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Executive Function in Nephropathic Cystinosis

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Abstract

Objective—We studied executive function in children and adolescents with cystinosis.

Background—Cystinosis is a genetic metabolic disorder in which the amino acid cystine accumulates in all organs of the body, including the brain. Previous research has shown that individuals with cystinosis have visuospatial deficits, but normal intelligence and intact verbal abilities. Better understanding of the behavioral phenotype associated with cystinosis could have important implications for treatment.

Methods—Twenty-eight children with cystinosis and 24 control participants (age range 8-17 years) underwent selected Delis-Kaplan Executive Function System (D-KEFS) tests for neuropsychological assessment of executive function, and the participants' parents completed the Behavior Rating Inventory of Executive Function (BRIEF).

Results—Participants with cystinosis performed significantly more poorly than controls on all D-KEFS indices examined and on the BRIEF Metacognition Index and Global Executive Composite.

Conclusions—Executive function is an area of potential risk in cystinosis. Our data have implications not only for the function of affected children and adolescents in school and daily life, but also for disease management and treatment adherence. Our findings can aid in the design and implementation of interventions and lead to a greater understanding of brain-behavior relationships in cystinosis.

Keywords

cystinosis; executive function; Delis-Kaplan Executive Function System; Behavior Rating Inventory of Executive Function; nonverbal learning disability

Cystinosis is an inherited metabolic disorder in which the amino acid cystine accumulates in all the organs of the body, including the brain. The medical consequences of untreated cystinosis are well documented and include renal dysfunction, ophthalmologic

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All of the authors played an integral part in planning and executing the study and in preparing the manuscript.

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abnormalities, failure to thrive, and thyroid dysfunction (Adamson et al., 1989; Gahl et al., 2007; Gahl et al., 2002). Patients can also have central nervous system abnormalities such as subcortical and cortical atrophy, brain white matter abnormalities, abnormal EEGs, and motor incoordination (Bava, 2007; Broyer et al., 1987; Cochat et al., 1986; Ehrich et al., 1979; Fink et al., 1989; Nichols et al., 1990; Ross et al., 1982; Trauner et al., 1988; Vogel et al., 1990).

Previous research has shown that individuals with cystinosis display a characteristic cognitive profile: visuospatial difficulties against a background of normal intelligence and intact verbal abilities (Ballantyne & Trauner, 2000; Besouw et al., 2010; Fink et al., 1989; Trauner et al., 1988). Individuals with cystinosis have also been found to perform more poorly than matched controls on measures of visual memory (Schatz, 2002; Trauner et al., 1989), tactile recognition and motor coordination (Colah & Trauner, 1997; Trauner et al., 2010), mathematical and other academic skills (Ballantyne et al., 1997), social skills (Delgado et al., 2005), and behavioral function (Spilkin & Ballantyne, 2005). Individuals with cystinosis who have deficits in these areas may exhibit a pattern consistent with a nonverbal learning disorder (Mammarella et al., 2006; Nechelli & Venneri, 1995; Palombo, 2006; Rourke, 1995a; Voeller, 1986; Voeller, 2005; Weintraub & Mesulam, 1983). Nonverbal learning disorders are a feature of such neurocognitive conditions as fetal alcohol syndrome, hydrocephalus, multiple sclerosis, toxicant-induced encephalopathy, traumatic brain injury, periventricular nodular heterotopia, and velo-cardio-facial syndrome, and affected individuals show deficits in executive function (EF) (McCann et al., 2008; Rourke, 1995c; Swillen et al., 1999). Until now, EF in cystinosis had not been studied. That gap was the rationale for our investigation.

EF is a multidimensional construct that includes higher-order cognitive processes such as initiation, planning, problem solving, cognitive flexibility, behavioral regulation, metacognition, and feedback utilization (Delis et al., 2001; Powell & Voeller, 2004; Strauss et al., 2006). EF draws on the individual's more basic cognitive skills, such as attention, language, and perception (Delis et al., 2001), and is largely subserved by the prefrontal cortex, which has rich cortical and subcortical connections throughout the brain (Damasio & Anderson, 1993). EF plays a role in academic achievement, adaptive behaviors, and functional independence (Barkley et al., 2002; Bull & Scerif, 2001; Clark et al., 2002; Hart & Bean, 2011; Marlowe, 2000; Spinella et al., 2004). EF impairments are seen in many genetic, neurologic, and metabolic disorders (Powell & Voeller, 2004), including Turner's syndrome (Ross et al., 2000), fragile X syndrome (Bennetto et al., 2001), attention-deficit hyperactivity disorder (ADHD; Barkley, 1997; Fischer et al., 2005), fetal alcohol syndrome (Mattson et al., 1999; McGee et al., 2008; Schonfeld et al., 2001), and nonverbal learning disabilities (Rourke, 1995c).

We investigated EF in children and adolescents with cystinosis. Our hypothesis was that individuals with cystinosis would perform more poorly than controls on a neuropsychological assessment of EF, the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001), and on a parent-report measure of EF, the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000). Deficits in these higher-order cognitive processes could adversely affect the everyday function of individuals with cystinosis, as well as their disease management, treatment adherence, and overall quality of life. Learning more about the behavioral phenotype associated with cystinosis could have important implications for treatment.

METHODS

Participants

We gave selected tests from the D-KEFS to 28 children with nephropathic cystinosis (17 boys, 11 girls) and 24 control participants (12 boys, 12 girls). The participants' parents (28 cystinosis and 22 control parents) completed the entire BRIEF parent-report inventory of EF.

We recruited the participants with cystinosis through the Cystinosis Foundation, the Cystinosis Research Network, and the Cystinosis Research Foundation. We recruited the control participants through advertisements placed in magazines for parents and through flyers placed at public libraries, YMCAs, and other child-friendly places throughout the community. All of the controls had normal developmental and medical histories.

We group-matched the participants by age and socioeconomic status (SES) (Hollingshead, 1975). The mean age of the cystinosis group was 12 years 2 months (range: 8 years 0 months – 17 years 6 months), and the mean age of the control group was 12 years 1 month (range: 8 years 1 month – 17 years 9 months). The mean SES was 1.96 for the cystinosis group and 1.58 for the control group on the Hollingshead scale, in which scores range from 1 (highest SES) to 5 (lowest SES).

A nephrologist or metabolic disorders specialist confirmed infantile nephropathic cystinosis in our participants on the basis of their clinical history and elevated leukocyte cystine levels. All of the affected children were being treated with the standard medical regimen including cysteamine, vitamin D, calcium and phosphate replacement, and thyroid hormone (Adamson et al., 1989). Eight of these children had undergone renal transplant and their renal function was in an acceptable range at the time of testing. No participants with cystinosis were on renal dialysis at the time of testing.

Individuals with cystinosis were excluded from the study if they had uncorrected vision problems or a history of early vision impairment, if they had untreated thyroid dysfunction, or if they were in renal failure, as these complications might affect their cognitive test performance. The exclusionary criteria helped us avoid confounds in interpreting the cognitive data. Through an earlier study that we had done of patients with cystinosis, we had MRI results on 16 of the 28 children with cystinosis in this study. All scans were read by a clinical neuroradiologist who did not know the patients' diagnosis.

We obtained informed consent for each participant according to the University of California, San Diego Human Research Protections Program procedures, and that office approved the study.

Procedure

This was a cross-sectional study for which we administered all measures to each participant and parent during a single visit.

Neuropsychological Assessment

We gave selected tests from the D-KEFS (Delis et al., 2001), a standardized set of tests for the comprehensive assessment of EF in children and adults, normed for individuals 8 through 89 years old. The D-KEFS uses the “cognitive process approach” to assess key components in both verbal and nonverbal aspects of EF. The D-KEFS tests that we gave to our participants were the Trail Making Test, Verbal Fluency Test, Design Fluency Test, Color-Word Interference Test, and Sorting Test. In keeping with the cognitive process approach, the tests have multiple conditions and provide indices of component or more

fundamental skills, as well as higher-level cognitive functions. The D-KEFS tests provide age-based scaled scores (mean = 10, standard deviation [SD] = 3). Following is a short description of each test that we gave in our study (Delis et al., 2001) (for more detailed information, see the Examiner's Manual [Delis et al., 2001]).

D-KEFS Trail Making Test—This test consists of a visual cancellation task and a series of connect-the-circles tasks. There are 5 conditions: Visual Scanning, Number Sequencing, Letter Sequencing, Number-Letter Switching, and Motor Speed. The primary EF condition is Number-Letter Switching, which is a visual-motor sequencing task that assesses flexibility of thinking. The other conditions assess component cognitive and executive processes related to performance on Number-Letter Switching. Scaled scores are based on the number of seconds the examinee needs to complete each condition. The cognitive skills that contribute to performance include visual scanning, attention, motor functions, numerical processing, sequencing, inhibition of responses to distracting stimuli, and cognitive flexibility.

D-KEFS Verbal Fluency Test—This test examines the ability to generate words fluently. There are 3 conditions: Letter Fluency, Category Fluency, and Category Switching. For each trial within each condition, examinees need to generate as many items as possible within 60 seconds. Scaled scores are based on the number of correct words given within each 60-second trial. The cognitive skills that contribute to performance include verbal knowledge, rapid retrieval of lexical items, simultaneous processing and monitoring, initiating and sustaining performance, attention, and cognitive flexibility.

D-KEFS Design Fluency Test—Design Fluency assesses the examinee's ability to draw as many different designs as possible in 60 seconds. Rows of boxes containing an array of dots are presented and the examinee must draw a different design in each box, using only 4 lines to connect the dots. Design Fluency has 3 conditions: Filled Dots, Empty Dots, and Switching (alternating between filled and empty dots). Scores for each condition are based on the number of correct designs that the examinee draws within the 60-second time limit. The cognitive skills that contribute to performance include visual attention, motor speed, visuoperceptual and constructional skills, initiation, fluency, creativity, memory, simultaneous processing, adhering to rules and restrictions, inhibition, and cognitive shifting.

D-KEFS Color-Word Interference Test—This is a Stroop-like task (Stroop, 1935) that has 4 conditions: Color Naming, Word Reading, Inhibition, and Inhibition/Switching. Baseline tasks are the first 2 conditions—naming of color patches and reading of color words (eg, “green”) printed in black ink. The inhibition task requires the examinee to inhibit reading the words and instead name the dissonant ink colors in which the color words are printed. In the Inhibition/Switching task, the examinee must switch back and forth between naming the dissonant ink colors and reading the words, depending on whether the word appears in a box. Scaled scores for each condition are based on the number of seconds taken to complete the task. The cognitive skills that contribute to performance include naming skills, reading speed, memory, verbal inhibition, rule following, and cognitive flexibility.

D-KEFS Sorting Test—This test is designed to isolate and measure multiple components of concept formation and problem-solving abilities. The test has 2 conditions: Free Sorting (Correct Sorts and Description) and Sort Recognition Description. In Free Sorting, the examinee must sort cards that show printed words with such perceptual features as variations in color, size, and placement. In Sort Recognition, the examiner sorts the cards and the examinee must identify the sorting principle. Scaled scores are based on the number

of confirmed correct sorts and the number of correct descriptions of sorting principles. The cognitive skills that contribute to performance include linguistic and visuospatial skills, initiation of problem-solving behavior, verbal and nonverbal problem solving, concept formation, inhibition, flexibility, and abstract thinking.

Executive Function Behavioral Questionnaire

Parents of the study participants completed the BRIEF questionnaire (Gioia et al., 2000). The 86 items in the BRIEF cover 8 non-overlapping clinical scales and 2 validity scales (Inconsistency and Negativity). The scales form 2 main indices: the Behavioral Regulation Index, which is based on 3 of the clinical scales, and the Metacognition Index, which is based on the other 5 clinical scales. The Global Executive Composite is a summary score for the entire questionnaire. The BRIEF yields T-scores (mean = 50, SD = 10), with higher scores indicating greater impairment. Following are summaries of the BRIEF scales and indices, as described in the BRIEF Professional Manual (Gioia et al., 2000).

Behavioral Regulation Index—This index reflects the child's ability to control emotions and behavior, as well as flexibility in thinking. The index's 3 clinical scales are Inhibit (ability to inhibit, resist, or not act on an impulse; the ability to stop one's own behavior at the appropriate time), Shift (ability to move freely and flexibly from 1 situation, activity, or aspect of a problem to another), and Emotional Control (ability to modulate emotional responses). Behavioral regulation is believed to be a necessary foundation for adequate metacognitive processing (Gioia et al., 2000).

Metacognition Index—This index reflects the child's ability to initiate, plan, and organize thoughts and behaviors; to use working memory for problem solving; and to self-manage tasks and monitor one's own performance. This index's 5 clinical scales are Initiate (ability to begin a task or activity and independently generate ideas), Working Memory (ability to hold information in memory for the purpose of completing a task; attention and concentration), Plan/Organize (ability to organize and plan for future tasks, such as setting goals, developing appropriate steps to carry out an activity, understanding main points, and organizing information), Organization of Materials (ability to keep work, play, and storage spaces in order), and Monitor (ability to monitor one's progress and check one's own work; ability to keep track of the effect that one's behavior has on others).

Analyses

We used independent samples *t* tests for between-group (cystinosis vs control) analyses of age at testing and SES.

We conducted separate multivariate analysis of variance (MANOVA) tests for each D-KEFS test: Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Sorting. In each MANOVA, the independent variable was group membership (cystinosis vs control) and the dependent variables were the test conditions (eg, Trail Making conditions: Visual Scanning, Number Sequencing, Letter Sequencing, Motor Speed, Number-Letter Switching). When the MANOVA indicated a significant ($P < 0.05$) main effect of group membership, we followed up with between-group analyses for each test condition and we examined effect sizes. We also examined correlations between age and D-KEFS test scores in both groups.

To understand better the nature of D-KEFS performance in the 2 groups, we coded each participant's scaled scores for the highest-level EF condition within each test as "below normal limits" or "within normal limits," using the cutoff of 1 standard deviation below the mean of the subtest (subtest means are 10 ± 3 , and so scaled scores ≤ 6 were below normal

limits). We calculated percentage data and used chi-square analyses to examine the relationship between group membership (cystinosis or control group) and D-KEFS performance (within or below normal limits).

For the BRIEF data, we used 1-way ANOVAs for between-group analyses of the summary index scores: Behavioral Regulation Index, Metacognition Index, and Global Composite. For the scales that comprise the Behavioral Regulation Index and Metacognition Index, we conducted separate MANOVAs.

We considered P significant at <0.05 .

RESULTS

Demographic Variables and Brain MRI

There were no significant differences between the cystinosis and control groups in SES or age at testing. Of the 16 participants with cystinosis who had undergone MRI scanning as part of a separate study, 12 scans were read as normal, 1 showed a Chiari I malformation, and 3 showed mild to moderate cortical volume loss for age.

Neuropsychological Assessment of Executive Function

Table 1 shows mean performance on the D-KEFS. Multivariate analyses indicated that the cystinosis group performed significantly more poorly than the control group on each D-KEFS test (see Table 1 for the MANOVA results for each test). Between-group follow-up tests showed that on all conditions for each D-KEFS test, the cystinosis group scored significantly lower than the control group. Moreover, correlational analyses revealed no significant associations between age and D-KEFS measures in either group.

As described above in the “Analyses” section, we coded each participant’s D-KEFS scaled scores as “below normal limits” or “within normal limits.” For this analysis, we used the highest-level EF condition within each test (designated by an asterisk in Table 1), as the highest-level conditions have complex and multifaceted processing demands that better reflect overall EF. Moreover, because the cystinosis group performed similarly across the conditions of each test, the highest-level conditions serve as representative exemplars. On each D-KEFS higher-level condition, a markedly higher percentage of participants in the cystinosis group scored below normal limits than did participants in the control group (range = 21% to 50% of the cystinosis group, and 0% to 8% of the control group). See Figure 1 for the percentages of cystinosis and control participants who scored below normal limits on these higher-level EF tasks.

Executive Function Behavioral Questionnaire

Before starting any statistical analyses, we examined the Inconsistency and Negativity validity scales of the BRIEF; all BRIEF questionnaires for both the cystinosis and control groups were valid. Compared with age- and SES group-matched controls, the cystinosis group showed significantly higher scores on the Metacognition Index ($F = 11.66$, $P = 0.001$) and the Global Executive Composite ($F = 8.92$, $P = 0.004$), but not on the Behavioral Regulation Index ($F = 0.45$, $P = \text{not significant}$) (Figure 2).

For the BRIEF Behavioral Regulation scales, multivariate analyses showed that the parent ratings for the cystinosis and control groups were not significantly different (Table 2). In contrast, overall MANOVA results indicated that parents rated the cystinosis group as significantly more impaired than the control group on the Metacognition scales. Tests of

between-subjects effects revealed that the cystinosis group had significantly higher scores than controls on each of the individual Metacognition scales (Table 2).

DISCUSSION

Our results indicate that children and adolescents with cystinosis are at risk for EF impairment. Our participants with cystinosis had a higher incidence of executive dysfunction, as assessed by the D-KEFS, than did age- and SES group-matched controls. We found impairments both on higher-level EF tasks and on component tasks that involve more fundamental aspects of EF. The finding that the cystinosis group performed more poorly than matched controls on *all* D-KEFS measures points to pervasive difficulties in EF, rather than to a subtle deficit that is revealed only by the higher-level switching tasks with their increased processing demands. Individuals with cystinosis are at risk for myriad EF impairments, including problems with attention, initiation, motor speed, fluency, simultaneous processing, and speed of processing, in addition to problems with higher-level skills including cognitive flexibility, managing increased processing demands, inhibiting prepotent responses, and abstract thought.

Impairments in fundamental and higher-level aspects of EF have implications for the neurobehavioral phenotype of cystinosis. Our results indicate that individuals with cystinosis may have involvement of frontal systems. Although structural neuroimaging performed in 16 of our 28 children with cystinosis showed that most had no evidence of gross structural abnormalities, it is possible that volumetric analyses would demonstrate differences in frontal lobe morphology or volume reflecting the EF abnormalities. Alternatively, given the distributed neural network that subserves EF, as well as the possibility that metabolic (Besouw et al., 2012; Figueiredo et al., 2009; Gahl et al., 2007; Kessler et al., 2008) rather than structural problems underlie the cognitive manifestations, it is perhaps not surprising that frank structural abnormalities were not visible.

Given the known deficit in visuospatial ability in individuals with cystinosis, it is noteworthy that our cystinosis group performed at about equal levels on both visual and verbal tasks. The 2 subtests on which they performed most poorly, Trail Making and Sorting, are both visual tasks. Because Trail Making is a highly spatial task, it is possible that the cystinosis group's visuospatial deficits interfered with their performance on that task. Sorting, however, is not a spatial task; it is highly conceptual, requiring abstract thinking and reasoning ability. Furthermore, the cystinosis group's performance on other nonvisual and nonspatial tasks was also poorer than the controls', and a considerably higher percentage of the participants with cystinosis scored below normal limits on all of the EF tasks. These findings suggest that the cystinosis group's performance on the D-KEFS was not merely a reflection of their underlying visuospatial deficits.

We did not use intelligence quotient (IQ) as a covariate in this study, for 2 primary reasons. First, tests of intelligence consist in part of tasks that rely on executive skills such as working memory, attention, and problem solving. Second, in writing about IQ in the study of neurodevelopmental disorders, Dennis and colleagues (2009) stated, "The use of IQ as a...covariate has produced anomalous, over-corrected, counterintuitive, and theoretically vacuous findings about neurocognitive functioning." EF is thus most appropriately assessed independent of global IQ, to evaluate most reasonably the skills of reasoning, abstract thinking, cognitive flexibility, and related functions that allow an individual to act independently in decision making and other complex behaviors.

In over 20 years of work with children and families affected by cystinosis, we have learned that these children's learning differences are frequently "missed" by school professionals.

Perhaps this is because their primary deficit tends to be in nonverbal function (Ballantyne & Trauner, 2000; Scarvie et al., 1996; Spilkin et al., 2009; Trauner et al., 2007), which often is not the focus of the academic curriculum, and because the children typically have average IQs and are generally well-mannered. Individuals with normal cognitive abilities (most commonly measured by IQ), especially those with primary medical disorders rather than primary learning and/or cognitive behavioral disorders, may not “raise any red flags” in the school system, and thus school professionals may miss their impaired EF (Little, 1999).

In school settings, assessments usually consist of IQ and achievement tests; these draw more heavily on verbal skills (Delis et al., 2007), which have been found to be a relative strength for individuals with cystinosis (Ballantyne et al., 1997; Spilkin et al., 2007; Spilkin et al., 2009). Delis and colleagues (2007) noted that the risk of having relative strengths in more rote-verbal skills but relative weaknesses in the capacity for abstract, high-level thinking is that these children may be thought of as competent, and thus their areas of weakness are not identified and remediated.

Importantly, EF impairment in individuals with cystinosis may seriously affect their ability to carry out the complex behaviors needed to manage the medical aspects of the disorder. Research in older adults has shown that EF is related to medication adherence (Insel et al., 2006) and individuals with EF deficits may be at risk for failure to take their medication as prescribed. Interventions designed to remediate and/or compensate for these higher-level EF difficulties may be essential to the well-being and independence (Little, 1999) of the individual with cystinosis.

Our BRIEF data suggest that children and adolescents with cystinosis have greater executive dysfunction in the area of metacognition (eg, initiating behaviors, planning and organizing, working memory) than do age- and SES group-matched controls. Although not in the “clinical range,” the metacognition scores were significantly higher in our participants with cystinosis than our typically developing matched controls. The cystinosis participants did not differ from the controls in behavioral regulation. It appears that school-age children with cystinosis have sufficient inhibitory control and behavioral regulation, both necessary precursors of metacognitive executive processes (Gioia et al., 2000); however, when using cognitive self-management and self-monitoring in active problem solving, individuals with cystinosis may demonstrate difficulties. Our BRIEF data suggest that metacognitive difficulties in cystinosis are not caused by a lack of basic emotional and behavioral regulation. Moreover, a recent study found the BRIEF Working Memory scale to correlate with frontal lobe volume in children (Mahone et al., 2009), suggesting a possible neuroanatomic correlate to the EF difficulties in our cystinosis group.

Our results demonstrating EF decrements in individuals with cystinosis, along with previous findings of deficits in tactile perception, visuospatial processing, visual memory, arithmetic, and social competence, indicate that individuals with cystinosis may fit the profile associated with a nonverbal learning disorder (Palombo, 2006; Rourke, 1995c; Voeller, 1986; Voeller, 2005; Weintraub & Mesulam, 1983; Worling et al., 1999). Rourke (1995) suggests that white matter dysfunction may underlie the nonverbal learning disorder syndrome in a number of neurodevelopmental disorders, such as Turner syndrome, fetal alcohol syndrome, and Williams syndrome. It is possible that this pattern of neuropsychological findings is influenced by treatment with cysteamine (Fitzgerald & Dokla, 1989; Justino et al., 1997; Maurice et al., 2009). This scenario is unlikely, however, because cognitive-behavioral data collected years before and after the advent of cysteamine treatment indicate that individuals with cystinosis show specific cognitive deficits, regardless of whether they have been treated with cysteamine (Ballantyne & Trauner, 2000;

Besouw et al., 2010; Trauner et al., 1988; Trauner et al., 2007; Trauner et al., 2010; Ulmer et al., 2009).

Currently, the standard of care for cystinosis is cysteamine treatment. It is not ethically possible to withdraw or withhold this life-extending medication, making it impossible to control for potential medication effects. Moreover, although we did not assess the anatomic correlates of EF in cystinosis, previous research has shown structural brain differences in affected individuals (Bava, 2007; Fink et al., 1989; Levine & Paparo, 1982; Vogel et al., 1990). Future studies of cystinosis should examine the correlations between EF and brain integrity, eg, frontal lobe volume; white matter integrity, especially within the frontal lobes; and fiber tracts that connect the frontal lobes to other brain areas.

The management of a chronic illness such as cystinosis requires individuals to plan, organize, and monitor the medical aspects of their disorder (Von Korff et al., 1997). Self-care relies heavily on EF. Research shows that patient education alone may not be sufficient to ensure adherence, and that active problem solving and behavioral interventions can aid in disease management (Dean et al., 2010; Von Korff et al., 1997). Such practices can turn “knowing what to do” into more reliably “doing it.” In the case of a metabolic disorder, better treatment adherence has implications for health and well-being. Given our findings that individuals with cystinosis are at risk for EF difficulties, often against a backdrop of a normal IQ, the need to design appropriate proactive interventions is paramount. Many neurocognitive strategies are available to aid individuals with similar types of metacognitive problems (Birnboim & Miller, 2004; Franzen et al., 1996; Laatsch, 2001; Nadeau, 1994; Powell & Voeller, 2004; Rourke, 1995b), eg, providing organization and structure, using routines, promoting consistency, breaking large tasks down into smaller steps, employing organizational aids such as planners and checklists, and using behavioral reinforcers to shape behavior (Powell & Voeller, 2004). Technological advances such as personal data assistants and cell phones with alarms and messaging capabilities can be used in formulating behavioral interventions.

Our results also have implications for a greater understanding of brain-behavior relationships. EF is an additional area of potential risk in cystinosis. Current and future MRI studies can help shed light on the brain bases for the cognitive phenotype that we have documented.

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FIGURE 1.

Percentage of participants in the cystinosis and control groups scoring below normal limits (scaled score ≤ -6 ; >1 SD below the mean) on the highest-level executive function condition within each test given from the Delis-Kaplan Executive Function System (D-KEFS). Chi-squared P s = 0.000, 0.076, 0.004, 0.111, and 0.001, respectively. As shown in Table 1, the cystinosis group performed similarly across the conditions of each test; thus, these indices serve as representative exemplars of the group's D-KEFS performance.

FIGURE 2.

Index and Composite scores for the cystinosis and control groups on the Behavior Rating Inventory of Executive Function (BRIEF). Cystinosis vs control group Behavioral Regulation Index P = not significant. Metacognition Index and Global Executive Composite P s < 0.01.

TABLE 1
Performance by the Cystinosis and Control Groups on the Delis-Kaplan Executive Function System (D-KEFS) Tests Given

D-KEFS Test and Condition	Cystinosis (n = 28)		Control (n = 24)		Between Group (Cystinosis vs Control)		Effect Size
	Mean ± SD		Mean ± SD		F	P	
Trail Making (MANOVA)					5.38	0.001	
Visual Scanning	7.57 ± 3.05		10.46 ± 2.36		14.22	< 0.001	0.221
Number Sequencing	7.68 ± 3.60		11.08 ± 1.35		19.11	< 0.001	0.277
Letter Sequencing	7.36 ± 3.51		11.33 ± 2.22		22.92	< 0.001	0.314
Motor Speed	7.79 ± 3.95		11.08 ± 1.50		14.87	< 0.001	0.288
*Number-Letter Switching	6.46 ± 4.18		10.75 ± 2.23		20.27	< 0.001	0.229
Verbal Fluency (MANOVA)					5.93	0.002	
Letter Fluency	8.61 ± 3.12		11.67 ± 3.67		10.57	0.002	0.175
Category Fluency	9.75 ± 2.93		12.04 ± 3.57		6.47	0.014	0.115
*Category Switching (Accuracy)	8.86 ± 2.82		11.46 ± 2.26		13.11	0.001	0.208
Design Fluency (MANOVA)					5.73	0.002	
Filled Dots	8.68 ± 2.82		10.88 ± 2.47		8.79	0.005	0.149
Empty Dots	9.18 ± 3.08		11.75 ± 2.95		9.36	0.004	0.158
*Switching	8.79 ± 3.38		12.33 ± 3.02		15.70	< 0.001	0.239
Color-Word Interference (MANOVA)					5.79	0.001	
Color Naming	8.64 ± 3.29		11.38 ± 2.18		12.00	0.001	0.194
Word Reading	8.21 ± 3.33		11.42 ± 2.21		16.14	< 0.001	0.244
Inhibition	9.00 ± 2.91		12.04 ± 1.85		19.48	< 0.001	0.280
*Inhibition/Switching	8.64 ± 3.59		11.04 ± 3.03		6.65	0.013	0.117
Sorting (MANOVA)					6.04	0.001	
Free Sorting Correct	8.04 ± 2.95		10.46 ± 2.23		10.87	0.002	0.179
Free Sorting Description	7.71 ± 2.93		10.46 ± 2.06		14.76	< 0.001	0.228
*Sort Recognition Description	6.79 ± 3.11		9.63 ± 1.88		15.22	< 0.001	0.233

Significant *P* values (*P* < 0.05) are shown in bold type.

MANOVA indicates multivariate analysis of variance.

* Highest-level executive function condition within each test.

TABLE 2
Performance by the Cystinosis and Control Groups on the Behavior Rating Inventory of Executive Function (BRIEF)

BRIEF Index and Scale	Cystinosis (n = 28)		Control (n = 22)	Between Group (Cystinosis vs Control)		Effect Size
	Mean ± SD	Mean ± SD	Mean ± SD	F	P	
Behavioral Regulation (MANOVA)						
Inhibit (T Score)	49.68 ± 8.61	49.45 ± 8.30	—	—	—	0.000
Shift (T Score)	54.11 ± 8.42	50.95 ± 8.43	—	—	—	0.035
Emotional Control (T Score)	51.25 ± 11.59	50.14 ± 9.36	—	—	—	0.003
Metacognition (MANOVA)						
Initiate (T Score)	56.18 ± 8.17	48.05 ± 8.42	11.89	0.001		0.199
Working Memory (T Score)	58.32 ± 10.53	49.95 ± 11.30	7.30	0.01		0.132
Plan/Organize (T Score)	55.14 ± 9.17	46.41 ± 7.12	13.54	0.001		0.220
Organization of Materials (T Score)	54.61 ± 9.92	47.82 ± 11.54	5.00	0.03		0.094
Monitor (T Score)	54.86 ± 8.67	49.09 ± 10.64	4.46	0.04		0.085

Significant *P* values (*P* < 0.05) are shown in bold type.

MANOVA indicates multivariate analysis of variance; SD, standard deviation; —, scale for which tests of between-subjects effects were not applicable because the multivariate analysis result was not significant.