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Associations Between Medical History, Cognition, and Behavior in Youth With Down Syndrome: A Report From the Down Syndrome Cognition Project

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Abstract

The cause of the high degree of variability in cognition and behavior among individuals with Down syndrome (DS) is unknown. We hypothesized that birth defects requiring surgery in the first years of life (congenital heart defects and gastrointestinal defects) might affect an individual's level of function. We used data from the first 234 individuals, age 6–25 years, enrolled the Down Syndrome Cognition Project (DSCP) to test this hypothesis. Data were drawn from medical records, parent interviews, and a cognitive and behavior assessment battery. Results did not support our hypothesis. That is, we found no evidence that either birth defect was associated with poorer outcomes, adjusting for gender, race/ethnicity, and socioeconomic status. Implications for study design and measurement are discussed.

Keywords

Down syndrome; trisomy 21; cognition; behavior; neuropsychological assessment; intellectual disability; congenital heart defect; gastrointestinal defect; birth defect

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Trisomy 21 results in the constellation of features known as Down syndrome (DS). In all, more than 80 clinical conditions occur more frequently in people with trisomy 21 than in those without the extra chromosome 21, but not all conditions manifest in all individuals (reviewed in Karmiloff-Smith et al. [2016]). Further, a given clinical condition may be highly variable in its severity across individuals. For example, intellectual disability (ID) occurs in nearly everyone with DS, but the range of effects spans from just below average to severely impaired. Although genetic and environmental factors certainly affect this variability, associated factors and their underlying mechanisms are not well understood. This variability represents an enormous challenge in providing precision medicine; that is, providing care for DS at an individual level. By the same token, this variability also offers essential clues into the fundamental processes that underlie the various health conditions.

The study of DS-associated outcomes poses a unique challenge: It is a highly complex genetic condition resulting from the cascading effects of the dysregulation of 500 genes in every cell. Thus, this disorder cannot be effectively approached using the paradigms established for single gene disorders (e.g., cystic fibrosis). Clearly, a unique holistic approach is required for trisomy 21. Given these facts, we have initiated a clinical research infrastructure that will be essential to further the field. This includes a network of assessment sites that integrate basic and clinical research to investigate multiple components of the DS phenotype. This first report from the Down Syndrome Cognition Project (DSCP) focuses on the description of the infrastructure used to phenotype the first 234 participants.

As a first application of the collected DSCP data, we tested the hypothesis that congenital heart defects (CHD) or gastrointestinal (GI) defects explain, in part, the severity of cognitive and behavior outcomes. We focused on birth defects, and specifically CHD, as there is strong evidence that children with CHD who have a euploid chromosome constitution are at increased risk for neurodevelopmental problems (Gerstle, Beebe, Drotar, Cassedy, & Marino, 2016; Latal, 2016; Marino et al., 2012; Triedman & Newburger, 2016). Neurodevelopmental problems due to CHD may occur both prenatally and post-operatively (Donofrio, Duplessis, & Limperopoulos, 2011). To date, studies have shown that CHD influences cognition and behavior in individuals with DS in the early years of their life. Visootsak and her colleagues (2016) conducted direct assessments on 20 toddlers with DS with atrioventricular septal defects (AVSD) (DS+AVSD) cases and 37 toddlers with DS and no heart defect (DS-CHD) controls, all between 12–14 months of age. They found that the group with DS+AVSD, compared with controls, had statistically significant lower scores in all developmental domains including cognition, expressive language, and gross motor function. They also had less optimal home environments and higher parental stress. In a separate study of an older group of toddlers with DS with CHD (DS+CHD: n=12; mean age 31.2 months) and without CHD (DS-CHD: n=17; mean age 32.1 months), those with DS +CHD had lower scores in multiple areas, including fine motor skills and expressive and receptive vocabulary, although differences were not statistically significant (Visootsak, Hess, Bakeman, & Adamson, 2013).

The question of whether these differences persist into later years was explored by Alsaied et al. (2016). They conducted a retrospective chart review of 178 patients with DS, comparing those with heart defects that required surgery in the first year to those without CHDs. The age groups in this cross-sectional analysis included 12 and 24 infants/toddlers (0–2 years) with and without CHD, respectively, 7 and 31 preschoolers (3–5 years), and 26 and 78 school-age children (6–18 years). Similar to Visootsak et al. (2016), they found that infants and toddlers with DS+CHD had significantly lower language scores and marginally significantly lower motor scores as compared with children with DS-CHD. The preschool DS+CHD group also showed language deficits, although the difference between groups was not statistically significant. The older school-age children with DS+CHD did not show differences in any of the cognitive, achievement, or neurodevelopmental scores compared with the DS-CHD group.

In the current study, we used the data from 234 participants to address a similar question, whether a CHD requiring surgery around the first year of life leads to an increased risk for deficits in a school-age population of individuals with DS, ages 6–25 years. As no studies have asked this same question for those with GI structural defects that require surgery, we also used the DSCP to fill this gap.

Methods

Participants and Overview of Design

Individuals with DS were identified through clinics (DS specialty clinics, pediatric cardiology clinics, general genetics clinics), community events/referral (e.g., local DS parent groups), conferences, advertisements, or participation in past research projects by multiple

assessment sites across the United States. Each site obtained their institute's human subjects approval to conduct the project. Each assessment site went through training to standardize recruitment and data collection protocols and ensure quality data. The progress of each site was monitored by the Emory Data Coordinating Center.

Sites were responsible for identifying and screening eligible families. Eligibility criteria included: (1) participant with DS being ages 6–25 years; (2) English as a primary language; (3) documented full trisomy 21 (excluding individuals with chromosome translocations and mosaic trisomy 21); and (4) the biological mother available for participation. The lower age of 6 was set due to the limitation of the test battery (Edgin et al., 2017). The upper age of 25 was defined to avoid complications of mild cognitive impairment related to DS-associated dementia. Medical exclusions included: (1) birth prior to 35 weeks gestation; (2) past head injury resulting in a loss of consciousness greater than five minutes; (3) other brain trauma (e.g., meningitis, bleeds, cerebral palsy, etc.); (4) lack of oxygen at birth; (5) untreated epilepsy or other seizure disorder; (6) history of chemotherapy; (7) accidental poisoning; (8) untreated severe hearing or vision loss; and (9) other chromosomal anomalies. These medical exclusions were in place to avoid other known neurological differences that could have undue influence on the cognitive and behavior outcomes that were not directly attributable to trisomy 21.

Parents provided written consent, and their child with DS provided verbal or written assent, when possible. Once consent was obtained, the following data and samples were collected:

1. parent-report of participant with DS and their medical conditions
2. maternal health and pregnancy history through a phone interview
3. permission to obtain medical records, collection, and abstraction of those records
4. administration of the Arizona Cognitive Test Battery (ACTB), a neurocognitive and behavioral battery of assessments
5. biological sample from the participant with DS (most often venous blood collected during a medically-necessary draw; if a blood draw was not possible, a saliva sample was requested)
6. saliva samples from available biological parents

Families were initially screened for eligibility using a telephone questionnaire (Step 1). A subset was found not to be eligible during Steps 2–4, as each step was not necessarily sequential and each step provided more information about the child. Figure 1 shows the number of families who were involved at the various stages of information collection. For example, some participants completed the in-person testing prior to our ability to obtain medical records. Figure 1 shows that 29 of such participations were found to be ineligibile based on medical records after the testing administration was completed. Three families refused to complete other parts of the protocol, although they did complete testing. Overall, 42% were eligible and completed the in-person testing out of the 556 we attempted to contact. Among those who we were able to contact and who were eligible, 76% completed the in-person testing (234/307; Figure 1).

All biological samples were sent to the Emory laboratory for processing and storage. For blood samples of adequate amounts, lymphoblastoid cell lines were established. DNA was extracted from all saliva samples for future genetic studies. Abstracted medical record forms (in some instances, full medical records that were de-identified) and maternal questionnaires were reviewed by one clinician (G.C.) to standardize and finalize eligibility. These data were also reviewed to provide final diagnoses of medical conditions. A pediatric cardiologist (K.J.D.) reviewed all records associated with heart status to obtain a consensus diagnosis for the type of congenital heart defect. For this study, all participants who completed the first four steps above were included in the analyses ($n = 234$; Figure 1). The demographics of the final study population are provided in Table 1, and the frequencies of birth defects are provided in Table 2.

Measures and Procedures

We used the ACTB, a neuropsychology battery developed to be sensitive to cognitive strengths and limitations of individuals with DS (Edgin et al., 2010, Edgin et al., 2017). It includes measures of memory, executive function, and motor skills to assess cognitive variation in this study. Good test-retest reliability has been demonstrated for the tests in this battery for individuals with DS (Edgin et al., 2017). The test administrators were trained and monitored by Dr. Edgin to ensure that each tester administered the ACTB in a similar manner. Most often, we administered tests at the assessment site, but on some occasions, they were conducted at the participant's home or at another convenient site. The two-hour battery was presented in two fixed, counterbalanced orders as detailed in Edgin et al. (2017). While the child was engaged in the assessment, the parent or caregiver completed standardized parent-report instruments about their child's behavior. Table 3 presents the tests and questionnaires administered, along with the primary outcome measures used in the analyses. Further description of each test is presented in Edgin et al. (2017).

All data were entered and managed through Research Electronic Data Capture (REDCap; (Harris et al., 2009). Each site was responsible for double entry of test results from non-computerized tests and questionnaires. Further quality control measures were completed at the Univerisity of Arizona (J.O.E.; A.P.) for ACTB data.and clinical and demographics at the Emory Data Coordinating Center (T.C.R.; D.H.).

Data Analysis

We focused on two birth defects as possible risk factors that might explain the variation in cognitive and behavioral outcomes: AVSD and structural GI defects (Table 2). Because of our previous work, we were particularly interested in AVSD, a severe heart CHD that must be repaired within the first year of life (Visootsak et al., 2013; Visootsak et al., 2016; Visootsak et al., 2011). We created an indicator variable to define the presence of AVSD, with the referent group defined as those with a structurally normal heart (including those with only patent foramen ovale [PFO] or only patent ductus arteriosis [PDA]); that is, we excluded those with CHD other than AVSD. As a follow-up investigation, we also defined an indicator variable for those with any type of CHD (not limited to those that required surgery) versus the same referent group of those with structurally normal hearts.

We also examined GI defects that required surgery around the time of birth using an indicator variable for those with and without such defects. We considered this type of surgery, like heart surgery, a significant environmental "insult" around the time of birth that might affect cognition or behavior.

For each test administered, we carefully chose the outcome measures for analysis based on their variability and the distribution in our study population. When a standardized score was available and was variable, it was prioritized for use. When a large number of individuals measured on the floor, we instead used raw scores. Thus, we used a mix of the raw and standardized score to ensure that we captured the most variability in the population. For all outcome measures, we provide the median and range calculated from the study sample (Table 4). For measures that were determined to have a normal distribution or could be transformed to normal, we provide the sample mean and standard deviation (Table 4). For some measures, distributions were highly skewed and could not be normalized; thus, they were dichotomized according to the shape of the distribution. For all dichotomized measures, zero indicates better performance and one indicates lower performance. The percentages of those with lower performance are provided (Table 4).

Prior to examining the independent variables of interest (presence of the specified birth defect), we examined the association of the following covariates with each outcome measure to understand their effects on test performance: age at testing (continuous), sex of the participant (female=0, male=1), race/ethnicity (white=0, non-white=1), highest level of education attained by either parent (college degree or more=0, less than college degree=1), household income (>$50,000=0, ≤$50,000=1), initiation of early intervention (≤4 weeks=1, >4 weeks - 12 weeks=2, >12 weeks - 20 weeks=3, >20 weeks=4). We used linear or logistic regression depending on the outcome measure (continuous or binary, respectively). We report those that were statistically significant at $p<0.05$ in Table 4. We also examined the association of site of assessment using an indicator variable for each site and found no statistically significant association with the outcome measures. Thus, this site variable was not included in further models. We also tested for collinearity of covariates in the model and found no evidence of collinearity using both the Variation Inflation Factor and the Condition Index.

For our specific analyses to test whether the medical conditions (any CHD, AVSD, GI defects) were associated with the neurodevelopmental outcome measures, we conducted linear or logistic regression depending on the outcome measure and adjusted for all covariates noted above to be consistent among models. We report all *p*-values without multiple testing corrections, because the goal of this first study of these comprehensive outcome measures among individuals with DS is descriptive in nature. However, we caution the reader that a moderate number of tests were performed and there will be greater than 5% rate of false discovery study-wide. SAS version 9.4 was used for all statistical analyses.

Results

Sample Descriptive Characteristics

Figure 1 shows the number of participants at each step of the protocol, from identification of the individuals with DS through to their completion of the entire protocol. A participation rate was difficult to define, as each site had different methods of identifying possible participants (e.g., clinical or community referral). None were population-based. Of the 428 who we were able to contact and invite into the study, 194 did not enroll or did not complete the protocol. Of those, 5% could not be located after the first contact, 57% were not eligible, and 38% refused. Of the families who refused, 14% stated they were too busy, 8% said it was too far to travel, 9% thought their child could not do the testing, 3% did not want to provide biological samples, 26% were passive refusals (i.e., they never completed the full protocol), and the remainder (40%) did not provide a reason. Of the families that were not eligible, 16% of the children were adopted or the biological mother was not available, 8% were not English-speaking, 19% were outside the age limit, 15% had a gestational age <35 weeks, 32% had a medical exclusion, and 10% were not full trisomy 21 or had additional chromosome abnormalities.

The demographics of the 234 families who completed testing are provided in Table 1. On average, participating families tended to be educated with a college degree or higher, had a relatively high household income, and self-reported as Caucasian. The majority of the families started early intervention for their child with DS prior to three months of age.

The frequency distributions of the presence of CHD or GI defects are provided in Table 2. With respect to CHDs, about 46% of participants had a structurally normal heart (those with only a PDA or PFO were included in this group) and about 19% had an AVSD. These frequencies are similar to those that we found in a U.S. population-based sample of live births with DS (Freeman et al., 2008). About 13% had a GI structural defect that was severe enough to require surgery. This figure is slightly higher than that found in our previous population-based study, 6.7% (Freeman et al., 2009), probably due to small numbers in the present study. The absolute numbers for AVSD (n=42) and for GI defects (n=29) out of the total were relatively small; thus, results on their effects on cognition and behavior must be interpreted with caution.

Covariates Associated with Neurodevelopmental Measures

Age at testing—As expected, age at testing was a significant variable for almost all cognitive outcome measures that were based on raw scores (Table 4), where older individuals had better performance. Some domains of the parent-reported behaviors, however, were not associated with age at testing: NCBRF (Insecure/anxious, Overly sensitive and Ritualistic) and Social Communication Questionnaire (SCQ) total score.

Sex—For some measures, the sex of the participant was statistically significant in the models (Table 4). For the KBIT-2 metrics of cognition, 2% of the variance for Riddles subtest (p=0.02) and 4% of the variance for Matrices subtest (p=0.004) was explained by sex, where males appeared to perform worse than females, on average. Similarly, for scales

of adaptive behavior (SIB-R) (5% of the variance, $p<0.001$) and Behavior Regulation Index of the BRIEF (2% of the variance, $p=0.05$), parents endorsed more problems among males, on average, than females. For the NCBRF behavior measures, parents reported that males, on average, had problems more often than females on the Adaptive/social scale (5% of the variance explained, $p=0.0002$) and the Compliance scale (2% of the variance, $p=0.05$). Only for the scale of Overly Sensitive did parents endorse this trait more often for females than males (odds ratio (OR)=0.43; 95% confidence interval (CI): 0.23–0.83).

Socioeconomic status and initiation of early intervention—Lower income was statistically associated with lower scores on the KBIT-2 Riddles (2% of the variance, $p=0.01$) and worse performance on the CANTAB SSP measure of Span Length (4% of the variance, $p=0.005$) (Table 4). For the parent-reported measures, lower income was statistically associated with adaptive behavior (SIB-R, 6% of the variance, $p=0.003$) and social communication (SCQ, 6% of the variance, $p=0.003$) in the direction of lower income leading to greater endorsement of problems. For measures of behavior on the NCBRF, only the Ritualistic score was associated with another covariate beyond the age at testing and sex: Parents with lower education (less than college) reported that their child had more ritualistic behaviors ($OR=0.15$; 95% CI: 0.36–0.67).

Only two measures were associated with later initiation of early intervention and both in the direction of later initiation with poorer performance (Table 4). For the measure of spatial associative memory (CANTAB PAL, total errors adjusted) the time at which intervention was started explained 3% of the variance ($p=0.03$). For the measure of simple reaction time (CANTAB SRT) commission errors, the OR associated with later intervention was 1.32 (95% CI: 1.01–1.74).

Birth Defects as Predictors of Neurodevelopmental Measures

Figures 2 and 3 provide the summary of the results from the regression analyses to test the hypothesis that having a specific birth defect is associated with poorer performance on cognitive or behavioral outcomes, after accounting for all covariates. Twenty outcome measures were examined to test whether the presence of a birth defect explained a portion of the variance in scores. For presentation, we provide the direction of the association to indicate worse or better performance for those with the birth defect compared with those without the birth defect, along with the –(log(p-value)) for the related beta coefficient.

For the presence of any CHD, and specifically for AVSD which requires surgery around the time of birth, we found no association with outcome measures (i.e., all –(log(p-value) were close to the horizontal zero line, Figure 2). The association of better performance on the KBIT-2 Riddles, a measure of verbal comprehension, reasoning, and vocabulary knowledge, was statistically significant at $p=0.03$ with the presence of AVSD. However, the amount of variance explained was minimal, only 1.4%, after adjusting for covariates.

For GI defects, we found an association that explained 6.7% of the variance of the BRIEF Metacognition Index at the level of $p=0.0006$, where parents of participants with a GI defect reported fewer problems compared with parents of those without GI defects. This index measures an individual's ability to initiate, plan, organize, self-monitor, and sustain working

memory. We conducted a secondary analysis to determine which of the subscales that make up the Metacognition Index (Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor scales) contributed to the suggested association. We found that the presence of a GI defect was associated with Plan/Organizing (4.9% of the variance, p=0.003), Organization of Materials (2.1% of the variance, p=0.04), Working Memory (2.7% of the variance, p=0.016), and Self-Monitoring (3.8% of the variance, p=0.004). All were positively associated with better performance when the GI defect was present. Thus, parent-report of their children's metacognitive executive function skills appears to be associated with fewer impairments in the presence of a GI structural defect.

Discussion

The DSCP has completed its first goal to examine the variation in cognitive and behavioral outcome measures using the ACTB modified battery, one that was specifically developed to assess the strengths and limitations of individuals with DS. Although it is difficult to determine whether this cohort is representative of the larger population of individuals with DS in this age range of 6–25 years, we made significant efforts to enroll a representative sample and eliminate several potential confounding factors. First, we had several eligibility criteria (see Methods) that need to be recognized, including the following: (1) full trisomy 21, (2) birth after 35 weeks gestational age, (3) no major brain trauma prior to testing and (4) English as the primary language. The first three were implemented because a primary goal of the study is to identify risk factors that play a role in the severity of cognition and behavior and we wanted to rule out factors for which we knew could influence function. The restriction for English-speaking participants was a limitation of our ability to administer the tests in other languages.

With respect to participation rates, we can roughly estimate that among those who were screened and eligible, 76% completed the battery. Although we are unable to calculate the more typical participation rate (those completing the battery divided by those initially contacted), we think that the low refusal rates during the enrollment process suggest that this cohort may be representative of the overall population. This is further indicated by the rates of CHD found in this cohort compared with population-based studies. The overall demographics of those who completed the testing show that participants come from a somewhat heterogeneous group of families with respect to race/ethnicity, education, and income (Table 1). Thus, with some caution, we suggest that we can extend our findings to the broader community.

The ACTB is well validated for individuals with DS, and the majority of tests have been proposed as excellent outcome measures that could be used in clinical trials to show efficacy of interventions (Edgin et al., 2010; Edgin et al., 2017). Here we used a modified version of the ACTB to capture the variation in function to begin to define factors—genetic and environmental—that influence severity. Not surprisingly, we found that it is important to consider covariates, beyond age at testing, for several of the tests when investigating predictors of interest (Table 4). However, if we use the recommended minimum effect size of R^2 = 0.04 or OR=2.0 to represent a "practical" significant effect for social science data (Ferguson, 2009), we find that the majority of statistically significant covariates had smaller

effect sizes and thus are of limited clinical relevance. However, they should be considered at the analytical level to ensure that the ability to detect a statistically significant signal of the predictor variable of interest is maximized.

We did find that the effect size of components of socioeconomic status (household income and education) were relevant for some parent-reported behaviors, based on the above criteria. For example, parents with lower household income endorsed more SIB-R and SCQ problems than those with higher incomes (explaining 6% of the variance in parent-reported behaviors). Lower education was associated with parent endorsement of Ritualistic behaviors (NCBRF)(*OR*=0.15). Again, these results are important properties that need to be considered when testing for associations of performance among those with DS. They may also point to the need to target support to families with individuals with DS who have fewer resources.

We used clinical information abstracted from medical records to examine the effect of AVSD and structural GI defects, both of which are surgically repaired early in life. Adjusting for covariates, we did not find evidence for an association of the presence of these birth defects and lower performance in individuals with DS ages 6–25 years, contrary to our hypothesis. The one finding that should be highlighted is presence of GI defects and its association the stronger metacognitive executive function, as measured by the parent-reported BRIEF Metacognition Index, which explained about 6.7% of the variance (p=0.0006, Figure 3). There are at least two possible explanations. One could be that children with GI defects may have to learn dietary management skills early in life to cope with associated GI problems. Thus, they would gain early life experiences associated with planning,organizing and self-monitoring. Another possible explanation is parent response bias. Similarly, Wochos, Semerjian, and Walsh (2014), used the BRIEF to compare executive function outcomes in pediatric brain tumor survivors compared with healthy children. They found that parents endorsed far fewer problems than teachers among the survivors. They suggested that parents of survivors may adjust to their child's needs, may provide a higher level of support, or may diminish the child's disruptions in the home setting. This type of parent response bias may be a potential for children with DS who have made it through a significant surgery in the first year of life. However, this finding warrants further investigation, especially because we did not see this same pattern for those with AVSD and this measure.

Whatever the explanation, our results suggest that having an AVSD or a GI structural defect does not significantly predict worse cognitive or behavioral outcomes in school-age children with DS. These results are similar to those found by Alsaied et al. (2016) in their retrospective chart review of children with DS+CHD. As discussed earlier, significantly lower cognitive performance was observed for those with DS+CHD compared with DS-CHD during the first years of life (Alsaied et al., 2016; Visootsak et al., 2011; Visootsak et al., 2013; Visootsak et al., 2016;). Thus, perhaps with early intervention, children are able to overcome associated problems. One might ask why there is a difference in observations among those with CHDs who do or do not have DS. The neurodevelopmental and later cognitive deficits among children with CHD and a normal chromosome constitution are reported to be relatively subtle (Gerstle et al., 2016; Latal, 2016; Marino et al., 2012;

Triedman & Newburger, 2016). Perhaps the cognitive impairment caused by trisomy 21 masks the effects of impairment caused by an abnormal heart.

Once confirmed, the implications of our findings are particularly relevant in two ways. First, in terms of study design, our findings suggest that it is important to include variables associated with participant demographics (e.g., sex, age at testing, household income, education level of parents, and timing of early intervention) in statistical models in order to sharpen a signal related to a variable of interest. Although the amount of variation explained per covariate may be small, it is significant. Taking together the effects of covariates that we used in our statistical models, they explained about 12–15% of the variance in an outcome measure (not including age at testing for raw scores). Second, our results are consistent with the study of Alsaied et al. (2016) who also found no significant association of presence of a DS-associated CHD and level of impairment. This finding could be reassuring to families who care for children with DS who have severe birth defects treated early in life.

There are several limitations in our study. First, even though this is the largest sample size to date with such comprehensive phenotype data, it is limited in its power to detect small effect sizes of limited clinical relevance when examining a large number of outcomes. We conservatively estimated that with a sample size of 200, we could detect with 80% power a predictor variable that explains 6% of the variance, adjusting for covariates, at a significance level of 0.0025 (adjusting for 20 tests). Thus, our findings suggest that we can rule out moderate to large effect sizes related to the presence of severe birth defects playing a role in the level of impairment in individuals with DS. Also, because of the relatively small sample size and the fact that families belonged to a convenience sample, drawn from the community and from specialty clinics, we cannot state conclusively that this sample represents the general population of families with DS. A population-based cohort study would be important to confirm our results.

Second, any test battery has its limitations and ours is no exception. We used one based on the ACTB, which was developed and validated to assess the specific cognitive profile of individuals with DS. However, we know that our current battery is lacking in tests of executive function and language, as noted most recently in Edgin et al. (2017). We have now improved the battery by filling these gaps and are currently piloting its administration in our second phase of data collection.

Lastly, it will be important to incorporate the genetic information to determine whether there is a subset of individuals who may be more susceptible to the effects of birth defects or whether there are pleiotropic effects. For example, we and others have found evidence for the ciliome to be involved in DS-associated AVSD (Ramachandran et al., 2014; Ramachandran et al., 2015; Ripoll et al., 2012). For those who carry mutations in this pathway, perhaps they will be predisposed to more impaired cognitive function due to the perturbed function of primary cilia. Again, increased samples sizes are needed to identify these important risk factors that explain the wide variation in cognition and behavior among individuals with DS. Identification of genetic factors that explain this variation and perhaps explain specific associated phenotypes (e.g., behaviors associated with ASD or severe cognitive impairment) will potentially lead to the discovery of important underlying

biological pathways. This will be the first step towards individualized treatment strategies. We think that the DSCP serves as a foundation for a larger collaborative effort to collect genotype and phenotype data to achieve these goals.

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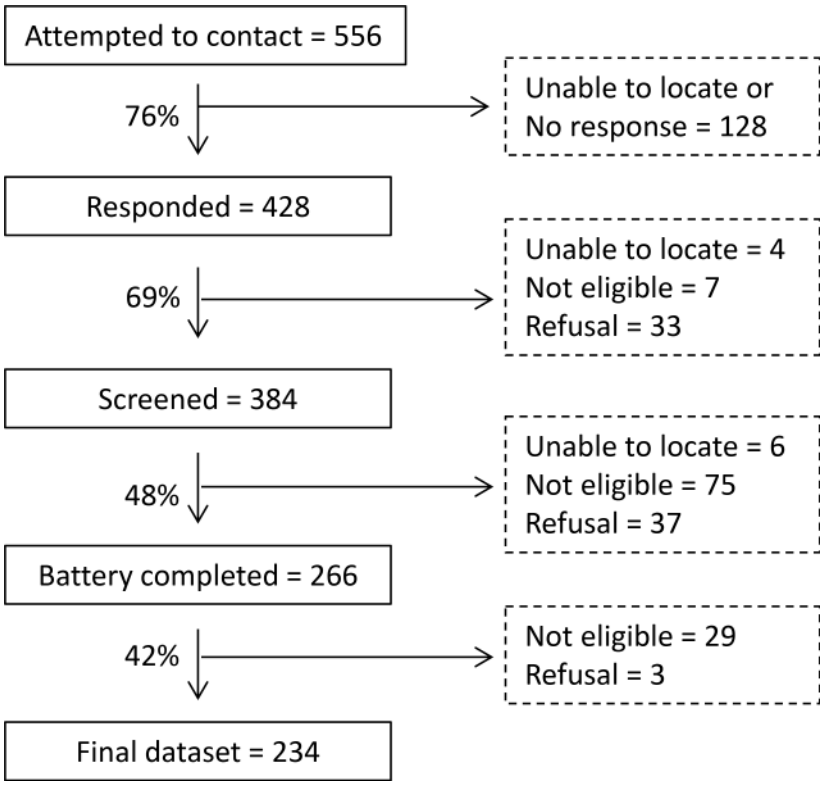

Figure 1.

Summary of the study protocol and number of participants engaged at each step. Frequencies to the left of the arrows are based on all families that were attempted to be contacted. The participation rate based on those who could be contacted and were screened eligible was 76% (234/307).

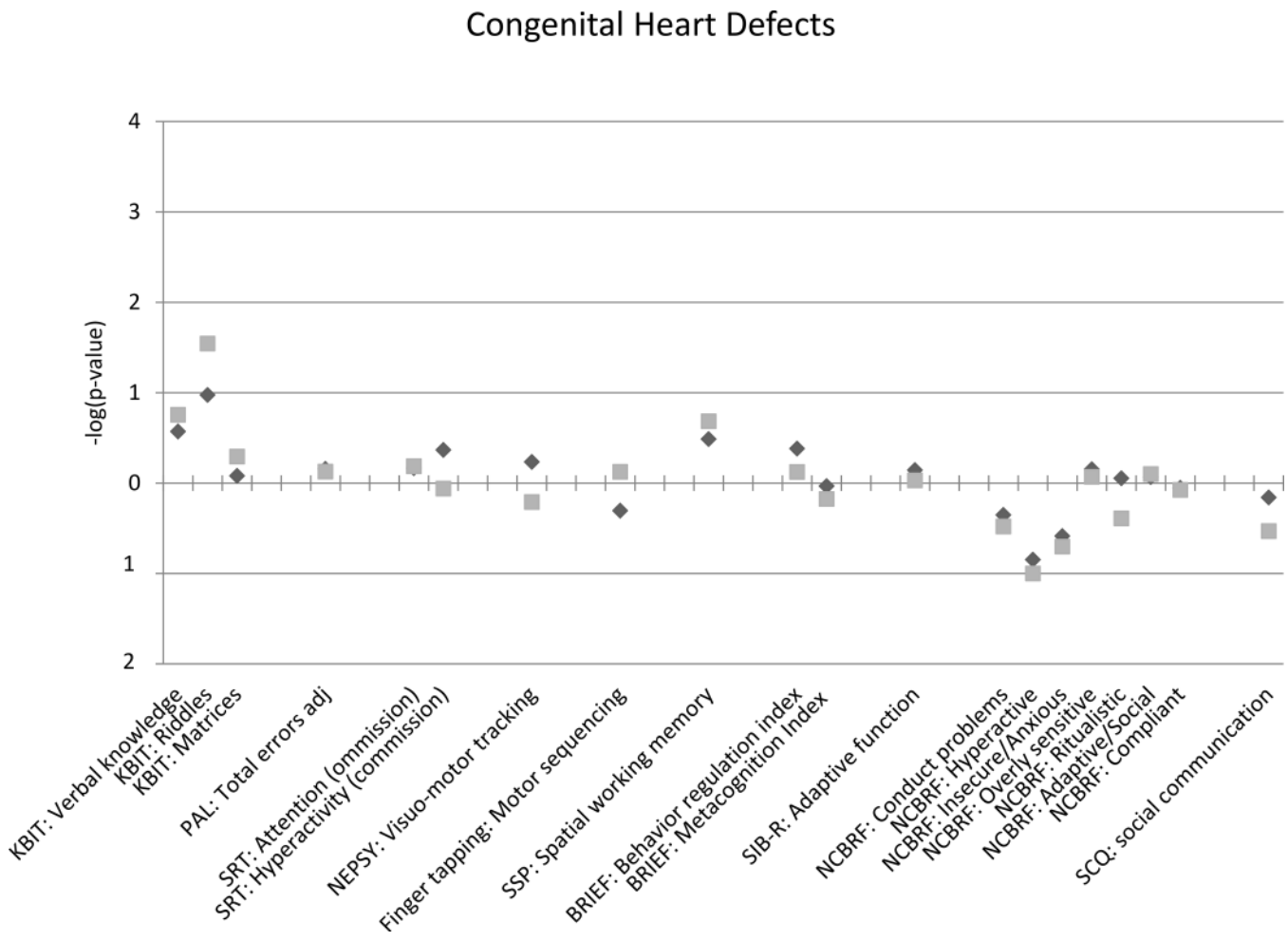

Figure 2.

Results from the regression analyses examining the association of the presence of any congenital heart defect (CHD, diamonds) or specifically atrioventricular septal defects (AVSD, square) with continuous (linear regression) or dichotomized (logistic regression) cognitive and behavioral outcome measures. -log (*p*-values) are provided for the beta coefficient of variable defining absence (=0) and presence (=1) of the CHD, adjusting for the following covariates: age at testing, sex of the participant, race/ethnicity, highest level of education attained by either parent, household income, initiation of early intervention. –log (*p*-values) above the zero horizontal line denote better performance on the outcome measure among those with a CHD and –log(*p*-values) below the zero horizontal denote worse performance among those with a CHD.

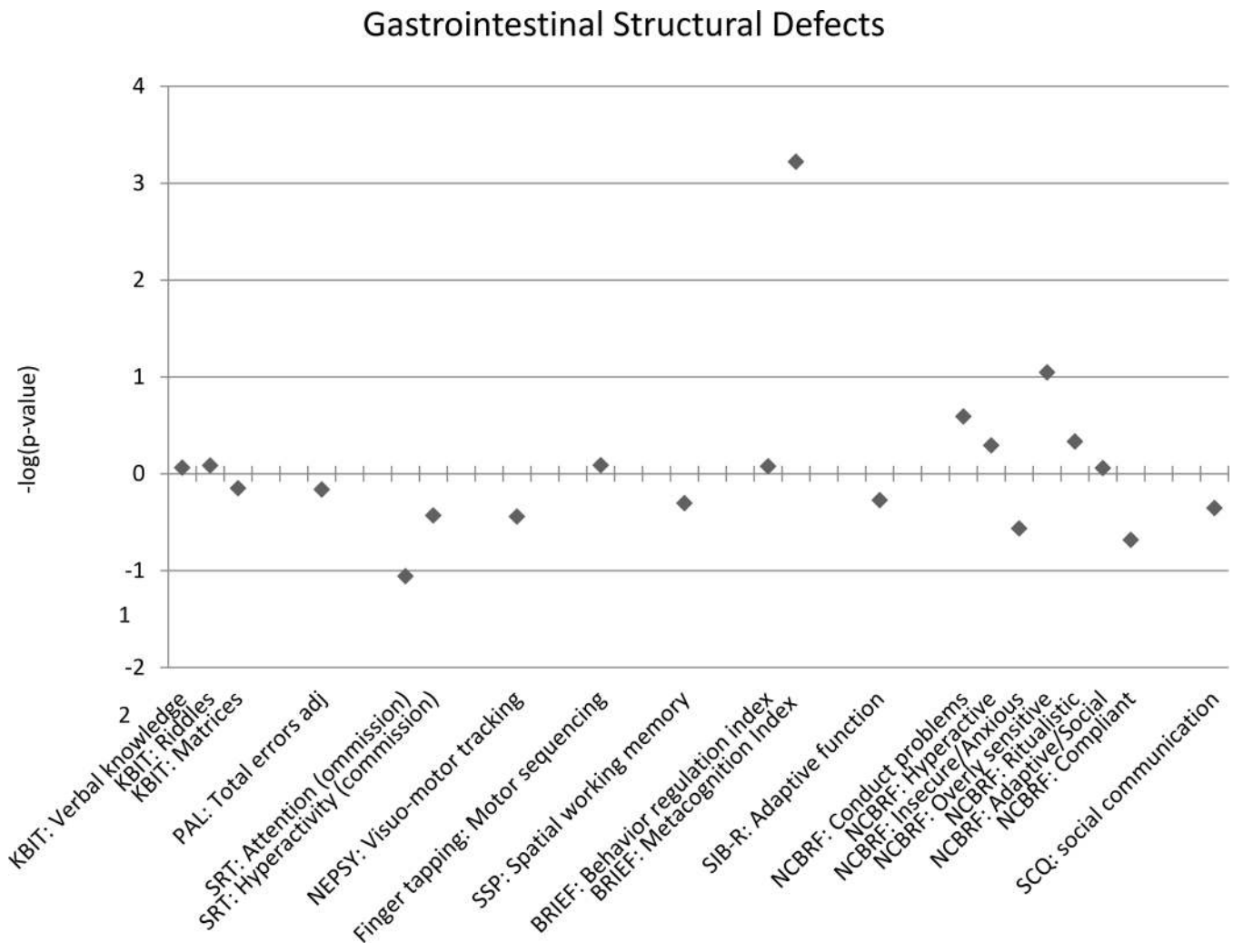

Figure 3.

Results from the regression analyses examining the association of the presence of a gastrointestinal (GI) structural defect requiring surgery with continuous (linear regression) or dichotomized (logistic regression) cognitive and behavioral outcome measures. -log (*p*-values) are provided for the beta coefficient of variable defining absence (=0) and presence (=1) of a GI structural defect, adjusting for the following covariates: age at testing, sex of the participant, race/ethnicity, highest level of education attained by either parent, household income, initiation of early intervention. –log (*p*-values) above the zero horizontal line denote better performance on the outcome measure among those with a GI defect and –log(*p*-values) below the zero horizontal denote worse performance among those with a GI defect.

Table 1

Description of the Study Participants

		Percent	Mean	Standard deviation	Median	Range
Participants with DS (*n*=234)						
	Age at testing (years)		13.49	4.53	12	6 – 25
	Sex					
	Female	48.3%				
	Male	51.7%				
	Race					
	White	72.6%				
	Black	8.1%				
	Hispanic	3.4%				
	Asia/Pacific Islander	0.9%				
	Other	15.0%				
	Weeks since birth to enter early intervention (9 missing)					
	≤4 wks	27.1%				
	5–12 wks	37.3%				
	13–20 wks	8.9%				
	>20 wks	26.7%				
Parents (*n*=234)						
	Maternal age		34.35	5.42	35	18 – 45
	Paternal age (8 missing)		35.80	5.63	36	19 – 55
	Household Income (3 missing)					
	<$25,000	3.0%				
	$25,000 – $50,000	9.5%				
	$50,000 – $75,000	19.0%				
	$75,000 – $100,000	15.2%				

		Percent	Mean	Standard deviation	Median	Range
	>$100,000	53.2%				
	Highest education level of either parent (1 missing)					
	0–11 years	0.4%				
	Completed high school	4.7%				
	Earned GED	1.3%				
	Completed technical school	2.2%				
	Completed 1–3 years college	9.0%				
	4 Years of college or Bachelor's degree	41.2%				
	Master's degree	26.2%				
	Higher than Master's (MD, PhD, JD)	15.0%				

Table 2

Percentage and Sample Size of Those with Birth Defects

	Percent	*N*
Congenital heart defect (CHD) (8 missing)		
No CHD (including those with only patent foramen ovale or only patent ductus arteriosis)	46.0%	104
Any CHD	54.0%	122
Atrioventricular septal defect only	18.6%	42
Total		226
Gastrointestinal (GI) structural defect (7 missing)		
No structural GI defect	87.2%	198
Structural GI defect	12.8%	29
Total		227

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Table 3

Description of Neurodevelopmental Tests with the Variables Used as Outcome Measures in Data Analyses

Domain/Measure	Primary Ability Assessed	Outcome Variable	Score Type
Admistered Assessments			
CANTAB Paired Associates Learning (PAL)	Spatial associative memory	Total errors adjusted	Raw
CANTAB Simple Reaction Time (SRT)	Motor response time and attention	Total omission errors	Raw
		Total commission errors	Raw
Finger Sequencing Task (Edgin & Nadel, unpublished paradigm)	Motor sequencing	Maximum sequence reached	Raw
NEPSY Visuomotor Precision (ages 3–4) (Korkman, 1998)	Visuo-motor tracking, hand-eye coordination	Total score (generated from a combination of completion time and number of errors)	Raw
Kaufman Brief Intelligence Test-2nd ed. (KBIT-2) (Kaufman and Kaufman, 2004)	Verbal comprehension, production, and problem solving	Verbal knowledge	Raw
		Riddles	Raw
		Matrices	Raw
CANTAB Spatial Span (SSP)	Immediate memory for spatial-temporal sequences	Span length	Raw
Parent Report Measures			
Scales of Independent Behavior- Revised (SIB-R) (Bruininks et al., 1996)	Adaptive behavior	Composite	Standard
Behavioral Rating Inventory of Executive Function-School Age (BRIEF) (Gioia et al., 2000)	Domains of prefrontal function, behavioral regulation, and metacognition	Behavioral Regulation Index	Standard
		Metacognition Index	Standard
Nisonger Child Behavior Rating Form-Parent (NCBRF) (Aman et al., 1996)	All scales used (see Outcome Measures) except Self-Injury/Stereotypic behavior due to poor retest reliability and low frequency of such behaviors	Conduct Problems	Raw
		Hyperactivity	Raw
		Insecure/Anxious	Raw
		Overly Sensitive	Raw
		Ritualistic	Raw
		Social Adaptive Skills	Raw
		Compliance	Raw
Social Communication Questionnaire-Lifetime (SCQ) (Rutter et al., 2003)	Developmental history and current behavior indicating autism spectrum disorder risk	Total score	Raw

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Table 4:

Description of the Distribution of Neurodevelopmental Outcome Measures and Statistically Significant Associated Covariates Identified in Regression Models

Outcome Measure	Age group	N	Median	Range	Continuous traits[b]		Dichotomized traits[b]	Significant covariates[c]
					Mean	Standard deviation	Percent with poorrer performance	
Administered Assessments								
CANTAB PAL: Total errors adjusted	>10 yrs	170	66.5	1 – 220	94.88	78.23		Intervention
CANTAB SRT: Total omission errors >0	all	219	0	0 – 49			49.3%	Age
CANTAB SRT: Total commission errors >4	all	219	5	0 – 85			50.7%	Age, Intervention
Finger Sequencing Task: Maximum sequence <4	>10 yrs	169	4	1 – 4			18.9%	none
NEPSY Visuomotor Precision: Total Raw Score	all	222	15	1 – 23	13.72	5.66		Age
KBIT-2: Verbal knowledge	all	234	15	0 – 35	14.79	8.29		Age
KBIT-2: Riddles	all	234	10	0 – 27	10.03	5.66		Age, Sex, Income
KBIT-2: Matrices	all	234	13.5	0 – 29	12.37	6.21		Age, Sex
CANTAB SSP: Span length	all	208	3	0 – 6	2.41	1.71		Age, Income
Parent report								
SIB-R: Composite score[a]	all	228	59	0 – 115	55.09	24.20		Sex, Income
BRIEF: Behavioral Regulation Index[a]	<19 yrs	199	58	35 – 90	57.91	10.38		Sex
BRIEF: Metacognition Index[a]	<19 yrs	190	62	33 – 83	61.63	9.31		none
NCBRF: Conduct problems	all	232	6	0 – 30	7.34	5.91		Age
NCBRF: Hyperactive	all	232	6	0 – 21	6.55	4.49		Age
NCBRF: Insecure/anxious ≥6	all	232	3	0 – 17			27.6%	none
NCBRF: Overly sensitive ≥5	all	232	3	0 – 14			24.1%	Sex
NCBRF: Ritualistic ≥6	all	232	3	0 – 17			22.0%	Education
NCBRF: Adaptive/social	all	232	7	2 – 12	7.19	2.05		Age, Sex
NCBRF: Compliant	all	231	12	6 – 18	11.64	2.77		Age, Sex
SCQ: Total Raw Score	all	169	8	0 – 28	8.80	5.82		Sex, Income

Note:

[a] Age-standardized score.

[b] For variables with normal distributions, the mean and standard deviation are provided. For those that could not be normalized, the dichotomized variable is described and the percent of individuals with the poorer performance is provided.

[c] Covariates included in all models included: Age at testing (continuous), sex of the participant (female=0, male=1), race/ethnicity (white=0, non-white=1), highest level of education attained by either parent (college degree or more=0, less than college degree=1), household income (>$50,000=0, ≤$50,000=1), initiation of early intervention (≤4 weeks=1, >4 weeks - 12 weeks=2, >12 weeks - 20 weeks=3, >20 weeks=4). Those that were statistically significant at $p<0.05$ are listed.

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