled differently and the covariates had a differential impact on each measure.

The present study has implications for our understanding of the neurocognitive effects of cystinosis and for remediation of specific cognitive deficits that may be problematic for the individual. There has been recent interest in the neurocognitive aspects of genetic disorders. This study is unique in that it identifies a specific neurocognitive deficit in an autosomal recessive genetic disorder. In the current study, a dissociation within a cognitive domain (visual processing) was identified in children with cystinosis, whereas cognitive studies of other genetic disorders have predominantly identified differences between domains (e.g., linguistic vs visual cognition in Williams syndrome [91], right vs left hemisphere specialization in Turner syndrome [89]). Interestingly, a recent study of Williams syndrome (92) provided the "first evidence" of visual processing deficits specific to the dorsal stream as opposed to the ventral stream. Our study is similarly novel in terms of the degree of specificity in characterizing the cognitive deficit.

More importantly, however, the implications of this research extend beyond the group of individuals with cystinosis because carriers of the gene also have elevated cystine levels (4,9,20) and identified gene deletions (8,10). If a genetic alteration can cause a difference in cognitive

function, there may be implications for otherwise asymptomatic carriers of the gene. In fact, recent studies of cystinosis carriers have documented mild cognitive deficits (93) and event-related brain potential (ERP) abnormalities (94). Even more far-reaching implications relate to carriers of other recessive gene disorders, who may possess subtle cognitive differences secondary to the presence of an aberrant gene. The results of the current study thus serve as a strong impetus for more widespread studies of gene-behavior relationships.

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