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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 s rather than 1 s. Fifteen matched controls were administered the 1-s 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.

Infantile nephropathic cystinosis is a rare autosomal recessive disease with an incidence of between 1 in 100,000 and 1 in 200,000 (Adamson, Anderson, & Gahl, 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, Thoene, & Schneider, 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 lifespan 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 AFMb307*zg5* 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

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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, Drachman, Gagnadoux, Pariente, & Broyer, 1986; Ehrich, Stoeppler, Offner, & Brodehl, 1979; Fink et al., 1989; Gahl & Kaiser-Kupfer, 1987; Jonas et al., 1987; Nichols, Press, Schneider, & Trauner, 1990), 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, Strife, Towbin, & Bove, 1982). A recent volumetric magnetic resonance imaging (MRI) study demonstrated focal grey matter decreases in the posterior parietal cortex and in the primary somatosensory cortex in children with cystinosis (Sach, Vu, Ludlum, Poehlmann, & Trauner, 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, Chase, Scheller, Katz, & Schneider, 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, Schneider, & Trauner, 1994; Wolff, Ehrich, Offner, & Brodehl, 1982, 1989). Despite normal intelligence, these individuals may demonstrate specific visuospatial deficits with intact verbal abilities (Ballantyne & Trauner, 2000; Spilkin, Ballantyne, Babchuck, & Trauner, 2007; Trauner, Chase, Ballantyne, Tallal, & Schneider, 1989). In a MRI study, Nichols, Press, et al. (1990) 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, Spilkin, Williams, & Babchuck, 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 visuoperceptual 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 visuoperceptual performance in young children with cystinosis (3 through 8 years) found the same pattern of widespread visuospatial deficits with relatively spared visuosperceptual abilities (Trauner et al., 2007). Moreover, deficits have been observed on tests of visual motor integration (Scarvie, Ballantyne, & Trauner, 1996), visual closure (Nichols, Ballantyne, Hodge, & Trauner, 1990), 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.

1. 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 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.

1.1. Methods: Study I

1.1.1. 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 5.00–50.33 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.

1.1.2. Measures

1.1.2.1. 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, Kramer, Kaplan, & Ober, 1987). Some of the stimuli used are from the Visual Spatial Learning Test (Malec, Ivnik, & Hinkeldey, 1991). The subject is shown a series of 15 abstract stimulus designs, at a rate of 1 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 5 trials; the order of presentation