Published in final edited form as:

J Inherit Metab Dis. 2019 May ; 42(3): 545–552. doi:10.1002/jimd.12062.

Hierarchical Processing of Visual Stimuli In Nephropathic Cystinosis

Aakash Sathappan, BA and Doris Trauner, M.D.*

Departments of Neurosciences and Pediatrics, UC San Diego School of Medicine, and Rady Children's Hospital, San Diego, CA, USA

Abstract

Previous studies have shown that individuals with cystinosis may exhibit difficulty with visuospatial tasks. Global and local (hierarchical) processing are specific types of visuospatial tasks mediated by the right and left parietal lobes respectively. The study objective was to determine whether individuals with cystinosis and carriers of the cystinosis gene mutation show deficits in global and/or local processing. The study included 48 children (32 controls, 16 cystinosis) and 56 adults (25 controls, 25 carriers, 6 cystinosis). Participants were instructed to replicate ten hierarchical stimuli to assess global-local processing. The primary outcome measure was mean global and local performance on the hierarchical stimuli task between subgroups. Error subtypes were included to further assess each image. Compared to the control subgroups, adult and child cystinosis patients as well adult carriers demonstrated significant deficits in the global processing of a hierarchical stimulus against a background of unimpaired local processing. Child cystinosis patients performed significantly more poorly than controls on all error subtypes except local shape distortion. Adult cystinosis patients and carriers made significantly more global shape distortion errors than the controls. Our study shows that the cognitive profile documented in cystinosis patients and carriers includes significant difficulties with the global processing of an image. Results of the carrier population are important since they suggest that the cognitive impairments observed in patients cannot be attributed to symptomatic manifestations of the

*Corresponding Author: Doris Trauner, M.D., [Mailing Address:](#), UCSD School of Medicine, , 9500 Gilman Drive, La Jolla CA 92093-0935, USA, Phone: 858-822-6700, dtrauner@ucsd.edu.
Author Contributions

1. Aakash Sathappan, BA led the synthesis and analysis of the collected data and prepared the manuscript.
2. Doris Trauner, MD is the senior author. She conceived of the research ideas, designed the research study, supervised the conduct of the study, and provided major contributions towards the intellectual design of the manuscript and implementation of research. She edited the manuscript in detail.

All authors have approved of the final article.

Conflicts of Interests

Aakash Sathappan, BA declares that he has no conflicts of interests. Doris Trauner, MD has received research funding from the Cystinosis Research Foundation and the Cystinosis Research Network.

COMPLIANCE WITH ETHICS GUIDELINES

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Informed consent was obtained prior to testing for all patients in accordance with procedures of the University of California, San Diego Institutional Review Board. Children signed assent forms and their parents gave informed consent for the children to participate.

disease. Instead, the global processing deficits observed provide insight into the potential role of the cystinosis gene mutation on neurodevelopmental differences seen in these individuals.

INTRODUCTION

Infantile nephropathic cystinosis is a rare, autosomal-recessive, lysosomal storage disorder that leads to the deposition of cystine crystals in multiple organ systems (Nesterova and Gahl 2013a; Ivanova et al. 2014). The genetic defect in cystinosis has been attributed to the inactivation of the cystinosis gene (17p13), which codes for the lysosomal membrane transport protein cystinosis (CTNS) (Anikster et al. 1999; Gahl, Thoene, and Schneider 2002; Wilmer et al. 2011). Inactivation of cystinosis leads to intracellular cystine accumulation, since cystine is unable to cross the lysosomal membrane without the assistance of the cystinosis protein (Nesterova and Gahl 2013b).

Although the pathophysiology of tissue damage is still unclear, cystinosis patients typically present with renal tubular Fanconi syndrome within the first year of life, and in untreated cases, renal transplant surgery is usually required by the age of ten (Gahl, Thoene, and Schneider 2001). Furthermore, untreated individuals can present with a host of non-renal manifestations including hypothyroidism, delayed pubertal development, progressive myopathy, retinal changes, and photophobia due to corneal cystine accumulation (Wilmer et al. 2011; Nesterova and Gahl 2013b). However with the advent of the cystine-depleting drug cysteamine and the ability to delay the progression of renal failure by many years, it has been possible to address the significant functional consequences of cognitive dysfunction caused by this disorder.

A particular cognitive profile has been observed in cystinosis patients, in which visual motor and visual spatial processing deficits emerge against a foundation of normal visual perceptual and intellectual functioning (D. Trauner et al. 1988; Williams, Schneider, and Trauner 1994; Ballantyne and Trauner 2000; D. A. Trauner et al. 2007; Aly et al. 2014). Impairments in visual motor and visual spatial processing may pose challenges with learning for these children, as many academic subjects such as arithmetic and geography require significant visual-spatial processing (Ballantyne, Scarvie, and Trauner 1997; D. A. Trauner et al. 2007). One study notes that 37% of cystinosis children scored below the normal range on arithmetic and spelling tests (Ballantyne, Scarvie, and Trauner 1997), suggesting that these individuals may be more susceptible to learning difficulties.

While the underlying neuropathology to explain these cognitive deficits is still unclear, it is possible that cystine accumulation in neuronal and glial cells (Levine and Paparo 1982; Jonas et al. 1987; Broyer and Tete 1999; Vogel et al. 1990) could lead to cellular damage and impaired cognitive function over time. However, other studies suggest that the effect of the cystinosis gene on early brain development may be more influential than the temporal effects of cystine accumulation, since the pattern of visual motor and visual spatial deficits has been seen even in very young children with cystinosis (D. A. Trauner et al. 2007; Viltz and Trauner 2013). A study conducted by Niemiec et al. (2012) substantiates this claim, demonstrating that asymptomatic carriers of the CTNS mutation also display visual spatial impairments when compared to controls (Niemiec, Ballantyne, and Trauner 2012). These

findings suggest that a high cystine load is not likely to be the primary factor responsible for these cognitive deficits.

The neural network most closely associated with the visual spatial processing system is the dorsal visual processing network (VPN), the “where system”, which projects from the occipital lobe along a dorsal pathway to the parietal cortex. This occipitoparietal pathway is thought to be involved in the spatial processing of a visual image, including its rotational orientation and spatial location amongst other objects in a visual field. In contrast, processing of the details of the visual image, including object identification, object perception, and pattern integration are mediated by the ventral VPN, “the what system”, which projects from the occipital lobe through regions of the temporal lobe (Mishkin, Ungerleider, and Macko 1983; Goodale and Milner 1992; Creem and Prott 2001; Stiles et al. 2008). The significantly impaired performance of cystinosis patients on visual spatial tasks against a background of intact visual perceptual functioning provides evidence for a clear dissociation between the dorsal and ventral visual processing pathways in these patients (Ballantyne and Trauner 2000). A study conducted by Bava *et al.* (2010) provides structural evidence for dorsal pathway changes using magnetic resonance diffusion tensor imaging techniques, showing bilaterally reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in inferior and superior parietal lobes, but comparable FA and MD in the inferior temporal lobes between cystinosis children and controls (Bava et al. 2010b).

A pivotal milestone in visual cognitive development is the ability to discern the individual components of a visual stimulus (local processing) and the ability to integrate these local parts into a global whole (global processing). A much-used approach to study global-local processing has been the use of hierarchical stimuli, which are objects or shapes composed of smaller elements (Delis, Robertson, and Efron 1986; Dukette and Stiles 2001; Stiles et al. 2008). For example, a large G made of smaller K's or a large diamond formed of smaller plus signs would constitute a hierarchical stimulus. The primary regions involved in the global processing of an image are the right parietal lobe and temporal-parietal junction, while the left parietal lobe and temporal-parietal junction subserve local processing. (Robertson, Lamb, and Knight 1988; G. R. Fink et al. 1996; Volberg et al. 2009; Boksem et al. 2012; Gable, Poole, and Cook 2013). Studies of both adults and children who have suffered a unilateral stroke have shown that individuals with a focal lesion of the right hemisphere show a deficit in spatial, global processing of hierarchical stimuli; those with a focal lesion of the left hemisphere show a deficit in featural, local processing (Stiles et al. 2008). Many studies report similar hemispheric bias for global and local processing of a stimulus, although the distinction is by no means absolute (Robertson, Lamb, and Knight 1988; G. R. Fink et al. 1996; Volberg and Hübner 2004; Volberg et al. 2009; Gable, Poole, and Cook 2013).

Given the evidence for visual spatial dysfunction in children with cystinosis, and the structural differences observed within visual processing pathways (Bava et al., 2010), the present study was designed to determine whether there were deficits in hierarchical processing of visual stimuli in children, and adults with cystinosis as well as adult carriers of the cystinosis gene. Such findings would add new information about the role of the

cystinosis gene in brain development, specifically its influence on brain hemisphere development.

METHODS

Participants

Study participants included 48 children (32 controls, 16 cystinosis patients) and 56 adults (25 controls, 25 carriers, 6 cystinosis patients). For the child population the controls ranged in age from 7 years 3 months to 14 years 2 months, and the cystinosis patients ranged in age from 7 years to 14 years 2 months. For the adult population the controls ranged in age from 22 years 8 months to 41 years 9 months, the carriers from 26 years to 39 years 8 months, and the cystinosis patients from 23 years 5 months to 39 years 7 months. None of the child or adult cystinosis patients were in renal failure or required dialysis at the time of this study. In addition to establishing comparable age ranges within groups, t-tests were conducted between group subsets to ensure that the mean ages were comparable, and to confirm that there was no significant variation among age distributions.

Since cystinosis is an autosomal recessive disease, all parents of children with cystinosis are obligate heterozygotes. As such, we used parents of child cystinosis patients to study carriers of the gene mutation. None of the carriers exhibited any of the clinical symptoms of cystinosis, including renal complications. Cystinosis patients and carriers were recruited primarily through the National Cystinosis Foundation, Cystinosis Research Network, and Cystinosis Foundation as well as during local cystinosis conferences held in San Diego over several years. Control participants were recruited from the local community via advertisements and fliers. All control participants were screened for normal medical and developmental histories prior to the study to ensure that they did not display any cognitive deficits. All subgroups were also matched in terms of gender and socio-economic status. Informed consent was obtained prior to testing for all participants in accordance with procedures of the University of California, San Diego Institutional Review Board.

Cognitive Measures

Global-Local Testing—The test for global-local processing was created based on a series of hierarchical stimuli implemented by Dukette and colleagues (Dukette and Stiles 2001). Ten hierarchical stimuli were used, each consisting of small, local features that were positioned in a matrix to form a larger global whole (for example, a large A made of small M's). This specific model was chosen since it places comparable demands on the individual for both global and local processing, effectively eliminating any systematic differences in the effort and accuracy needed for both of these distinct tasks (Stiles et al. 2008).

For each stimulus, participants were given 5 seconds to study the image followed by a 5 second delay. Subsequently, each participant was instructed to reproduce the image from memory on a 8.5 × 11 piece of white paper. Results of the test were calculated based on two comparable (0-2) point scales to assess both the overall global and local level accuracy of the ten drawings (See Table 1). The resulting total score for each participant was the sum of their global and local scores.

Error Subtypes—Error subtypes were also examined to gather further information about visual processing with this task (See Table 2). The six error subtypes included were Global Rotation Errors, Local Rotation Errors, Misplacement, Global Shape Distortion Errors, Local Shape Distortion Errors, and Local Number Errors. A point scale was devised to quantify the number of errors each participant made in these respective categories.

Analyses were conducted separately for the child and adult populations because of assumed superiority in performance by the latter in the hierarchical stimulus task. In the child population, t-tests were performed to compare the mean scores for overall global-local performances and the six error subtypes between the cystinosis and control children and to determine whether the cystinosis group was more prone to making a specific error type than the control group. For the adult population, an analysis of variance statistical model (ANOVA) was used to determine if there were any statistically significant differences between the means for both the global-local scores and the six error subtypes for each of the three adult subgroups.

RESULTS

Hierarchical Stimuli Test (Global-Local)

The results of the adapted hierarchical stimuli test are shown in Table 3 for the child participants, Table 4 for the adult participants, and graphically for all groups in Figures 1 and 2. As expected, adult controls performed significantly better than child controls. Each table shows the mean, SD, and *P*-value for each subset of the hierarchical stimuli task (global, local, total). As seen in Table 3, child cystinosis patients performed significantly more poorly than child controls on the global aspect of the task, but did not differ significantly in performance on the local aspect of the task. As a result of their significantly poorer global mean score, the child cystinosis patients also had a significantly lower total mean score compared to the child controls. Table 4 shows that both the adult carriers and cystinosis patients performed significantly more poorly than the adult controls on the global aspect of the task. However, there was no significant difference between the carrier and cystinosis populations for the mean global score. There was no significant difference among all three adult subgroups for the mean local score. Figure 1 illustrates the scores for all groups, and further demonstrates that the adult carriers scored at an intermediate level between controls and cystinosis patients, similar to what might be expected for a “carrier effect” where the carriers have one copy of the mutant gene, the patients have both copies, and the controls have no copies.

Error Subtypes

The results of the error subtypes are shown in Table 5 for the child participants and Table 6 for the adult participants. Each table shows the mean, SD, and *P* value for each error subtype. For all the subtypes except local shape distortion, the child cystinosis patients performed significantly more poorly than the controls and had a higher mean error score. In the adult population, there was no significant difference among subgroups for 4 error subtypes: global rotation errors, local rotation errors, local shape distortion, and local number errors. However, carriers made significantly more misplacement errors than either

the adult controls or cystinosis patients, with no significant difference between the latter two. Both adult cystinosis patients and carriers made significantly more global shape distortion errors than the controls, with no significant difference existing between the cystinosis patients and carriers.

DISCUSSION

Results of the current study indicate that patients with cystinosis demonstrate a significant deficit in the global processing of a hierarchical stimulus, while displaying no such deficit in local processing. In addition, carriers of the CTNS gene mutation, who are asymptomatic, also showed a deficit in global processing when compared to controls. The results of the carrier population are important since they indicate that these cognitive impairments observed in patients cannot be attributed to symptomatic manifestations of the disease, including renal complications and high cystine load.

The impairment in overall global processing among adult and child cystinosis patients, against a foundation of intact local processing, suggests that there may be asymmetric neurodevelopmental changes between the left and right hemisphere during the early period of life of cystinosis patients. One potential explanation is that the integrity of the right parietal lobe in these individuals is compromised during early neurostructural development. In fact this had been already demonstrated in an earlier study by Bava *et al.* (2010) who conducted a within-group analysis of cystinosis children showing that in addition to having a reduced fractional anisotropy of parietal versus temporal pathways, fractional anisotropy was significantly reduced in the right inferior parietal lobule compared with the left inferior parietal lobe. These findings suggest that the structural changes that occur during the formation of these white matter tracts not only affect visual spatial processing but also seem to exhibit a right hemisphere bias, resulting in the manifestation of global processing deficits seen in cystinosis patients. Furthermore, in a study conducted by Chechlacz *et al.* (2015), the white matter tracts coursing through the right parietal cortex were shown to subserve global attention. Specifically, deficits in global feature processing were associated with disconnections in two white matter pathways- the third segment of the right superior longitudinal fasciculus (SLF III) and the long segment of right perisylvian network (Chechlacz *et al.* 2015). These white matters tracts are significant due to their association with visual spatial processing. Studies of patients with a stroke of the right hemisphere have linked the right perisylvian network with visual spatial processing (Doricchi *et al.* 2008; Thiebaut de Schotten *et al.* 2008). The SLF III, which projects from the inferior parietal lobe to inferior frontal gyrus, has also been associated with visual spatial attention capture (Corbetta and Shulman 2002; Thiebaut de Schotten *et al.* 2011, 2012).

Furthermore, an examination of error types was useful in determining whether cystinosis patients and carriers tended to make more visual spatial or visual perceptual errors. The significantly higher means of cystinosis children on “Global Shape Distortions” and “Global Rotation Errors” indicate impairment in visual spatial processing because distortional and rotational errors demonstrate a lack of attention to configuration and spacing (Ballantyne and Trauner 2000). The significantly higher means of cystinosis children on “Local

Rotational Errors”, “Local Number Errors”, and “Misplacement Errors” also demonstrate a spatial processing deficit, but on a micro scale.

Indeed, a similar study on hierarchical stimuli has shown that “misorientation of local-level elements” was an error subtype seen in children who had a right hemisphere stroke (Stiles et al. 2008). Since these children also demonstrated a global-processing impairment, the paper postulates that these subjects may have erroneously rotated these local figures along the axis of the segment (instead of axis of the page of paper) as a strategy to “assist in the reproduction of the global structure”, and compensate for their global processing deficiencies (Stiles et al. 2008).

Errors in “Misplacement” and “Local Number Errors” also point towards a problem in visual-spatial processing. For example if a stimulus “A” is comprised of 14 “M”s, a reproduction of the drawing with 30M’s (local number error) or with the middle stem higher or lower than indicated in the image (misplacement error) points towards deficits in processing spatial cues. While adult carriers demonstrated significant impairment in misplacement errors, adult cystinosis patients did not which may be a reflection of the small number of adults in this study. Also, the observation that adults did not make as many errors as children is likely due to general cognitive maturation and refinement of visual processing with age, and does not detract from the overall findings.

In summary, this study provides evidence for the role of the cystinosis gene in influencing neurodevelopmental changes in both cystinosis patients and carriers of the CTNS mutation. While we have known that spatial processing occurs in the parietal lobes and that cystinosis patients exhibit spatial impairment, the results of our study provide novel insight into a specific type of visual spatial task cystinosis patients and carriers struggle with – global processing. Recognition of this specific cognitive deficit has helped bridge the gap between functional, visual spatial deficits and structural, white matter changes seen in the parietal lobes of these patients. Furthermore, our findings provide an impetus for examining deficits in hierarchical, visual processing in other genetic disorders where visual spatial deficits have been documented including Turner syndrome, fragile X, & Williams syndrome (Hong, Kent, and Kesler 2009; Atkinson and Braddick 2011; Gandhi et al. 2014). Most importantly, this knowledge of neurocognitive differences may help cystinosis patients better understand areas of potential challenges, specifically situations involving the use of global processing.

ACKNOWLEDGMENTS

This work was funded by NIH grants: NINDS #NS043135 (D. Trauner PI), and NIH # 5T35HL007491-35 (summer research award to A. Sathappan). We would like to thank all the families who participated in the study for their time and cooperation.

REFERENCES

- Aly Reham, Makar Samuel, El Bakri Azza, and Soliman Neveen A. 2014 “Neurocognitive Functions and Behavioral Profiles in Children with Nephropathic Cystinosis.” *Saudi Journal of Kidney Diseases and Transplantation* 25 (6): 1224–31. [PubMed: 25394439]
- Anikster Y, Lucero C Touchman W, Huizing M, McDowell G, Shotelersuk V, Green ED, and Gahl WA. 1999 “Identification and Detection of the Common 65-Kb Deletion Breakpoint in the

- Nephropathic Cystinosis Gene (CTNS).” *Molecular Genetics and Metabolism* 66 (2): 111–16. 10.1006/mgme.1998.2790. [PubMed: 10068513]
- Atkinson Janette, and Braddick Oliver. 2011 “From Genes to Brain Development to Phenotypic Behavior. ‘Dorsal-Stream Vulnerability’ in Relation to Spatial Cognition, Attention, and Planning of Actions in Williams Syndrome (WS) and Other Developmental Disorders.” *Progress in Brain Research* 189: 261–83. 10.1016/B978-0-444-53884-0.00029-4. [PubMed: 21489394]
- Ballantyne Angela O., Scarvie Kathleen M., and Trauner Doris A.. 1997 “Academic Achievement in Individuals with Infantile Nephropathic Cystinosis.” *American Journal of Medical Genetics - Neuropsychiatric Genetics* 74 (2): 157–61. [PubMed: 9129715]
- Ballantyne Angela O., and Trauner Doris A.. 2000 “Neurobehavioral Consequences of a Genetic Metabolic Disorder: Visual Processing Deficits in Infantile Nephropathic Cystinosis.” *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 13 (4): 254–63.
- Bava Sunita, Theilmann Rebecca J., Sach Miriam, May Susanne J., Frank Lawrence R., Hesselink John R., Vu Duc, and Trauner Doris A.. 2010a “Developmental Changes in Cerebral White Matter Microstructure in a Disorder of Lysosomal Storage.” *Cortex* 46 (2): 206–16. 10.1016/j.cortex.2009.03.008. [PubMed: 19427638]
- Bava Sunita, Theilmann Rebecca J., Sach Miriam, May Susanne J., Frank Lawrence R., Hesselink John R., Vu Duc, and Trauner Doris A.. 2010b “Developmental Changes in Cerebral White Matter Microstructure in a Disorder of Lysosomal Storage.” *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 46 (2): 206–16. 10.1016/j.cortex.2009.03.008. [PubMed: 19427638]
- Boksem Maarten AS, Kostermans Evelien, Tops Mattie, and de Cremer David. 2012 “Individual Differences in Asymmetric Resting-State Frontal Cortical Activity Modulate ERPs and Performance in a Global-Local Attention Task.” *Journal of Psychophysiology* 26 (2): 51–62. 10.1027/0269-8803/a000067.
- Broyer M, and Tete MJ. 1999 “Central Nervous System Complications in Cystinosis” In *Cystinosis*, edited by Broyer M, 75–80. Paris: Elsevier.
- Chechlac Magdalena, Mantini Dante, Gillebert Celine R, and Humphreys Glyn W. 2015 “Asymmetrical White Matter Networks for Attending to Global versus Local Features.” *Cortex*, 2, 1–11. 10.1016/j.cortex.2015.01.022.
- Corbetta Maurizio, and Shulman Gordon L. 2002 “Control of Goal-Directed and Stimulus-Driven Attention in the Brain.” *Nature Reviews. Neuroscience* 3 (3): 201–15. 10.1038/nrn755. [PubMed: 11994752]
- Creem Sarah H, and Prott Dennis R. 2001 “Defining the Cortical Visual Systems: ‘What’, ‘Where’, and ‘How.’” *Acta Psychologica* 107: 43–68. [PubMed: 11388142]
- Delis DC, Robertson LC, and Efron R. 1986 “Hemispheric Specialization of Memory for Visual Hierarchical Stimuli.” *Neuropsychologia* 24 (2): 205–14. 10.1016/0028-3932(86)90053-9. [PubMed: 3714025]
- Doricchi Fabrizio, de Schotten Michel Thiebaut, Tomaiuolo Francesco, and Bartolomeo Paolo. 2008 “White Matter (Dis)Connections and Gray Matter (Dys)Functions in Visual Neglect: Gaining Insights into the Brain Networks of Spatial Awareness.” *Cortex* 44 (8): 983–95. 10.1016/j.cortex.2008.03.006. [PubMed: 18603235]
- Dukette Dianne, and Stiles Joan. 2001 “The Effects of Stimulus Density on Children’s Analysis of Hierarchical Patterns.” *Developmental Science* 4 (2): 233–51. 10.1111/1467-7687.00168.
- Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, and Dolan RJ. 1996 “Where in the Brain Does Visual Attention Select the Forest and the Trees?” *Nature* 382 (6592): 626–28. 10.1038/382626a0. [PubMed: 8757132]
- Gable Philip A, Poole Bryan D, and Cook Mary S. 2013 “Asymmetrical Hemisphere Activation Enhances Global – Local Processing.” *Brain and Cognition* 83 (3): 337–41. 10.1016/j.bandc.2013.09.012. [PubMed: 24144929]
- Gahl WA, Bashan N, Tietze F, and Schulman JD. 1984 “Lysosomal Cystine Counter-Transport in Heterozygotes for Cystinosis.” *American Journal of Human Genetics* 36 (2): 277–82. [PubMed: 6711558]
- Gahl WA, Thoene JG, and Schneider JA. 2001 “Cystinosis: A Disorder of Lysosomal Membrane Transport” In *The Metabolic and Molecular Basis of Inherited Disease*, edited by Scriver CR,

- Beaudet AL, Sly WS, and Valle D, Edi Eighth, 5085–5108. New York: McGraw-Hill Companies, Inc.
- Gahl William A., Thoene JG, and Schneider JA. 2002 “Cystinosis.” *New England Journal of Medicine* 347 (2): 111–21. [PubMed: 12110740]
- Gandhi Réno M, Kogan Cary S, Messier Claude, and Macleod Lindsey S. 2014 “Visual-Spatial Learning Impairments Are Associated with Hippocampal PSD-95 Protein Dysregulation in a Mouse Model of Fragile X Syndrome.” *Neuroreport* 25 (4): 255–61. 10.1097/WNR.000000000000087. [PubMed: 24323121]
- Goodale MA, and Milner AD. 1992 “Separate Visual Pathways for Perception and Action.” *Trends in Neurosciences* 15 (1): 20–25. [PubMed: 1374953]
- Hong David, Kent Jamie Scaletta, and Kesler Shelli. 2009 “Cognitive Profile of Turner Syndrome.” *Developmental Disabilities Research Reviews* 15 (4): 270–78. 10.1002/ddrr.79. [PubMed: 20014362]
- Ivanova Ekaterina, De Leo Maria Giovanna, De Matteis Maria Antonietta, and Levchenko Elena. 2014 “Cystinosis: Clinical Presentation, Pathogenesis and Treatment.” *Pediatric Endocrinology Reviews: PER* 12 Suppl 1 (9): 176–84. [PubMed: 25345100]
- Jonas Adam J, Speller Rebecca, Conley Susan B, and Rosenberg Harvey. 1987 “Central Nervous System Cystine Storage in Cystinosis.” *Pediatric Research* 21 (4): 291A–291A. 10.1203/00006450-198704010-00741.
- Levine S, and Paparo G. 1982 Brain lesions in a case of cystinosis., 57 *Acta Neuropathologica* 217–20. [PubMed: 7124349]
- Mishkin M, Ungerleider LG, and Macko KA. 1983 “Object Vision and Spatial Vision: Two Cortical Pathways.” *Trends in Neurosciences* 6 (10): 414–17. 10.1016/0166-2236(83)90190-X.
- Nesterova Galina, and Gahl William A.. 2013a “Cystinosis: The Evolution of a Treatable Disease.” *Pediatric Nephrology (Berlin, Germany)* 28 (1): 51–59. 10.1007/s00467-012-2242-5.
- Nesterova Galina, and Gahl William A.. 2013b “Cystinosis: The Evolution of a Treatable Disease.” *Pediatric Nephrology* 28 (1): 51–59. 10.1007/s00467-012-2242-5. [PubMed: 22903658]
- Nichols SL, Press GA, Schneider Jerry A, and Trauner DA. 1990 “Cortical Atrophy and Cognitive Performance in Infantile Nephropathic Cystinosis.” *Pediatric Neurology* 6 (6): 379–81. 10.1016/0887-8994(90)90004-K. [PubMed: 2073300]
- Niemiec Stephen, Ballantyne Angela, and Trauner Doris A. 2012 “Cognition in Nephropathic Cystinosis: Pattern of Expression in Heterozygous Carriers.” *American Journal of Medical Genetics. Part A* 158A (8): 1902–8. 10.1002/ajmg.a.35467. [PubMed: 22786804]
- Robertson LC, Lamb MR, and Knight RT. 1988 “Effects of Lesions of Temporal-Parietal Junction on Perceptual and Attentional Processing in Humans.” *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 8 (10): 3757–69. [PubMed: 3193178]
- Smolin LA, Clark KF, and Schneider JA. 1987 “An Improved Method for Heterozygote Detection of Cystinosis, Using Polymorphonuclear Leukocytes.” *American Journal of Human Genetics* 41 (2): 266–75. [PubMed: 3618595]
- Stiles Joan, Stern Catherine, Appelbaum Mark, Nass Ruth, Trauner Doris, and Hesselink John. 2008 “Effects of Early Focal Brain Injury on Memory for Visuospatial Patterns: Selective Deficits of Global-Local Processing.” *Neuropsychology* 22 (1): 61–73. 10.1037/0894-4105.22.1.61. [PubMed: 18211156]
- Thiebaut de Schotten Michel, Dell’Acqua Flavio, Forkel Stephanie J, Simmons Andrew, Vergani Francesco, Murphy Declan G M, and Catani Marco. 2011 “A Lateralized Brain Network for Visuospatial Attention.” *Nature Neuroscience* 14 (10): 1245–46. 10.1038/nn.2905. [PubMed: 21926985]
- Thiebaut de Schotten Michel, Dell’Acqua Flavio, Valabregue Romain and Catani Marco. 2012 “Monkey to Human Comparative Anatomy of the Frontal Lobe Association Tracts.” *Cortex* 48 (1): 82–96. 10.1016/j.cortex.2011.10.001. [PubMed: 22088488]
- Thiebaut de Schotten Michel, Kinkingnéhun Serge, Delmaire Christine Lehericy Stéphane, Duffau Hugues Thivard Lionel, Volle Emmanuelle, Levy Richard, Dubois Bruno, and Bartolomeo Paolo. 2008 “Visualization of Disconnection Syndromes in Humans.” *Cortex* 44 (8): 1097–1103. 10.1016/j.cortex.2008.02.003. [PubMed: 18602092]

- Trauner DA, Chase C Scheller J Katz B, and Schneider JA. 1988 “Neurologic and Cognitive Deficits in Children with Cystinosis.” *Journal of Pediatrics*, no. 112: 912–14. [PubMed: 3373397]
- Trauner Doris A., Spilkin Amy M., Williams Jennifer, and Babchuck Lynne. 2007 “Specific Cognitive Deficits in Young Children with Cystinosis: Evidence for an Early Effect of the Cystinosis Gene on Neural Function.” *Journal of Pediatrics* 151 (2): 192–96. 10.1016/j.jpeds.2007.02.062. [PubMed: 17643777]
- Viltz Lisa, and Trauner Doris A. 2013 “Effect of Age at Treatment on Cognitive Performance in Patients with Cystinosis.” *The Journal of Pediatrics* 163 (2): 489–92. 10.1016/j.jpeds.2013.01.027. [PubMed: 23462307]
- Vogel DG, Malekzadeh MH, Cornford ME, Schneider JA, Shields WD, and Vinters HV. 1990 Central nervous system involvement in nephropathic cystinosis., 49 *Journal of neuropathology and experimental neurology* 591–99. [PubMed: 2230837]
- Volberg Gregor, and Hübner Ronald. 2004 “On the Role of Response Conflicts and Stimulus Position for Hemispheric Differences in Global/Local Processing: An ERP Study.” *Neuropsychologia* 42 (13): 1805–13. 10.1016/j.neuropsychologia.2004.04.017. [PubMed: 15351629]
- Volberg Gregor, Kliegl Katrin, Hanslmayr Simon, and Greenlee Mark W.. 2009 “EEG Alpha Oscillations in the Preparation for Global and Local Processing Predict Behavioral Performance.” *Human Brain Mapping* 30 (7): 2173–83. 10.1002/hbm.20659. [PubMed: 18830957]
- Williams BLH, Schneider JA, and Trauner DA. 1994 “Global Intellectual Deficits in Cystinosis.” *American Journal of Medical Genetics* 49 (1): 83–87. 10.1002/ajmg.1320490115. [PubMed: 8172256]
- Wilmer Martijn J, Schoeber Joost P, van den Heuvel Lambertus P, and Levchenko Elena N. 2011 “Cystinosis: Practical Tools for Diagnosis and Treatment.” *Pediatric Nephrology* (Berlin, Germany) 26 (2): 205–15. 10.1007/s00467-010-1627-6.

Figure 1. Mean global score on the hierarchical stimulus test for all study groups. Significant differences were observed when comparing the mean global scores of child controls and child cystinosis patients. Significant differences were also observed when comparing adult carriers against adult controls as well as adult cystinotics against adult controls. (*= $P < 0.05$)

Figure 2. Mean local score on the hierarchical stimulus test for all study groups.

No significant differences in mean local score were observed when comparing child controls against child cystinosis patients. Similarly, no significant differences were observed when comparing adult controls, carriers, and cystinosis.

Table I.
Global & Local Scoring System.

Scoring criteria modeled after Stiles et al. (2008) (adapted from Dukette et al., 2001)

Global Score	Criteria
2	❖ Image was an accurate replication of the stimulus and contained no rotations or distortions
1	❖ Image contained 1 distortion or 1 rotation error of $< 45^\circ$
0	❖ Image contained 1 or more distortion and/or rotation errors $> 45^\circ$
Local Score	Criteria
2	❖ Each Local Figure was clearly recognizable and each segment or curve had 50% or more of the local figures in correct orientation
1	❖ Each Local Figure was clearly recognizable but each segment or curve had less than 50% of the local figures in correct orientation. OR ❖ The image contained local figures that had 1 or more distortions (still recognizable) but all of the figures were correctly oriented along each segment or curve.
0	❖ The image contained local figures that had 1 or more distortion (still recognizable) and not all of the figures were correctly oriented along each segment or curve. OR ❖ The image contained local figures that were incorrect or unrecognizable.

Table II.
Error Subtypes Scoring System.

Error subtypes modeled after Stiles et al. (2008) and created before the start of analysis.

Global rotation errors	
0	= none
1	= figure is rotated off axis <45°
2	= figure is rotated off axis >45°
<hr/>	
Local Rotation errors	
0	= none
1	= >25% of the figures are rotated off axis
2	= 25-50% are rotated off axis
3	= >50% are rotated off axis
<hr/>	
Misplacement errors	
0	= none
1	= one misplacement (e.g., horizontal line of the A is positioned too low)
2	= >one misplacement (e.g., for G, the “gap” in G is nonexistent/ too wide)
<hr/>	
Global Shape distortion errors	
0	= none
1	= any one global distortion (e.g., A with top flat instead of pointed top)
2	= more than one global distortion
<hr/>	
Local Shape distortion errors	
0	= none
1	= 10-25% of local figures are distorted, (e.g., bracket that looks like an E)
2	= >25% of local figures are distorted
<hr/>	
Local number errors	
0	= none
1	= > 50% too many or too few local figures compared to the stimulus image

Table III:Performance of Child Controls & Child Cystinosis Patients on the Hierarchical Stimuli Test (Mean $\pm$ SD)

Subtest	Controls	Cystinosis Patients	Significance
Global	9.9 $\pm$ 2.9	7.94 $\pm$ 2.3	0.023
Local	13.34 $\pm$ 4.0	11.94 $\pm$ 3.9	0.252
Total	23.25 $\pm$ 6.0	19.88 $\pm$ 6.0	0.072

Table IV:Performance of Adult Controls, Cystinosis Patients, & Carriers on the Hierarchical Stimuli Test (Mean $\pm$ SD)

Subtest	Controls	Cystinosis Patients	Carriers	Significance
Global	15.08 $\pm$ 2.9	11.50 $\pm$ 1.5	12.64 $\pm$ 2.2	0.001
Local	16.72 $\pm$ 2.8	17.00 $\pm$ 2.1	16.92 $\pm$ 3.4	0.950
Total	31.84 $\pm$ 5.0	28.50 $\pm$ 1.6	29.16 $\pm$ 3.8	0.053

Table V:Mean Error Subtype Results for Child Controls & Child Cystinosis Patients (Mean $\pm$ SD)

Subtest	Controls	Cystinosis Patients	Significance
Global Rotation Errors	1.22 $\pm$ 1.2	3.63 $\pm$ 1.9	0.000
Local Rotation Errors	9.66 $\pm$ 7.2	15.38 $\pm$ 7.2	0.012
Misplacement	3.28 $\pm$ 1.7	4.75 $\pm$ 2.3	0.016
Global Shape Distortion	13.22 $\pm$ 3.9	15.63 $\pm$ 2.4	0.012
Local Shape Distortion	12.34 $\pm$ 4.7	12.25 $\pm$ 4.2	0.947
Local Number Errors	1.88 $\pm$ 2.1	3.50 $\pm$ 2.0	0.014

Table VI:Mean Error Subtype Results for Adult Controls, Carriers, & Cystinosis Patients (Mean $\pm$ SD)

Subtest	Controls	Cystinosis Patients	Carriers	Significance (ANOVA)
Global Rotations Errors	0.28 $\pm$ 0.6	0.33 $\pm$ 0.5	0.52 $\pm$ 0.7	0.391
Local Rotation Errors	4.28 $\pm$ 4.1	3.33 $\pm$ 2.4	4.44 $\pm$ 3.5	0.802
Misplacement	1.56 $\pm$ 1.3	1.17 $\pm$ 0.8	2.28 $\pm$ 1.2	0.044
Global Shape Distortion	5.80 $\pm$ 3.3	9.00 $\pm$ 1.3	9.16 $\pm$ 4.0	0.004
Local Shape Distortion	7.60 $\pm$ 4.1	8.50 $\pm$ 3.8	8.84 $\pm$ 3.9	0.543
Local Number Errors	0.08 $\pm$ 0.3	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	0.288