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Visual and Verbal Learning in a Genetic Metabolic Disorder

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Abstract

Visual and verbal learning in a genetic metabolic disorder (cystinosis) were examined in the following three studies. The goal of Study I was to provide a normative database and establish the reliability and validity of a new test of visual learning and memory (Visual Learning and Memory Test; VLMT) that was modeled after a widely used test of verbal learning and memory (California Verbal Learning Test; CVLT). One hundred seventy-two neurologically intact individuals ages 5 years through 50 years were administered the VLMT and the CVLT. Normative data were collected and the results suggested that the VLMT is a reliable and valid new measure of visual learning and memory. The aim of Study II was to examine possible dissociations between verbal and visual learning and memory performances in individuals with cystinosis as well as to assess changes in performance as individuals with the disorder age. Thirty-seven individuals with cystinosis and 37 matched controls were administered a new test of visual learning and memory (Visual Learning and Memory Test; VLMT) and the California Verbal Learning Test (CVLT). Individuals with cystinosis performed at a lower level than controls on almost all indices of visual learning and memory while no differences were found between the groups on the verbal measure. Examination of the results on the VLMT indicated that the visual learning and memory impairment in cystinosis may result from difficulty with processing visual information quickly. Study III aimed to remediate the observed visual learning and memory deficit by implementing an intervention that increased the exposure time for visual stimuli. Fifteen individuals with cystinosis were administered a version of the VLMT in which the stimuli were exposed for 3-seconds rather than 1-second. Fifteen matched controls were administered the 1-second version of the VLMT. The results of Study III indicated that by increasing the exposure time for each visual stimulus, individuals with cystinosis were able to perform at the same level as control subjects. This is the first study to demonstrate impaired visual learning and spared verbal learning in individuals with cystinosis. These results may provide the foundation for designing cognitive interventions, may lead to further hypotheses regarding the underlying mechanism of the observed visual learning and memory deficit, and have implications for a greater understanding of gene-behavior relationships.

Keywords

cystinosis; learning; memory; CVLT; white matter; non-verbal learning disability; lysosomal storage disease; visuospatial

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Infantile nephropathic cystinosis is a rare autosomal recessive disease with an incidence of between 1 in 100,000 and 1 in 200,000 (Adamson et al., 1989). It is a disease of lysosomal cystine storage, in which the amino acid cystine accumulates within the lysosomes of all cells in the body. The initial manifestations of cystinosis are usually complications of the renal tubular Fanconi syndrome, namely dehydration, electrolyte imbalances, and failure to thrive (Gahl et al., 2001). As individuals with the disorder age, other organs, such as the thyroid, pancreas, and cornea, become affected by cystinosis as well. Without treatment, cystinosis leads to end-stage renal disease and death by approximately 10 years of age. While no cure has been found, renal transplantation and medications (cysteamine) have increased the life span of individuals with cystinosis into the fourth decade. Pre-existing injury is not reversed by medication and progressive accumulation of cystine (and concomitant deterioration of functions) still occurs, albeit at a slower rate. These advances in treatment allow for the study of the cumulative effects of this metabolic disorder, including changes in cognitive functioning as a direct or indirect result of cystine accumulation in the brain. In 1995, the Cystinosis Collaborative Research Group (McDowell et al., 1995) localized the genetic abnormality to the short arm of chromosome 17 between markers AFMb307zg5 and D17S796 using linkage analysis. The deletions in cystinosis involve the loss of the 5' end of the gene and eleven separate mutations in this gene were identified in this first study. The cystinosis gene (CTNS) was discovered in 1998 (Town et al., 1998). CTNS encodes a novel protein, called cystinosin, with features of a lysosomal protein. The complete topology and exact role of this protein have yet to be understood.

Data from neuroimaging, post-mortem, neurological, and cognitive studies have documented a wide variety of changes in the CNS of individuals with cystinosis. The pattern of findings is extremely heterogeneous and, as yet, the mechanism of CNS involvement in cystinosis is unknown. The literature suggests that cystinosis, either directly or indirectly, leads to brain pathology. Structural neuroimaging of the brain has shown cerebral atrophy (Broyer & Tete, 1999; Cochat et al., 1986; Ehrich et al., 1979; Fink et al., 1989; Gahl & Kaiser-Kupfer, 1987; Jonas et al., 1987; Nichols et al., 1990b), white matter necrosis (in particular necrosis of the internal capsule) (Fink et al., 1989), areas of multifocal patchy demyelination (Vogel et al., 1990), and ventricular dilatation (Ehrich et al., 1979; Jonas et al., 1987; Ross et al., 1982). A recent volumetric MRI study demonstrated focal grey matter decreases in the posterior parietal cortex and in the primary somatosensory cortex in children with cystinosis (Sach et al., 2007).

Post-mortem pathological studies have reported the finding of cystine crystal deposition in the choroid plexus (Jonas et al., 1987; Levine & Paparo, 1982; Ross et al., 1982). Cystine levels have also been found to be increased in all parts of the brain studied (Jonas et al., 1987). Autopsy findings have documented the atrophy, ventricular dilatation, and white matter necrosis (Levine & Paparo, 1982; Vogel et al., 1990) that have been observed in neuroimaging studies (Jonas et al., 1987; Levine & Paparo, 1982).

Clinical neurological studies suggest that there are clinical correlates to the observed CNS changes. Neurological findings in cystinosis patients include small head circumference, impaired gross and fine motor skills, intention tremor, hypotonia, seizures and diffuse EEG slow wave abnormalities (Cochat et al., 1986; Ehrich et al., 1979; Fink et al., 1989; Ross et al., 1982; Trauner et al., 1988). Broyer and Tete (1999) found that patients did not develop gross neurological symptoms before age 18 years, but that by age 26 years approximately 50% of subjects had developed symptoms of CNS involvement including progressive encephalopathy, ataxia, and the pyramidal syndrome. However, Trauner et al. (1988) found gross and fine motor deficits in school-age children with cystinosis.

Neuropsychological research has shown that children and adults with cystinosis have normal overall intelligence (Fink et al., 1989; Trauner et al., 1988; Williams et al., 1994; Wolff et al., 1982; Wolff et al., 1989). Despite normal intelligence, these individuals may demonstrate specific visuospatial deficits with intact verbal abilities (Ballantyne & Trauner, 2000; Spilkin et al., 2007; Trauner et al., 1989). In a magnetic resonance imaging (MRI) study, Nichols et al. (1990b) examined intelligence in children and young adults with cystinosis who had either “high” or “low” amounts of cortical atrophy and found that both groups performed in the average range on the Stanford-Binet Intelligence Test. However, the high atrophy cystinosis group performed significantly more poorly than the low atrophy group in the area of short-term memory, with the visual short-term memory score lower than the composite of all the other remaining subtests, and the verbal memory score subtest higher than the composite of all other remaining subtests. Two recent studies of very young children with cystinosis (Spilkin et al., 2007; Trauner et al., 2007) found a similar pattern to that of older children and adults, with overall intellectual function in the normal range and a discrepancy such that non-verbal abilities were poorer relative to verbal abilities.

The non-verbal deficits observed on IQ testing have also been observed in comprehensive studies using specific neuropsychological measures. A study by Ballantyne and Trauner (2000) examined the consequences of cystinosis on visuospatial and visuo-perceptual abilities in children. Children with cystinosis and control children were administered a battery of spatial measures and perceptual measures. After covarying for demographic factors, results showed that individuals with cystinosis consistently performed poorly on spatial measures, while perceptual abilities appeared relatively intact. Similarly, a recent study examining visuospatial and visuo-perceptual performance in young children with cystinosis (3 through 8 years) found the same pattern of widespread visuospatial deficits with relatively spared visuo-perceptual abilities (Trauner et al., 2007). Moreover, deficits have been observed on tests of visual motor integration (Scarvie et al., 1996), visual closure (Nichols et al., 1990a), and tactile recognition (Colah & Trauner, 1997).

While deficits in visuospatial abilities and preserved verbal abilities have been demonstrated in previous studies, there has yet to be a study focusing on learning and memory in the visual and verbal domains. Study I aimed to provide a normative database and establish the reliability and validity of a new test of visual learning and memory. Study II aimed to determine whether there was a dissociation between visual and verbal learning abilities in children and adults with cystinosis. In particular, this study examined visual and verbal learning in children and adults with cystinosis, using comparable, comprehensive measures of the two different domains. To allow for the examination of differences in the developmental trajectories of visual and verbal skills in individuals with cystinosis, as well as the cumulative effects of the disorder as these individuals age, individuals of different ages were included in the study. Based on our findings in Study II of a visual learning and memory deficit in the cystinosis group, an intervention was implemented in Study III to determine if the deficit could be remediated. The implications of the current research are to better understand how individuals with cystinosis learn visual and verbal information, and to contribute to our understanding of gene-behavior relationships.

Study I: Normative Study of the Visual Learning and Memory Test (VLMT)

The purpose of Study I was to provide a normative database for the Visual Learning and Memory Test (VLMT) by gathering data on a large group of control subjects, as well as to establish the reliability and validity of the VLMT as a new measure of visual learning and memory.

Methods: Study I

Participants—The normative sample consisted of 172 neurologically intact individuals (83 males, 89 females). The mean age of the sample was 13.51 years (range 5.00 years to 50.33 years). To account for developmental changes in VLMT performance, care was taken to recruit at least 20 individuals per 2-year age group from 5 years through 16 years. Data from individuals age 17 years through 50 years were grouped into one adult sample. Participants of all ages were recruited as normal controls through newspaper and magazine advertisements, Child Expos, schools, and through pediatricians' offices. All individuals were screened with a comprehensive medical history questionnaire and were free of any medical, neurological, developmental and/or substance abuse problems.

Informed consent was obtained from the parents and/or participants prior to participation in the study, in accordance with Institutional Review Board procedures at the University of California, San Diego.

Measures

Visual Learning and Memory - Visual Learning and Memory Test: The VLMT is a test of visual learning and memory that makes minimal demands on language and motor skills. The test was designed in our laboratory and is modeled after a commonly used test of verbal memory (CVLT; Delis et al., 1987). Some of the stimuli used are from the Visual Spatial Learning Test (Malec et al., 1991). The subject is shown a series of 15 abstract stimulus designs, at a rate of one design per second. The subject is then given a 5×6 grid of designs (15 are the stimulus designs and 15 are foils) and must mark all of the stimulus designs that s/he can remember. This is done for five trials; the order of presentation for the 15 stimulus designs is always the same, but the designs are randomized on each marking grid. Upon completion of the 5 trials, the task is put away and the testing session continues with other tasks. After 20 minutes, a delayed recognition trial is administered in which the subject is given a 5×6 grid and asked to mark as many of the 15 stimulus designs s/he can recognize. For each participant, raw scores were computed for each learning trial and for the delayed recognition trial. These were then converted to d' ¹, which is the best measure of an individual's ability to discriminate between target items and foils on a recognition test.

The Mean d' score represents an individual's average performance across the five learning trials and is the best overall measure of learning performance on the VLMT. The individual d' scores were computed for each of the 5 learning trials and the 20-minute delay trial. The Trial 1 d' represents an individual's score after the first presentation of the stimuli and is suggestive of an individual's visual attention/short-term memory. The Trial 5 d' represents an individual's score after the fifth presentation of the stimuli and is suggestive of an individual's global learning performance. The Trial 6 d' reflects an individual's ability to retain visual information over time (i.e., visual memory).

California Verbal Learning Test – Children's Version (CVLT-C) and California Verbal Learning Test (CVLT): The California Verbal Learning Test (CVLT-C and CVLT) is a standardized measure of verbal learning and memory. Subjects between the ages of 5 years and 16 years, 11 months were administered the California Verbal Learning Test – Children's Version (CVLT-C) (Delis et al., 1994). This test evaluates an individual's ability to learn a list of 15 words in 3 categories (toys, fruits, and clothing) over 5 learning trials. The words were carefully chosen so as not to be the "prototypical" exemplar of each category (e.g., apple was

¹The range for d' is from 3.66 which would represent perfect discriminability (15 hits and 0 false positives) to -3.66 which would represent the opposite pattern (0 hits and 15 false positives). A d' of 0 represents no discriminability (equal number of hits and false positives). Positive d' scores indicate responding to more targets than foils, whereas negative d' scores indicate responding to more foils than targets.

not chosen for the Fruit category) to minimize the number of correct “guesses.” A second set of 15 words (a distractor list) is then presented for one trial, immediately followed by free and category cued recall of the first list. After a 20-minute delay, free and cued recall and recognition of the first list is tested. Total number of words learned on the 5 learning trials was calculated and used as a measure of overall verbal learning ability. Raw and standard scores of the learning trials and indices of 20-minute delayed recognition, and slope were computed by the CVLT computerized scoring program.

Subjects greater than or equal to 17 years of age were administered The California Verbal Learning Test (CVLT; Delis et al., 1987). This test follows the same format as the CVLT-C except it requires participants to learn a list of 16, rather than 15, nouns in four semantic categories (tools, fruits, spices, clothing). The distractor list is also comprised of 16 words. The same learning and memory indices were computed as with the CVLT-C.

Results: Study I

Figure 1 shows the normative data collected on the VLMT for the different age groups. Using repeated measures analysis of variance, significant effects on the VLMT were found for Trial (repeated measure; $F_{4.13, 652.41} = 199.47$, $p < .001$, $d = 2.15$) and Age_{1, 158} ($F = 32.79$, $p < .001$, $d = .87$), while Gender was not significant ($F = .573$, $p = \text{NS}$, $d = .12$). There was also a significant linear ($p < .001$) and quadratic ($p < .001$) Trial $\times$ Age effect. For ease of reporting, norms are presented for the following 7 age groups: 5–6 years, 7–8 years, 9–10 years, 11–12 years, 13–14 years, 15–16 years, and 17+ years. Table 1 presents d' for each Trial of the VLMT as well as the mean d' for the 5 learning trials as an overall index of visual learning. Data regarding the rate of learning, as represented by the least-squares regression slope, linear and quadratic beta coefficients, and intercepts are presented in Table 2.

Reliability

Internal Consistency: For this study, internal consistency reliability across trials (1–6) was assessed. d' for each of the trials was used instead of the target items individually. The overall intra-item correlations (ICC) for the VLMT was 0.93 (95% C.I. 0.92 – 0.95), which is considered excellent reliability (Bedard et al., 2000; Haugland & Wold, 2001). The single item ICC for the VLMT was 0.70 (95% C.I. 0.65 – 0.76), which is considered adequate to good. Reliability of the CVLT was also computed to compare ICCs between the two measures. The results were comparable to the VLMT with the overall ICC for the CVLT being 0.93 (95% C.I. 0.91 – 0.94) and the single item ICC for the CVLT being 0.68 (95% C.I. 0.63 – 0.74).

Inter-rater Reliability: The VLMT is scored objectively by counting up targets and foils marked on the response sheet by the subject. All tests were scored by one rater and completely checked by an independent rater until 100% inter-rater reliability was obtained.

Validity

Criterion Validity: In order to assess the criterion validity of the VLMT, all individuals in the standardization sample were also administered the CVLT or CVLT-C (depending on age), within one year of the administration of the VLMT. The two tests are similar in their structure including 5 learning trials and a 20-minute delay trial, although the test stimuli are from different domains (verbal and non-verbal). There is evidence to suggest that verbal and visual learning and memory are correlated in normal individuals (Delis et al., 1987; Tulsky et al., 1997)

Raw scores for the 5 learning trials and the 1 delayed recall trial were significantly correlated between the two measures. See Table 3 for correlations and significance values.

Construct Validity: In order to assess construct validity, evidence must be gathered from a wide number of studies that show that a particular measure relates to similar measures (convergent validity) and that it is able to discriminate among certain populations (divergent validity). The results of Study II lend evidence towards the construct validity of the VLMT due to its ability to discriminate among individuals with cystinosis and normally developing individuals (See Study II for results and discussion).

Discussion: Study I

The results of the normative study suggest that the VLMT is a reliable and valid new measure of visual learning and memory. The overall ICC for the VLMT suggests that the VLMT is a reliable measure of learning and memory overall and the reliability of individual trials was found to be adequate. The results also suggest that the VLMT is highly correlated with performance on the CVLT.

The VLMT allows for the scoring of a number of variables, including Mean d' Trials 1–5, d' Trial 1, d' Trial 5, d' Trial 6, and Least-Squares Regression Slope, and Linear and Quadratic beta coefficients. Each of these measures yields useful information about an individual's visual learning and memory. The results of this study suggest that age is a significant predictor of score and that as age increases, an individual tends to perform better on the VLMT. This is an important psychometric property and makes the test useful to assess individuals of different ages as well as age-related changes in visual learning. The large number of subjects tested for this study allows for the creation of a normative database to which other individuals' scores can be compared. There were no differences in performance on the VLMT based on gender. Thus mean scores for each age group are presented without reference to gender.

The VLMT was modeled after the format of the CVLT, which is one of the most widely used tests of verbal learning and memory. The current study found scores on the two tests to be highly correlated in normally developing children and adults, indicating its construct validity as a measure of learning and memory. The validity of the VLMT as a test of *visual* learning and memory in particular was less extensively examined in the present study, although it is clearly a more face-valid measure of visual learning and memory than the CVLT. Discriminant validity of the VLMT as a measure of visual learning and memory, as compared to the CVLT as a measure of verbal learning and memory, was assessed in Study II. Differences between VLMT and CVLT performances were observed in individuals with cystinosis and normally developing individuals, suggesting that the VLMT is assessing a different construct than the CVLT (i.e., visual versus verbal learning and memory).

A significant difference between the CVLT and the VLMT is that the VLMT uses a recognition response format whereas the CVLT uses a free recall response format. In order for the VLMT to tap visual learning and memory, without a motor component, it was important for the test to have a recognition format rather than requiring the individual to draw a response. A free recall format makes it more difficult to correctly "guess" an answer since individuals are required to generate responses on their own. By using the recognition format individuals have the opportunity to "guess" by marking stimuli even if they are not sure of the correct answer. To attempt to compensate for "guessing," responses for the VLMT were transformed from raw scores to d' . Although not without flaws, d' is the most widely used and well-accepted measure of recognition discriminability (Swets, 1996).

The VLMT is a unique test of visual learning and memory for a number of reasons. First, the stimuli are novel geometric figures that are not easily assigned a verbal label, and thus the test is likely to elicit a non-verbal learning strategy. Second, the design of the test allows multiple facets of learning and memory to be examined, including short-term memory/attention, rate of learning, and retention of non-verbal information over a delay. Third, the VLMT allows for a

thorough assessment of visual learning and memory without a motor component, which would confound visual memory ability with fine motor, gross motor, and/or psychomotor integration skills. Lastly the VLMT can be administered to a wide age range (5 years to 50 years). The results suggest that the ability to remember a greater number of stimuli increases with age and that the youngest group does not show a floor effect and the oldest group does not show a ceiling effect.

Study II: Visual and Verbal Learning and Memory

The aim of Study II was to examine possible dissociations between verbal and visual learning and memory performances in individuals with cystinosis as well as to assess changes in performance as individuals with the disorder age.

Methods: Study II

Participants—Participants were 37 individuals with cystinosis and 37 normal comparison (NC) participants. The mean age of the cystinosis group was 14.19 ± 8.19 years (range 5.92 – 31.58 years). Cystinosis participants were diagnosed by a nephrologist or metabolic disorder specialist based on clinical history and laboratory confirmation (i.e., elevated leukocyte cystine levels) of infantile nephropathic cystinosis. Individuals with cystinosis were *excluded from the study* if they had uncorrected vision problems, untreated thyroid dysfunction, and/or if they were in renal failure, as these are complications of the disorder that may affect cognitive test performance. Therefore the exclusionary criteria were instituted to avoid confounds in the interpretation of our cognitive data.

Normal comparison (NC) participants were recruited from the community and individually matched to subjects with cystinosis on age (± 1 year for children < 17 years and ± 5 years for adults ≥ 17 years), gender, and socioeconomic status (± 1) using the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975). The mean age of the NC group was 14.11 ± 7.67 years (range 6.58 – 34.75). Individuals in the NC group had normal developmental, educational, and medical histories and were free from significant use of drugs and/or alcohol as assessed by a detailed questionnaire.

Informed consent was obtained from the parents and/or participants prior to participation in the study, in accordance with Institutional Review Board procedures at the University of California, San Diego.

Measures

Intelligence - The Stanford-Binet Intelligence Scale, Fourth Edition: The Stanford-Binet Intelligence Scale, Fourth Edition (SB) (Thorndike et al., 1986) is a measure of general intellectual function. Composite IQ scores are determined for each subject using scores in 4 areas: Verbal Reasoning, Abstract/Visual Reasoning, Quantitative Reasoning, and Short-Term Memory. Standard Age Scores with a mean of 50 are calculated from the norms in the manual for individual tests. Area Standard Age Scores for each of the four broad cognitive areas and the Composite IQ's, based on the sum of Area Standard Age Scores, have a mean of 100 and a standard deviation of 16 points.

Visual Short-term Memory - Bead Memory Subtest of the Stanford-Binet, Fourth Edition: The Bead Memory subtest of the Stanford-Binet, Fourth Edition (Thorndike et al., 1986) is a test of visual short-term memory. This test was included as a standardized measure of visuospatial memory. Subjects are shown a picture of beads placed in a specific order and orientation on a stick. The beads differ in color (i.e., red, blue, and white) and shape (i.e., round, elongated, flat, or pyramid-shaped). The subject is shown the picture for 5 seconds; after 5

seconds the picture is removed and the subject must recreate the design from memory. Raw scores (number of items completed correctly) are converted into standard age scores.

Verbal Short-term Memory - Memory for Sentences Subtest of the Stanford Binet, Fourth Edition: The Memory for Sentences subtest of the Stanford-Binet, Fourth Edition (Thorndike et al., 1986) is a test of verbal short-term memory. This test was included as a standardized measure of immediate verbal attention and short-term memory. Subjects must repeat sentences of increasing length. Raw scores (number of items completed correctly) are converted into standard age scores.

Verbal Learning and Memory - California Verbal Learning Test – Children’s Version (CVLT-C) and California Verbal Learning Test (CVLT): For details on the administration and scoring of the CVLT-C and CVLT, please refer to the description of the test under the Measures section of Study I.

Visual Learning and Memory - Visual Learning and Memory Test: For details on the administration and scoring of the VLMT, please refer to the description of the test under the Measures section of Study I. Standardized scoring (T scores) for both the cystinosis and control participants were derived from the normative study, and included the indices of Mean d' Trials 1–5, d' Trial 1, d' Trial 5, d' Trial 6.

Visual Perception - Visual Form Discrimination: Visual Form Discrimination (Benton, 1974) examines complex visuoperceptual ability. This test was administered to examine subjects’ ability to perceive and discriminate among complex visual stimuli and was thought to be important in the interpretation of results on our test of visual memory. Subjects were administered the test in standardized fashion, by requiring subjects to look at a 16 2-dimensional forms. Each form consists of 3 objects (2 major objects and 1 peripheral object). Simultaneously, the subject is shown a card displaying 4 choices (1 correct and 3 foils) from which to choose the same form. The foils differ from the target form in either rotation or distortion of the major or peripheral figures. The total possible score is 32 with subjects receiving 2 points for each correct item, 1 point for each item involving an error of a peripheral figure, and 0 points for an item with an error involving a major figure (Benton et al., 1983).

Results: Study II

Intelligence and Visual Perception—Individuals with cystinosis scored significantly lower, although still within the average range, on Composite IQ than age-, gender, and SES-matched normal comparison (NC) subjects using one-way Analysis of Variance (ANOVA) ($F_{1, 72} = 27.13$, $p < .001$, $d = 1.21$). The cystinosis group scored significantly lower than the NC group on each of the four Area Scores that compose the Composite IQ score. In contrast, the cystinosis group did not score significantly lower than the NC group on Visual Form Discrimination, a test of simple visual perceptual abilities. See Table 4 for means, standard deviations, F values, significance values, and effect sizes (d).

Visual/Verbal Asymmetry—An asymmetry score was computed in order to examine asymmetric performances, without regard to level of performance (e.g., visual > verbal learning or vice versa) within the individual (Demadura et al., 2001). The most comprehensive index of overall learning on the VLMT is the mean d' for Trials 1–5 whereas for the CVLT overall learning is best described in the Total Number of Words Recalled in Trials 1–5 index. These scores were first translated into T-scores (mean = 50, SD = 10). The T-score for Total Trials 1–5 on the CVLT was subtracted from the T-score for Mean d' Trials 1–5 in the VLMT. Individuals who performed at the same level on both tests would receive an asymmetry score of approximately 0, which would represent symmetric performance between the domains.

Individuals who performed better on the CVLT than the VLMT would receive negative asymmetry scores and individuals with better performance on the VLMT than the CVLT would receive positive asymmetry scores. An asymmetry score was also computed using the Bead Memory and Memory for Sentences Area Scores from the Stanford-Binet using the formula described above.

The cystinosis group showed a significant asymmetry in the hypothesized direction in their overall pattern of VLMT/CVLT performance using univariate ANOVA ($F_{1,72} = 9.18$, $p = .003$, $d = .70$) as well as their pattern of performance on the Stanford-Binet Bead Memory/Memory for Sentences comparisons ($F_{1,72} = 8.96$, $p = .004$, $d = .69$). See Figure 2.

Visual Learning and Memory—Short-term visual memory was assessed using the SB Bead Memory subtest. Using ANOVA, the cystinosis group performed significantly lower than the NC group on the SB Bead Memory subtest ($F_{1,72} = 17.86$, $p < .001$, $d = .98$).

The d' and rate of acquisition during the 5 VLMT learning trials were analyzed using a repeated-measures analysis of variance (ANOVA) with Trial (1–5) as the within-subject variable and Group (cystinosis versus NC) as the between subjects variable. The results revealed a significant main effect of Group ($F_{1,72} = 25.68$, $p < .001$, $d = 1.03$), with the cystinosis group receiving lower scores on the VLMT than the NC group. There was also a significant main effect of Trial (repeated measure) ($F_{3,46,249.25} = 40.89$, $p < .001$, $d = 1.49$). The Trial $\times$ Group interaction was not significant ($F_{3,46,249.25} = 1.35$, $d = .27$), suggesting a similar rate of learning between the groups over the learning trials. See Figure 3 for learning curves. Retention of information over a 20-minute delay on the VLMT was examined using repeated-measures ANOVA. Recall (Trial 5 versus 20-minute delay) was the within subject variable and Group (cystinosis versus NC) was the between subject variable. There was a main effect of Group ($F_{1,71} = 21.32$, $p < .001$, $d = 1.05$) with the cystinosis group performing significantly lower than the NC group. The main effect of Trial ($F_{1,71} = .85$, $d = .22$) and the Trial $\times$ Group ($F_{1,71} = 2.14$, $d = .34$) interaction were not significant. See Figure 3.

Verbal Learning and Memory—SB Memory for Sentences subtest was used to assess verbal short-term memory. There was no difference between the groups on performance on SB Memory for Sentences ($F_{1,72} = 1.04$, $d = .24$).

Examination of the raw scores and acquisition rate for the CVLT using repeated measures ANOVA found a main effect for Trial ($F_{3,22,231.74} = 116.49$, $p < .001$, $d = 2.51$). The main effect of Group Trial ($F_{1,72} = 2.18$, $d = .34$) and the Trial $\times$ Group interaction Trial ($F_{3,22,231.74} = 2.06$, $d = .33$) were not significant. See Figure 4 for learning curves. Retention of verbal information over a 20-minute delay was analyzed using a repeated measures ANOVA with Trial (Trial 5 versus 20-minute free recall) as the within subject variable and Group as the between subject variable. The main effect of Trial was significant ($F_{1,72} = 29.81$, $p < .001$, $d = 1.27$) suggesting that both groups recalled fewer words after the 20 minute delay than they recalled after the five learning trials. The main effect of Group ($F_{1,72} = .65$, $d = .19$) and the Trial $\times$ Group interaction ($F_{1,72} = 1.41$, $d = .28$) was not significant suggesting a similar rate of forgetting between groups. See Figure 4.

Comparison of Performance of Children and Adults on Visual and Verbal Learning—Using repeated measures ANOVA, differences between performances of children and adults with cystinosis on the VLMT and CVLT were analyzed. The mean d' for Trials 1–5 of the VLMT and the mean number of words recalled on Trials 1–5 of the CVLT were transformed into T-scores, which were used as the dependent variable. The within subjects variable was Domain (Visual = VLMT and Verbal = CVLT) and the between subjects variable was Age (Child = Ages 5 years through 16 years and Adult = 17 years and above). There was

a main effect of Domain ($F = 10.96_{1, 35}$, $p = .002$, $d = 1.09$) such that individuals with cystinosis, regardless of age, performed better on the CVLT than the VLMT. There was also a main effect of group ($F = 28.05_{1, 35}$, $p < .001$, $d = 1.74$) such that adults performed worse than children on both the VLMT and the CVLT. The Age $\times$ Domain interaction was not significant ($F = .04_{1, 35}$, $d = .07$) suggesting that both domains were affected at an equal rate over time. See Figure 5.

Discussion: Study II

The results of Study II indicate that individuals with cystinosis do have a significant and circumscribed deficit on a test of visual learning and memory with sparing of verbal learning and memory. Their performance on the CVLT is statistically indistinguishable from a normal comparison group, in spite of differences in overall intellectual ability (albeit IQ scores for the cystinosis group were still in the average range). On visual learning and memory indices however, individuals with cystinosis consistently perform at a lower level than normal comparison subjects on almost every index of visual learning and memory assessed in the current study.

The use of asymmetry scores allows for the examination of discrepant performances between the visual and verbal domain without reference to level of performance. Overall, individuals with cystinosis showed a greater asymmetry between their scores on the VLMT and the CVLT, suggesting a more lateralized cognitive profile. Moreover, the asymmetry was in the hypothesized direction; e.g., verbal performance greater than visual performance. The mean T-score difference between verbal and visual learning performance in individuals with cystinosis was approximately 10 points, which is equivalent to one standard deviation difference in their performances. The difference on the Stanford-Binet Memory subtests was slightly less (approximately 5 T-score points). The greater asymmetry seen on the VLMT/CVLT comparison as compared to the Bead Memory/Memory for Sentences comparison may be accounted for by the more comprehensive and cognitively challenging nature of the former tests, which is likely to accentuate discrepant performances.

Although often utilized for clinical and research purposes, the reliability of difference scores has been questioned in the literature (Levy, 1966; Williams et al., 1996). Concern arises due to the possible limited variability of change in scores between the two tests, which makes the examination of the change scores unreliable using traditional statistical analyses that rely on variance. Examination of the asymmetry scores used in the current study revealed a large amount of variance which reduces the concern regarding reliability. However, the current study utilized difference scores to illustrate the degree and direction of the asymmetry between visual and verbal learning in cystinosis *within individual subjects*, while traditional and more reliable repeated measures ANOVA were used in order to examine the data more closely.

Examination of the VLMT learning curves revealed useful information regarding the nature of the visual learning and/or memory deficit in cystinosis. Overall, the cystinosis group consistently performed at a lower level than the NC group on the learning trials of the VLMT, although the groups had a similar *rate* of learning over the trials. This pattern would not be considered a typical “learning” deficit (i.e., difficulty in the acquisition of information over repeated trials). Furthermore, the cystinosis group lost approximately the same amount of information as did the NC group over the 20-minute delay, which does not suggest a “memory” deficit. However, Figure 3 clearly shows that the cystinosis group is performing at a lower level than the NC group on the VLMT. There are a number of possible explanations for this pattern of results. The results may suggest that individuals with cystinosis may have difficulty processing visual information quickly (VLMT stimuli are presented at a rate of 1 per second) and are unable to pick up the same number of “bits” of information as NC subjects during the rapidly presented learning trials. However, they learn at the same rate as NC subjects and are

able to retain the information over a delay, which is represented as a similar, but lowered curve, as compared to the NC group. Alternatively, reduced learning on the initial learning trial (Trial 1), may mediate impaired visual learning and memory performance on this task.

In contrast to the ability to learn and remember visual information, Figure 4 indicates that individuals with cystinosis do not have difficulty with verbal learning and memory, as their curve overlaps with that of the NC group. This is quite different from the significantly lowered learning curve for the cystinosis group on the VLMT and suggests that the learning and memory deficit is specific to the visual domain.

An interesting difference in performance between the VLMT and the CVLT was observed in the current study. Both groups retained most of the information they acquired over the five learning trials after a 20-minute delay on the VLMT, whereas both groups forgot a significant portion of the information they had originally encoded over the delay on the CVLT. There are differences between the two tests that may account for the different pattern of performance. First, the CVLT uses a free recall format whereas the VLMT uses a recognition format. The demands of freely generating words for the CVLT after the delay may be more difficult than recognizing the stimuli on the VLMT which makes it likely that individuals will recall fewer words after the delay. Also, there is an interference trial in the CVLT, whereas there is no interference in the VLMT, which may also cause a decline in CVLT performance over the delay.

In our cross-sectional sample of children and adults with cystinosis, both groups performed more poorly on the VLMT than on the CVLT. Regardless of age group, the pattern of poorer performance on visual rather than verbal tests remained constant. However, the results also indicate that as individuals with cystinosis age, their scores on both the VLMT and CVLT decline. Although recent studies on very young children with cystinosis have yielded evidence of an adverse effect on brain development, (Sach et al., 2007; Spilkin et al., 2007; Trauner et al., 2007), the present study demonstrates an overall decline in performance as individuals with the disease age, which suggests a progressive dysfunction over the lifespan that may be superimposed on a static developmental difference.

Although the data indicate a decline in performance over the lifespan in cystinosis, the actual trajectory of decline within subjects cannot be adequately assessed with the cross-sectional design of this study. There are significant differences between individuals in the child and adult group that may account for the pattern of scores observed. The adults with cystinosis in the current study most likely began treatment with cystine depleting drugs later in life than the children, due to the recent innovations in treatment. At this time, differences in outcome between individuals treated earlier versus later in life are unknown. It may be expected that individuals who receive treatment later in life may experience more physical and cognitive difficulty due to increased effects of the disease before treatment was started. However, it is also possible that treatment with a cystine-depleting drug at any time can ultimately reduce or reverse the detrimental effects of the disease. In the current study, inferences made about the cumulative effects of cystinosis are confounded with different times of beginning treatment. It will be important to follow children who were treated early in life as they age to examine the effects of cystinosis over time more extensively.

Hypothesized Brain Involvement in Visual Learning and Memory Deficit—The etiology of the deficit in visual learning in cystinosis is not known. Interestingly, individuals with many genetic disorders show a similar pattern of results on neuropsychological testing, namely intact verbal skills and impaired visuospatial skills. These individuals show impaired performance not only on tests of visual processing skills, but also on tests of arithmetic abilities, tactile perception, and social skills. This constellation of symptoms is consistent with the

syndrome of non-verbal learning disability (NVLD) (Rourke, 1995). As more data on the behavioral phenotype associated with cystinosis is collected, it appears that the disorder fits many of the common neuropsychological features associated with NVLD. Individuals with cystinosis have been shown to have deficits in visuospatial abilities (Ballantyne & Trauner, 2000), tactile perception (Colah & Trauner, 1997), arithmetic (Ballantyne et al., 1997), and social skills (Delgado et al., 2005), while auditory perception and reading skills (Ballantyne et al., 1997) seem less affected by the disease. The current study demonstrates a pattern of deficit in visual learning and memory with a relative sparing of verbal learning and memory, which fits the NVLD profile.

While the current study did not assess the anatomical correlates of the behavioral data, the results of the study lead to hypotheses regarding the mechanisms underlying the observed visual learning and memory deficit that may be tested in future studies. Rourke hypothesized a white matter deficit underlying NVLD (Rourke, 1995). Previous research has shown white matter involvement in individuals with cystinosis (Bava, 2007; Fink et al., 1989; Levine & Paparo, 1982; Vogel et al., 1990). It is reasonable to hypothesize that cystine crystal deposition in the white matter disrupts connections between different subcortical and cortical structures, resulting in the observed visual learning impairment. Although we do not know the extent that these results are disease-specific, or the result of general CNS insult, they nonetheless represent the behavioral phenotype associated with cystinosis. Future genetic studies may reveal the extent to which these findings are disease-specific.

Study III: Intervention Study: Use of the Visual Learning and Memory Test-3 Second Exposure Time (VLMT-3")

The current study aimed to remediate the observed visual learning deficit observed in cystinosis with an intervention that increased exposure time to visual information.

Methods: Study III

Participants—Subjects were 15 individuals with cystinosis and 15 normal comparison (NC) participants. Since cystinosis is a rare disorder, 8 individuals included in the cystinosis intervention group had received the VLMT previously. Five individuals with cystinosis received the VLMT two years before and 3 individuals with cystinosis received the VLMT the previous year. The mean age of the cystinosis group was 18.94 ± 10.89 years (range 9.00 – 39.00 years). Cystinosis subjects were diagnosed by a nephrologist or metabolic disorder specialist based on typical history and laboratory confirmation (i.e., elevated leukocyte cystine levels) of infantile nephropathic cystinosis. Exclusionary criteria were vision problems, thyroid dysfunction, and significant renal dysfunction or kidney failure (see Study II for exclusionary criteria rationale).

NC participants were matched to the cystinosis participants on the basis of age (± 1 year for children < 17 years and ± 10 years for adults ≥ 17 years), gender, and socioeconomic status (± 1 point) (Hollingshead, 1975). The mean age of the NC group was 19.68 ± 12.35 years (range 9.33 – 49.00). Individuals in the NC group had normal developmental, educational, and medical histories and were free from significant use of drugs and/or alcohol as assessed by a detailed questionnaire.

Informed consent was obtained from the parents and/or participants prior to participation in the study, in accordance with Institutional Review Board procedures at the University of California, San Diego.

Measures

Visual Learning and Memory - Visual Learning and Memory Test – 3 Second Exposure Time (VLMT-3")—The VLMT-3" is identical to the VLMT (see details of test under Measures section of Study I), except that the stimuli are shown to the participant with an exposure time to each stimulus of 3 seconds, rather than one second. This version of the VLMT was only administered to individuals with cystinosis, and comparisons were made to the standard, one-second version of the VLMT that had been administered to NC in the normative study.

Verbal Learning and Memory - California Verbal Learning Test – Children's Version (CVLT-C) and California Verbal Learning Test (CVLT). For details on the administration and scoring of the CVLT-C and CVLT, please refer to the description of the test under the Measures section of Study I.

Results: Study III

Visual Learning and Memory Intervention—Repeated measures analysis of variance found neither a significant main effect of Group ($F_{1,28} = .02$, $d = .05$) nor a Trial $\times$ Group interaction ($F_{2,79, 78.05} = .744$, $d = .32$) on visual learning performance when the NC group was administered the 1-second version of the test and the cystinosis group was administered the 3-second version of the VLMT. The main effect of Group and the Trial $\times$ Group interaction were not significant, suggesting that both groups performed at the same level over all the trials. The main effect of Trial (repeated measure) was significant ($F_{2,79, 78.05} = 38.59$, $p < .001$, $d = 2.27$), suggesting scores for both groups increased over the five learning trials. See Figure 6 for learning curves. Visual memory was assessed with repeated measures ANOVA with Trial as the within subjects variable (Trial 5 versus 20-minute delay) and Group as the between subjects variable. There were no significant main effects or interactions (Trial: $F_{1, 28} = 1.44$, $d = .44$; Group: $F_{1, 28} = .51$, $d = .26$; Trial $\times$ Group: $F = .25$, $d = .18$). See Figure 6.

A subanalysis was performed comparing the performance of the 8 participants who were previously tested on the VLMT versus the 7 participants who were not previously tested on the VLMT. There was no difference in mean performance on the VLMT between these two cystinosis subgroups, indicating no influence of any long-lasting priming effects on these results ($F_{1,13} = 1.403$, $p = \text{NS}$).

Verbal Learning and Memory—Using repeated measures ANOVA with Trial as the within subject variable and group as the between subjects variable, the main effect for Group and the Trial $\times$ Group interaction were not significant indicating similar learning performance between the groups (Group: $F_{1,28} = 2.7$, $d = .59$; Group $\times$ Trial: $F_{2,5, 69.9} = .03$, $d = .06$). The results found a significant main effect for Trial ($F_{2,5, 69.9} = 64.71$, $p < .001$, $d = 2.93$). Retention over the 20-minute delay was analyzed using repeated measures ANOVA with Trial (Trial 5 versus 20-minute Delay) as the within subject variable and Group as the between subjects variable. While the effect of Trial was found to be significant ($F_{1,28} = 5.99$, $p = .021$, $d = .89$), the main effect of Group and the Trial $\times$ Group interaction was not significant (Group: $F_{1,28} = 2.08$, $d = .53$; Trial $\times$ Group: $F_{1,28} = .67$, $d = .30$).

Discussion: Study III

The results of Study III indicate that by increasing the exposure time for each visual stimulus from 1 second to 3 seconds, individuals with cystinosis were able to perform at the same level as NC subjects on a visual learning and memory test. This increase in performance represents a significant improvement from their performance in Study II, in which the VLMT was administered in the original format with a 1-second exposure time.

By simply increasing the exposure time, there is a decrease in the demand for speeded processing of the visual information presented in the task. All other aspects of the test, including the requirements of visual perception of the stimuli, learning and remembering the stimuli, and scanning the response form, remain the same. These results suggest that the impaired performance seen in Study II is likely due to a short exposure time and that by increasing the time allowed to process visual information, individuals with cystinosis can dramatically improve their performance. These data may provide the foundation for designing cognitive interventions focused on providing individuals with cystinosis more time to process the visual information. For example, these individuals would likely benefit from more time for taking tests in school.

Importantly, the VLMT was designed as a test of visual learning and memory that minimized many of the confounds of traditional visual learning and memory tests, such as memory for spatial location as well as motor demands. Since individuals with cystinosis have documented deficits in tactile recognition, mental rotation, and topographical orientation (Ballantyne & Trauner, 2000), as well as fine motor abnormalities (Colah & Trauner, 1997; Trauner et al., 1993), the VLMT was designed specifically to eliminate confounds in areas likely affected by the disease. While the results of the current study suggest that individuals with cystinosis may perform within the average range when allowed more time to process the information on the VLMT, it is possible that given a more complex visual learning and memory task, in particular a task that involves other cognitive and motor processes that are documented to be affected in cystinosis, individuals with cystinosis may perform more poorly than NC subjects even if allowed extra exposure time. However, such individuals may be able to use their relative verbal strengths to compensate in these situations using verbal mediation for spatial tasks.

One of the difficulties in studying rare populations is that it is not always possible to have participants who have not been involved in previous research and been exposed to the stimuli. Eight of the 15 individuals with cystinosis included in Study III were participants in Study II and had previously been administered both the VLMT and CVLT. However, it should be noted that there was at least a one-year time span between the testings and we found no statistical difference in performance between those participants who were previously tested on the VLMT and those who were not previously tested on the VLMT. While preferable to have “naïve” participants in research, when studying rare conditions such optimal research designs are not always possible.

Overall Discussion

The current study has implications for a better understanding of the behavioral phenotype associated with cystinosis. The results indicate a dissociation between visual and verbal learning and memory such that visual learning and memory is significantly more affected than verbal learning and memory.

These results, taken collectively with the results from prior studies, indicate that individuals with cystinosis have deficits in visual learning and memory, visuospatial abilities (Ballantyne & Trauner, 2000), tactile perception (Colah & Trauner, 1997), arithmetic (Ballantyne et al., 1997), and social skills (Delgado et al., 2005), while verbal learning and memory, auditory perception and reading skills (Ballantyne et al., 1997) seem less affected by the disease. This pattern of cognitive and social deficits observed in cystinosis fall into the constellation of symptoms known as non-verbal learning disability (NVLD) (Rourke, 1995). Rourke hypothesized white matter involvement in many of the neurodevelopmental disorders that result in NVLD, such as Williams syndrome and multiple sclerosis (Rourke, 1995). Individuals with cystinosis have been found to have white matter abnormalities (Fink et al., 1989; Levine

et al., 1987; Vogel et al., 1990) as well, suggesting that cystinosis may be another genetic disorder that results in the NVLD syndrome.

Insights into normal neurocognitive functioning can be gained through the study of pathological conditions. Recent advances in molecular biology and recombinant DNA technology have allowed for the detection of genetic defects that cause certain developmental disorders, such as fragile X syndrome, Williams syndrome, and recently cystinosis. All of these developmental disorders arise from a mutation in a gene that codes for the development of a protein that is necessary for the normal development and functioning of the central nervous system (Brodsky & Lombroso, 1998). Since the genetic defect in cystinosis has recently been elucidated, cystinosis is a disorder that can be used to gain a deeper understanding of gene-behavior relationships. One important step in this process is to describe the behavioral phenotype associated with cystinosis.

Importantly, the results of the intervention study (Study III) have implications for the remediation of the visual learning and memory deficit in cystinosis and possibly other lysosomal storage diseases with similar neuropsychological profiles. The results suggest that given increased exposure time to visual information, individuals with cystinosis can perform in the normal range on tests of visual learning and memory. Passing on this information to parents, teachers, and others that interact with the individual will be important for designing appropriate interventions and expectations.

This research also has implications for a greater understanding of the neuropathological mechanism resulting in the observed deficit. One possibility is that cystine crystal deposition in the white matter may result in the impaired visual learning observed in cystinosis. Since the crystals are present from early in life, while the brain is developing, perhaps the young brain reorganizes in such a way as to spare the verbal domain at the expense of the visual domain (Lidzba et al., 2006a, 2006b; Stiles, 1995; Stiles et al., 2005). As the disease progresses and the extent of the white matter dysfunction increases and the brain becomes less able to compensate, other aspects of cognition, in particular verbal learning, may also become affected.

Limitations and Future Directions

The current study yields important information about the cognitive deficits in cystinosis, which can be examined further in future studies. The results of the current study suggest that processing visual information given a short exposure time may be the core deficit in VLMT performance in cystinosis. One potential hypothesis is that, perhaps, individuals with cystinosis have an impairment in visual processing speed. However, the VLMT was intended as a test of visual learning and memory, not of processing speed. It would be important to formally test processing speed ability in individuals with cystinosis in both the visual and auditory domains to further clarify the underlying mechanisms of the deficits seen in this study.

In the current study, although the sample size is small, the results regarding the cystinosis group performing more poorly on the VLMT and the improved performance given longer exposure time are fairly robust. However, the examination of VLMT and CVLT performance over time relies heavily on a small number of individuals in the older age range. Also there are differences between the children and adults in this study (e.g., individuals in the adult group may have started treatment later in life than the children). Although the results of the current study suggest a decrease in both domains in older subjects, it would be important to replicate this finding with a greater number of adults with cystinosis in a longitudinal design to ensure the reliability of this result. Due to recent medical advances, only now are individuals surviving into middle adulthood, which, for the time being, makes for a very small sample size. As more patients reach this age, we can conduct more in depth studies on the cumulative effects of cystinosis over time.

Neuroimaging studies will also be important to test the hypothesis that white matter dysfunction may be the underlying cause of the visual learning and memory deficit in cystinosis. Using diffuse tensor imaging techniques, correlations between extent of white matter lesions and performance on the tests of visual and verbal learning and processing speed can be computed.

Another goal for future research is to expand the neuropsychological domains of study to include other measures that have been found to be deficient in NVLD such as concept formation, problem solving, hypothesis testing, and social competence. Finally, it will be important to correlate the behavioral profiles with the genetic deletions in individuals with cystinosis to examine subtypes of the disorder and any possible differences therein.

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VLMT PERFORMANCE IN THE NORMATIVE SAMPLE

Figure 1.
Normative sample performance on the VLMT by age group.

VISUAL/VERBAL ASYMMETRY

Figure 2.

Mean T-Score difference between visual and verbal learning and memory indices for the cystinosis and control groups. Comparisons are made between the VLMT and CVLT as well as for Bead Memory and Memory for Sentences subtests from the Stanford Binet Intelligence Scale, Fourth Edition.

VISUAL LEARNING AND MEMORY

VLMT Learning (Trials 1 – 5)

VLMT Memory (Trial 5 and 20-minute Delay)

Figure 3. Visual learning and memory performance on the VLMT in the cystinosis and control groups.

VERBAL LEARNING AND MEMORY

CVLT Learning (Trials 1 – 5)

CVLT Memory (Trial 5 and 20-minute Delay)

Figure 4. Verbal learning and memory performance on the CVLT in the cystinosis and control groups.

VISUAL VERSUS VERBAL LEARNING IN CHILDREN AND ADULTS WITH CYSTINOSIS

Figure 5.

Mean T-score for overall VLMT and CVLT performance in children (n = 26) and adults (n = 11) with cystinosis.

VISUAL LEARNING AND MEMORY INTERVENTION

VLMT Learning (Trials 1 – 5)

VLMT Memory (Trial 5 and 20-minute Delay)

Figure 6.

Visual learning and memory performance in the cystinosis group (VLMT-3") and control group (VLMT).

Table 1
Mean Discriminability (d') over Trials for the Normative Sample

Age (years)	N	d' Trial 1		d' Trial 2		d' Trial 3		d' Trial 4		d' Trial 5		d' Trial 6		Mean d' 1-5	
		M $\pm$ SE	SD	M $\pm$ SE	SD	M $\pm$ SE	SD	M $\pm$ SE	SD	M $\pm$ SE	SD	M $\pm$ SE	SD	M $\pm$ SE	SD
5-6	29	.79 $\pm$.11		.78 $\pm$.12		.99 $\pm$.14		.97 $\pm$.14		1.25 $\pm$.15		1.32 $\pm$.12		.96 $\pm$.11	
		.59		.67		.73		.75		.83		.66		.58	
7-8	22	.87 $\pm$.12		1.42 $\pm$.16		1.70 $\pm$.19		1.79 $\pm$.17		1.77 $\pm$.20		1.77 $\pm$.17		1.51 $\pm$.14	
		.55		.75		.88		.80		.94		.82		.64	
9-10	22	1.21 $\pm$.13		1.66 $\pm$.14		1.74 $\pm$.12		2.31 $\pm$.15		2.38 $\pm$.14		2.20 $\pm$.17		1.86 $\pm$.10	
		.62		.68		.58		.69		.64		.78		.47	
11-12	26	1.27 $\pm$.10		1.89 $\pm$.15		2.08 $\pm$.13		2.74 $\pm$.16		2.82 $\pm$.17		2.61 $\pm$.16		2.16 $\pm$.11	
		.50		.76		.69		.84		.88		.80		.58	
13-14	23	1.17 $\pm$.10		1.88 $\pm$.10		2.19 $\pm$.07		2.68 $\pm$.09		3.01 $\pm$.09		2.81 $\pm$.13		2.19 $\pm$.05	
		.48		.48		.32		.44		.44		.63		.25	
15-16	20	1.37 $\pm$.14		2.05 $\pm$.22		2.49 $\pm$.21		2.95 $\pm$.17		2.91 $\pm$.21		2.89 $\pm$.19		2.35 $\pm$.17	
		.64		1.00		.93		.75		.94		.86		.77	
17+	30	1.73 $\pm$.09		2.38 $\pm$.09		2.82 $\pm$.11		3.19 $\pm$.09		3.37 $\pm$.07		3.25 $\pm$.08		2.70 $\pm$.06	
		.47		.49		.59		.49		.38		.46		.33	

Note: The range for d' is from 3.66 which would represent perfect discriminability (15 hits and 0 false positives) to -3.66 which would represent the opposite pattern (0 hits and 15 false positives).

M = Mean, SE = Standard error, SD = Standard deviation

Table 2

Mean Least Squares Regression Slope, Linear and Quadratic Beta Coefficients, and Intercepts for the Normative Sample

Age Group (years)	Least Squares Regression Slope	Linear Beta Coefficient	Quadratic Beta Coefficient	Intercept
5–6	.11 ± .03	−.04 ± .14	.03 ± .02	.80 ± .18
7–8	.22 ± .07	.79 ± .06	−.01 ± .01	.19 ± .08
9–10	.30 ± .04	.42 ± .26	−.02 ± .04	.83 ± .34
11–12	.40 ± .05	.66 ± .28	−.04 ± .05	.67 ± .36
13–14	.44 ± .04	.70 ± .15	−.04 ± .03	.55 ± .20
15–16	.40 ± .07	1.01 ± .14	−.10 ± .02	.45 ± .19
17+	.41 ± .05	.84 ± .04	−.07 ± .01	.97 ± .05

Note: The least squares regression slope describes the rate of learning from Trial 1 to Trial 5 without reference to level of performance. Using Trial Number (i.e., 1, 2, 3, 4, 5) as the independent variable, the intercepts as well as linear and quadratic beta coefficients may be used to create a regression equation that will construct the approximate learning curves for the different age groups.

Table 3

VLMT and CVLT Correlations

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Delay
N = 172	.35 *	.47 *	.49 *	.70 *	.65 *	.56 *

* Note: p < .001

Stanford Binet – 4th Edition (SB) and Visual Form Discrimination: Means, standard deviations, F values, significance values, and effect sizes (d)

	Cystinosis (n = 37)	Controls (n = 37)	F	d	p
SB Composite IQ	100.32 ± 12.95	114.00 ± 9.35	27.14	1.21	< .001
SB Verbal Reasoning	102.28 ± 13.47	114.70 ± 9.74	20.49	1.07	< .001
SB Visual Reasoning	102.28 ± 13.43	115.19 ± 13.51	16.76	.96	< .001
SB Quantitative Reasoning	94.16 ± 18.03	112.70 ± 13.20	25.48	1.17	< .001
SB Short-term Memory	96.57 ± 13.84	108.08 ± 13.65	12.97	.84	.001
Visual Form Discrimination	27.00 ± 4.65	28.86 ± 4.17	3.29	.42	NS