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Executive Function in Autism Probands With Average Intellectual Ability and Their Unaffected First-Degree Relatives

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Abstract

Objective—This study aims to characterize executive function (EF) in pedigrees of children with autism spectrum disorder (ASD) with average IQ. We examine the hypothesis that deficits in EF relate to lower levels of adaptive functioning, and we assess evidence for a cognitive extended phenotype in unaffected relatives in a large, well-characterized sample.

Method—Proband EF was assessed via parent report questionnaires (Behavior Rating Inventory of Executive Functioning [BRIEF], n=109) and child neuropsychological tests (Delis-Kaplan Executive Functioning System [DKEFS], n=35). EF was also examined in parents (D-KEFS, n=335) and unaffected siblings (BRIEF, n=114; DKEFS, n=57). Adaptive functioning was assessed via the Vineland Adaptive Behavior Scales- II (VABS-II, n=155). All data were obtained from the Autism Consortium Clinical Genetics Database.

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Results—Individuals with ASD demonstrated a high burden of EF weaknesses. Multiple regression analyses revealed that parent-reported EF deficits were related to profound reductions in adaptive functioning even after controlling for age, IQ, and severity of ASD symptoms. Parent-reported EF was also related to adaptive skills in preschoolers. First-degree unaffected relatives did not demonstrate difficulties with EF relative to normative data.

Conclusion—In our study, EF impairments do not appear to relate to broad familial risk factors for ASD but may be associated with factors relevant to the expression of ASD in probands. Results support the benefits of EF assessment as a way to identify potential therapeutic targets that could lead to improved adaptive behavior among children with ASD and average IQ.

Keywords

Autism Spectrum Disorder; Executive Functioning; Adaptive Functioning; IQ; Pedigree

INTRODUCTION

Autism Spectrum Disorder (ASD) is characterized by impairments in social communication and social interaction and by restrictive and repetitive behaviors. [1] Individuals with ASD vary considerably in levels of cognitive and adaptive functioning.[2] Adaptive behavior is a person's ability complete daily activities independently and includes skills related to communication, interpersonal relationships, and self-care.[3] Although adaptive function is strongly associated with general cognitive ability (IQ), executive function (EF) may account for substantial variability in adaptive function among individuals with ASD who have average IQ.[4,5] Specifically, while EF dysfunction does not appear to cause ASD symptomology, EF deficits are thought to impact later adaptive functioning among individuals with ASD.[6]

EF encompasses a wide range of skills including shifting of attention, mental flexibility, inhibition, self-control, impulsivity, initiation, working memory, and planning.[7,8] In conceptualizing specific EF domains, Miyake and colleagues[9] report a three-factor structure of EF that consists of “Shifting,” “Updating,” and “Inhibition.” “Shifting” involves mental flexibility in shifting set and generating novel responses. “Updating” involves continuous monitoring of potentially relevant information and updating working memory with this information when it is deemed to be relevant. “Inhibition” involves control over automatic responses. Among individuals with ASD, there is evidence to support a range of EF weaknesses,[8] presenting as early as preschool age.[10] Impairments in EF may contribute to the social deficits observed in individuals with ASD.[11] For example, difficulties in Shifting are thought to underlie weaknesses in joint attention and reciprocity,[12] deficits that are particularly prominent in individuals with ASD.[13] Weaknesses in the area of Updating are thought to underlie difficulties tracking conversations,[4,14] following social norms and responding appropriately,[4] and attending.[15] The ability to inhibit inappropriate impulsive behaviors is also essential in social interactions,[4] and poor inhibitory control is linked to repetitive and restricted behaviors.[16]

In addition to deficits in EF, individuals with ASD show a wide range of impairments in adaptive functioning. After controlling for IQ, adaptive deficits still present in individuals with ASD and average intelligence.[17] One possibility is that adaptive impairment is simply a correlate of ASD symptomatology. However, only weak associations were found between ASD symptoms and Vineland Adaptive Behavior Scales (VABS-II) abilities in the areas of socialization and communication[18] and daily living skills.[19] Moreover, a study of over 1,000 individuals with ASD found that ASD symptoms severity did not significantly correlate with any of the VABS-II composites.[20] This research suggests that adaptive impairment is more than a correlate of ASD symptoms.

Examining EF in unaffected relatives allows for a more complete understanding of the mechanisms underlying reduced EF in individuals with ASD. In general, findings of extended phenotypes may have implications for understanding the etiology of neuropsychiatric illnesses,[21] including ASD. Some researchers have posited that an "extended phenotype" may exist in ASD, where parents, siblings, or other relatives may have subclinical difficulties in the same areas or carry genes that contribute to the expression of ASD and/or related cognitive symptoms, without meeting diagnostic criteria.[22] To support this argument in EF, there is some evidence that parents and unaffected siblings of children with ASD may have specific weaknesses in EF. [23-26] However, in most studies probands had diminished IQs, largely IQ < 70. In contrast, in two samples of higher-functioning children with ASD, few differences were found in EF between parents, unaffected siblings, and comparison groups.[27,28] However, these two studies used relatively few measures of and were limited by small sample size and lack of gold-standard instruments in diagnostic validation of ASD[28] or findings of no EF deficits in probands,[27] limiting the ability to detect EF as an extended phenotype.

We sought to assess the relationship between EF and adaptive behavior in a large sample of individuals with ASD and average IQ. While questionnaires served as a primary outcome variable, these relationships were also explored with neuropsychological tests assessing EF. We also examined the presence of an extended ASD phenotype involving EF impairment in parents and unaffected siblings from simplex and multiplex families with ASD.

METHOD

Participants

Probands were 168 individuals (135 males) from the Autism Consortium Clinical Genetics Database for whom IQ was greater than 70. Participants in this database were recruited from a collaborative network of 5 hospitals where clinical assessments for ASD are conducted. All measures were administered by doctoral-level psychologists or highly trained research assistants. For diagnostic measures (e.g., the Autism Diagnostic Observation Schedule [ADOS], the Autism Diagnostic Interview-Revised [ADI-R]), examiners had obtained research reliability. Screening to ensure that parents and unaffected siblings did not have ASD was completed through the use of the Social Responsiveness Scale and the Social Communication Questionnaire. Out of the larger sample of participant data that was available from the database (i.e., 529 probands who received the ADI-R), we selected a subset of probands (n=175) who had received a Wechsler IQ measure (Wechsler Abbreviated Intelligence Scale [WASI], Wechsler Intelligence Scale for Children-Fourth Edition [WISC-IV], or the Wechsler Preschool and Primary Scale of Intelligence – Third

Edition [WPPSI]). Average age was 9.4 years (SD=4.65). Probands were primarily Caucasian (87.5%) with smaller proportions of Hispanic (3.6%), American Indian or Alaskan Native or Caucasian (2.4%), Asian (3%), African American (1.8%), and unknown or other (3.6%).

All unaffected family members of these probands (341 parents, 285 from simplex families and 55 from multiplex families, and 114 siblings) were included. Average parental age was 41.56 years (SD=7.11). One hundred fourteen unaffected siblings (48 males) were included. Average sibling age was 9.0 years (SD=4.98).

Measures

ASD Diagnosis and Symptom Severity—ASD diagnoses were confirmed through the use of the ADI-R, a standardized, caregiver interview, and the ADOS, a standardized, interactive play-based assessment, both of which evaluate symptoms of ASD relating to communication, reciprocal social interaction, and stereotyped behavior and restricted interests, and have strong reliability and validity.[29,30] For the ADI-R, both the classic and the Risi[31] modified algorithms were used. In addition, the ADOS-calibrated severity score[32] was utilized as a measure of severity of ASD symptoms. This scale ranges from 1-10, with higher scores representing greater severity of ASD symptoms; participants in this study had an average severity score of 7.87 (SD=1.92).

Executive Functioning—The BRIEF is a parent questionnaire for assessing EF in children ages 5 to 19. For this study two composites, the Behavioral Regulation Index (BRI), containing the scales Inhibition, Shifting and Emotional Control, and the Metacognition Index (MI), containing the scales Initiation, Working Memory, Planning/Organization, Organization of Materials, and Monitoring of Behavior, were utilized. Performance was compared to age-matched normative data. The BRIEF standardization sample includes 1,419 parent ratings and has good reliability and validity.[33] The BRIEF-Preschool (BRIEF-P) is used with children aged 2 to 5. The three composite scales are Inhibitory Self-Control (comprised of Inhibit and Emotional Control), Flexibility (comprised of Shift and Emotional Control) and Emergent Metacognition (comprised of Working Memory and Planning/Organization). The instrument has good reliability and validity.[34] On both BRIEF measures, T-scores of greater than 65 represent clinically significant problems, and higher scores represent poorer EF.

The Delis Kaplan Executive Functioning System (D-KEFS), which has good reliability and validity,[35] was used as a test of EF. Performance was compared to age-matched normative data based on a sample of 1,750 individuals, with higher-scaled scores (M=10, SD=3) being indicative of better EF. The D-KEFS includes nine subtests: Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Sorting, Twenty Questions, Word Context, Tower, and Proverbs. For the purposes of this study, three composite variables were created for the D-KEFS based on the factor analytic structure of the D-KEFS reported previously in the literature:[36] Specifically, Latzman and Markon[36] conducted a factor analysis using data from the D-KEFS standardization sample as reported in the technical manual, followed by replication in a group of early adolescent males. Results revealed the best fit for the data was a three factor model with 1) Conceptual Flexibility, consisting of 3 scores from the Sorting Test (Free Sort, Free Sort Description and Sort Recognition), 2) Monitoring, consisting of the Verbal Fluency Category Switching measures (Category Swithcing Total and Category Switching Accuracy) and 3) Inhibition, consisting of the Trail Making Test, Color-Word Inhibition and Color Word Inhibition/Switching. This structure fits with Miyake et al.'s[9] three factor model, described above, although different terminology was used (e.g., Flexibility vs. Shifting; Monitoring vs. Updating). Consequently, we conceptualized our data in accordance with these factors. An exploratory factor analysis of D-KEFS subtests that specifically assess EF was conducted for parents (but not probands, given the sample size) in the current sample. Using principal components analysis and varimax rotation, the subtests mapped onto the same three factors as described by Latzman and Markon,[36] with each subtest having a factor loading of .70 or above.

A smaller proportion of probands was administered EF measures than measures of IQ. One hundred nine received the BRIEF (65 school-aged and 44 preschool aged children), and 35-39 (depending on the subtest) received the D-KEFS. EF was also assessed in parents (D-KEFS n=335) and unaffected siblings (BRIEF n=114, D-KEFS n=57). To control for multiple comparisons, alpha was set at ≤.01 for all analyses.

Intellectual Functioning—Intellectual ability was assessed with the WASI,[37] WISC-IV,[38] or the WPPSI-III.[39] Each measure has good reliability and validity and provides a Full Scale IQ. The WASI was administered to 154 fathers and 187 mothers (for a total of 341 biological parents) of individuals with ASD.

Adaptive Functioning—The VABS-II – Parent/Caregiver Rating Form was used as a measure of adaptive functioning. Three of the Vineland composites were utilized: Communication (receptive, expressive and written), Daily Living Skills (personal, domestic and community), and Socialization (interpersonal relationships, play and leisure time, and coping skills). The VABS-II has good reliability and validity.[3] Composite scores have a mean of 100 and standard deviation of 15, with higher scores indicative of better adaptive skills.

RESULTS

Participants with ASD and average IQ exhibit profound impairments in EF

EF was first examined in probands and unaffected relatives using one-sampled *t*-tests in comparison to normative data. Probands had average Full Scale IQ (M =101.77, SD =17.67). Emerging literature has suggested that reports of EF and tests of EF may not always be capturing the same cognitive processes.[40] Given this issue, both questionnaires and tests of EF were utilized, and the relationships between the two were non-significant (r=-.06 to -.38, all *p*>.04). On questionnaires (BRIEF n=65, BRIEF-P n=44) a large percentage of probands were reported by parents to have clinically significant EF impairments. Additionally, they performed significantly worse than normative expectation on all indices (Table 1).

On tests of EF (D-KEFS, n=35-39, based on the subtests administered), probands performed worse than normative expectation on the Conceptual Flexibility and Inhibition, but not Monitoring, factors (Table 2). Full Scale IQ was significantly related to Conceptual Flexibility and Inhibition but not the Monitoring factor. In contrast, none of the questionnaire indices was related to Full Scale IQ (Table 3).

Deficits in adaptive behavior are observed in children with ASD and average IQ

On the VABS-II, a large portion of individuals with ASD (n=155) demonstrated impaired adaptive functioning, as defined by a standard score of 70 or less on at least one of the composites. The largest portion of probands were impaired in Socialization (29.5%, M =78.34, SD =15.43). Daily Living Skills were impaired in 14.7% of probands (M =84.31, SD =15.13) and 16.1% had impaired Communication (M =85.88, SD =17.16). There was a significant relationship between Full Scale IQ and Communication and Daily Living Skills, but not Socialization (see Table 3). None of the Vineland composites were significantly correlated with the calibrated symptom severity from the ADOS (all $p>.15$).

Questionnaire-based EF contributes to the prediction of adaptive behavior beyond the effects of age, IQ and ASD symptom severity

A series of stepwise multiple regressions were conducted to determine the contribution of questionnaire measures of EF on adaptive functioning after controlling for the effects of age, IQ, and severity of ASD symptoms (Table 4). For all regression analyses, age and IQ were entered into the first step of the equation, symptom severity (ADOS-calibrated severity score) in the second step, and parent-reported EF (Behavioral Regulation Index and Metacognition Index of the BRIEF) in the third step. Age was included as a predictor variable given recent evidence that parent-reported impairments in some aspects of EF increase with age in individuals with ASD.[41] Results show that VABS-II-Socialization is predicted by the BRIEF Metacognition Index. IQ, age and the BRIEF Metacognitive Index predicted VABS-II-Communication. The combination of Full Scale IQ and BRIEF Metacognition Index predicted VABS-II-Daily Living Skills.

Questionnaire-based EF relates to adaptive abilities in preschool-aged probands

As the size of our sample of preschool-aged children precluded the use of multiple regressions, correlations were conducted to assess associations between questionnaire EF (BRIEF-P) and adaptive functioning in preschool-aged children. The Emergent Metacognition was related to all three composites: Communication (r =-.476, p =.000), Daily Living Skills (r =-.447, p =.000) and Socialization (r =-.393, p =.001). Inhibitory Self Control was related to Socialization (r =-.411, p =.000). After controlling for IQ with partial correlations, the relationships between Emergent Metacognition and Communication (r =-.423, p =.007), and Inhibitory Self Control and Socialization (r =-.419, p =.007) remained significant.

Correlations between tests of EF and adaptive functioning in probands

As the size of our sample of probands who received EF tests precluded the use of multiple regressions, correlational analysis was utilized to determine the relationship between tests of

EF and VABS-II scores. Conceptual Flexibility was significantly related to Communication (r=.542, *p*=.001). Full Scale IQ was significantly related to both of the above variables (see Table 3), but when partial correlations were conducted to control for Full Scale IQ, the relationship between Conceptual Flexibility and Communication demonstrated a trend toward correlation but was not significant (r=.329, *p*=.06). Further studies in larger samples sizes will be necessary to discern if this is a true correlation as was the case for the questionnaire assessment of EF.

Unaffected family members had average intellectual abilities and intact EF

Parents in this sample had average Full Scale IQ (M =112.72, SD =11.46). Compared to normative data, parents performed better on each of the D-KEFS factors (see Table 2). When examined according to family status (simplex vs. multiplex), effect sizes were similar, ranging from .42 to .57. Each of the D-KEFS factors were significantly related to IQ: Conceptual Flexibility r=.59, *p* <.001; Monitoring r =.30, *p* <.001; Inhibition r=.44, *p* <.001.

Unaffected siblings had average Full Scale IQ (M =110.65, SD =13.57). On questionnaires, parents did not report unaffected siblings as exhibiting EF difficulties, and preschool-aged siblings were reported to have fewer difficulties on the Flexibility and Emergent Cognition Indices than the normative sample. On tests of EF, unaffected siblings performed better than normative expectation in the area of Monitoring (see Table 2). Full Scale IQ was related to the D-KEFS factors of Conceptual Flexibility and Inhibition, but not Monitoring, while questionnaire report of EF was not related to Full Scale IQ (see Table 3).

DISCUSSION

Among individuals with ASD and average IQ, EF weaknesses were demonstrated on both parent questionnaires and neuropsychological tests. The large sample size in this study allowed for the investigation of the relationship between EF and adaptive functioning, with findings that parent-reported EF deficits are predictive of adaptive functioning after controlling for age, IQ, and ASD symptom severity. In particular, the Metacognition Index of the BRIEF explained a significant amount of variance in adaptive functioning across domains (Socialization, Communication, and Daily Living Skills). Further, as the first study to examine the relationship between parent-report of EF and adaptive skills in preschool-aged children, findings demonstrate that EF deficits were negatively related to adaptive abilities in this age group.

Findings are consistent with previous research demonstrating parent-report of EF deficits in everyday settings[10,12,33] in individuals with ASD, and uniquely demonstrate that these deficits contribute to adaptive weaknesses in school-aged and preschool-aged children. These findings suggest that EF deficits are present at a young age, and also that they contribute to reduced adaptive functioning. This has implications for both assessment and treatment planning. Specifically, assessment of these skills may provide valuable information as to the child's weaknesses that may hamper development of adaptive skills. Given the severity of EF deficits in high-functioning children with ASD, it could be important to develop and assess interventions to target their EF weaknesses, as this could positively impact their EF, adaptive skills, and quality of life. Indeed, a recent study demonstrated that a relatively new EF intervention led to improvements in EF, social skills, and classroom behavior.[42] Furthermore, given research demonstrating that EF, as assessed via questionnaire, relates to neuroimaging findings,[43,44] EF, combined with neuroimaging measures, may help shed light on the mechanisms underlying adaptive deficits in children with ASD. Future studies in this area would help in continuing to refine our understanding of the neurocircuitry that underlies EF impairments in individuals with ASD.

Findings revealed a relationship between tests of conceptual flexibility and adaptive communication; however, this relationship not did remain significant after controlling for IQ. Notably, IQ was related to tests of conceptual flexibility and monitoring, and also related to communication and daily living skills. Thus, IQ may be a moderating variable in the relationship between tests of EF and adaptive functioning. However, in this study, there was a relatively smaller sample size for tests of EF, and the reduced statistical power may have contributed to these findings. Given that probands demonstrated reduced conceptual flexibility and inhibition, future studies with larger sample sizes would help to delineate the nature of the relationship between tests of EF and adaptive functioning.

Given that IQ was related to neuropsychological testing but not parent-report measures of EF, tests may be tapping a slightly different aspect of EF than questionnaires. These findings are consistent with previous work demonstrating dissociation between EF as measured by questionnaire versus EF as measured by participant tests in other clinical populations.[40,45,46] As parent report of EF and adaptive functioning are both assessments of functioning in everyday settings, questionnaire-assessed EF may help to explain variance in adaptive functioning among individuals with ASD and average IQ. It is important to consider that shared method variance may account for a portion of their relationship.

Our results did not provide evidence for an EF-extended phenotype in pedigrees with average IQ, as parents and unaffected siblings did not exhibit EF weaknesses. Findings support previous research that suggests that unaffected relatives of children with high-functioning ASD generally perform as well as neurotypical individuals,[28] in contrast to the EF deficits seen in parents and unaffected siblings in studies of children with ASD and lower IQ. [23-25]

Furthermore, in our sample, performance on EF measures by parents of simplex and multiplex families had equivalent effect sizes when compared to normative data. Taken together, one implication of these results is that, at least for individuals with ASD and average intellectual functioning, EF impairments may not relate to risk factors for ASD that run in the broader family, but rather may be associated with factors relevant to the expression of the disorder in the proband. Indeed, some authors have suggested that EF dysfunction does not directly cause ASD symptomology but may lead to deficits in adaptive functioning through alternate pathways. For example, early EF has been found to be predictive of later development of theory of mind.[6] The continued investigation of different EF intermediate phenotypes and moderating variables may help further characterize ASD and assist in clarifying the etiology of adaptive deficits.

The large sample size in this study allowed for greater power and the ability to examine the association between EF and adaptive skills after controlling for age, IQ, and severity of ASD symptoms. It is also the first study to examine the relationship between EF, IQ, and adaptive skills in preschoolers with ASD and average IQ. Although this study has several strengths, some limitations are noted. As this was a pre-existing clinical research sample, not all participants received all measures, and given the lack of a control group, individual performance was compared to normative data. Additionally, despite the large sample size, a relatively smaller number of study participants had data for EF, and the sample size for tests of EF was smaller than for questionnaires. In this sample the unaffected siblings group was comprised of a greater proportion of females than males, while the probands group was the opposite. As such, it is possible that differences or lack thereof in unaffected siblings compared to their relatives may be impacted by gender. However, this appears unlikely, as within both the proband and the unaffected sibling groups, there were no gender differences in performance on measures of EF or IQ. Although we have used data reduction methods, these results may be considered exploratory. Despite the multiple comparison burden, results such as reductions in EF and the relationships between EF and adaptive functioning are strong because the *p*-value was generally less than .007, and they are in line with previous independent observations. In summary, this study demonstrated significant EF weaknesses in children with ASD and average IQ beginning in preschool that are associated with reductions in adaptive functioning. Additionally, while this group of probands exhibited EF weaknesses, their unaffected relatives did not. Overall, results support evaluation of the incremental benefits of EF assessment as a way to identify treatment targets that could lead to improved adaptive behavior. Further research on the mechanisms underlying reduced EF in individuals with ASD is warranted.

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REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders. 5th ed.. American Psychiatric Association; Arlington, VA: 2013.
2. Joseph, R. The Significance of IQ and Differential Cognitive Abilities for Understanding ASD.. In: Fein, D., editor. The Neuropsychology of Autism. Oxford University Press; New York, NY: 2011. p. 281-294.
3. Sparrow, S.; Cicchetti, D.; Balla, D. Vineland Adaptive Behavior Scales Second Edition: Survey Forms Manual. Pearson; Minneapolis, MN: 2005.
4. Rozga, A.; Anderson, S.; Robins, D. Major current neuropsychological theories of ASD.. In: Fein, D., editor. The Neuropsychology of Autism. Oxford University Press; New York, NY: 2011. p. 97-120.
5. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. Journal of child psychology and psychiatry, and allied disciplines. 1996; 37(1):51–87.
6. Pellicano E. The development of executive function in autism. Autism research and treatment. 2012; 2012:146–132.
7. Lezak, M.; Howieson, D.; Bigler, E.; Tranel, D. Neuropsychological Assessment. 5th ed.. Oxford University Press; USA: 2012.
8. Eigsti, I-M. Executive functions in ASD.. In: Fein, D., editor. The neuropsychology of autism. Oxford University Press; New York: NY: 2011. p. 185-203.
9. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. Cognitive psychology. 2000; 41(1):49–100. [PubMed: 10945922]
10. Smithson PE, Kenworthy L, Wills MC, Jarrett M, Atmore K, Yerys BE. Real world executive control impairments in preschoolers with autism spectrum disorders. Journal of autism and developmental disorders. 2013; 43(8):1967–1975. [PubMed: 23283628]
11. Semrud-Clikeman M, Walkowiak J, Wilkinson A, Butcher B. Executive functioning in children with Asperger syndrome, ADHD-combined type, ADHD-predominately inattentive type, and controls. Journal of autism and developmental disorders. 2010; 40(8):1017–1027. [PubMed: 20140638]
12. Kenworthy LE, Black DO, Wallace GL, Ahluvalia T, Wagner AE, Sirian LM. Disorganization: the forgotten executive dysfunction in high-functioning autism (HFA) spectrum disorders. Developmental neuropsychology. 2005; 28(3):809–827. [PubMed: 16266250]
13. Gioia GA, Isquith PK, Kenworthy L, Barton RM. Profiles of everyday executive function in acquired and developmental disorders. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2002; 8(2):121–137. [PubMed: 12638065]
14. Gilotty L, Kenworthy L, Sirian L, Black DO, Wagner AE. Adaptive skills and executive function in autism spectrum disorders. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2002; 8(4):241–248. [PubMed: 12759821]
15. Kenworthy L, Black DO, Harrison B, della Rosa A, Wallace GL. Are executive control functions related to autism symptoms in high-functioning children? Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2009; 15(5):425–440. [PubMed: 19173090]
16. Sayers N, Oliver C, Ruddick L, Wallis B. Stereotyped behaviour in children with autism and intellectual disability: an examination of the executive dysfunction hypothesis. Journal of intellectual disability research : JIDR. 2011; 55(7):699–709. [PubMed: 21199048]
17. Bolte S, Poustka F. The relation between general cognitive level and adaptive behavior domains in individuals with autism with and without co-morbid mental retardation. Child psychiatry and human development. 2002; 33(2):165–172. [PubMed: 12462353]
18. Klin A, Saulnier CA, Sparrow SS, Cicchetti DV, Volkmar FR, Lord C. Social and communication abilities and disabilities in higher functioning individuals with autism spectrum disorders: the Vineland and the ADOS. Journal of autism and developmental disorders. 2007; 37(4):748–759. [PubMed: 17146708]

19. Duncan AW, Bishop SL. Understanding the gap between cognitive abilities and daily living skills in adolescents with autism spectrum disorders with average intelligence. Autism. Nov 25.2013
20. Kanne SM, Gerber AJ, Quirmbach LM, Sparrow SS, Cicchetti DV, Saulnier CA. The role of adaptive behavior in autism spectrum disorders: implications for functional outcome. Journal of autism and developmental disorders. 2011; 41(8):1007–1018. [PubMed: 21042872]
21. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. The American journal of psychiatry. 2003; 160(4):636–645. [PubMed: 12668349]
22. Baron-Cohen S, Hammer J. Parents of Children with Asperger Syndrome: What is the Cognitive Phenotype? Journal of cognitive neuroscience. 1997; 9(4):548–554. [PubMed: 23968217]
23. Hughes C, Plumet MH, Leboyer M. Towards a cognitive phenotype for autism: increased prevalence of executive dysfunction and superior spatial span amongst siblings of children with autism. Journal of child psychology and psychiatry, and allied disciplines. 1999; 40(5):705–718.
24. Hughes C, Leboyer M, Bouvard M. Executive function in parents of children with autism. Psychological medicine. 1997; 27(1):209–220. [PubMed: 9122301]
25. Delorme R, Gousse V, Roy I, et al. Shared executive dysfunctions in unaffected relatives of patients with autism and obsessive-compulsive disorder. European psychiatry : the journal of the Association of European Psychiatrists. 2007; 22(1):32–38. [PubMed: 17127035]
26. Wong D, Maybery M, Bishop DV, Maley A, Hallmayer J. Profiles of executive function in parents and siblings of individuals with autism spectrum disorders. Genes, brain, and behavior. 2006; 5(8): 561–576.
27. Losh M, Adolphs R, Poe MD, et al. Neuropsychological profile of autism and the broad autism phenotype. Archives of general psychiatry. 2009; 66(5):518–526. [PubMed: 19414711]
28. Sumiyoshi C, Kawakubo Y, Suga M, Sumiyoshi T, Kasai K. Impaired ability to organize information in individuals with autism spectrum disorders and their siblings. Neuroscience research. 2011; 69(3):252–257. [PubMed: 21129422]
29. Lord, C.; Rutter, M.; DiLavore, P.; Risi, S. Autism Diagnostic Observation Schedule. Western Psychological Services; Los Angeles, CA: 1999.
30. Rutter, M.; Le Couteur, A.; Lord, C. Autism Diagnostic Interview-Revised. Western Psychological Services; Los Angeles, CA: 2003.
31. Risi S, Lord C, Gotham K, et al. Combining information from multiple sources in the diagnosis of autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2006; 45(9):1094–1103. [PubMed: 16926617]
32. Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. Journal of autism and developmental disorders. 2009; 39(5):693–705. [PubMed: 19082876]
33. Gioia, GA.; Isquith, PK.; Guy, SC.; Kenworthy, L. Behavior Rating Inventory of Executive Function (BRIEF): Professional Manual. Psychological Assessment Resources; Lutz, FL: 1996.
34. Isquith PK, Crawford JS, Espy KA, Gioia GA. Assessment of executive function in preschool-aged children. Mental retardation and developmental disabilities research reviews. 2005; 11(3):209–215. [PubMed: 16161093]
35. Delis, D.; Kaplan, E.; Kramer, JH. Delis-Kaplan Executive Function System (D-KEFS): Technical Manual. The Psychological Corporation; San Antonio, TX: 2001.
36. Latzman RD, Markon KE. The factor structure and age-related factorial invariance of the Delis-Kaplan Executive Function System (D-KEFS). Assessment. 2010; 17(2):172–184. [PubMed: 20040723]
37. Wechsler, D. Wechsler Abbreviated Scale of Intelligence (WASI). The Psychological Corporation; San Antonio, TX: 1999.
38. Wechsler, D. Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). The Psychological Corporation; San Antonio, TX: 2003.
39. Wecshler, D. Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). The Psychological Corporation; San Antonio, TX: 2002.
40. Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world

behavior. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2011; 17(4):313–329. [PubMed: 21347908]

41. Rosenthal M, Wallace GL, Lawson R, et al. Impairments in real-world executive function increase from childhood to adolescence in autism spectrum disorders. Neuropsychology. 2013; 27(1):13–18. [PubMed: 23356593]
42. Kenworthy L, Anthony LG, Naiman DQ, et al. Randomized controlled effectiveness trial of executive function intervention for children on the autism spectrum. Journal of child psychology and psychiatry, and allied disciplines. 2014; 55(4):374–383.
43. Wilde EA, Merkley TL, Bigler ED, et al. Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience. 2012; 30(3):267–276. [PubMed: 22266409]
44. Ikuta T, Shafritz KM, Bregman J, et al. Abnormal cingulum bundle development in autism: a probabilistic tractography study. Psychiatry research. 2014; 221(1):63–68. [PubMed: 24231056]
45. Vriezen ER, Pigott SE. The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2002; 8(4):296–303. [PubMed: 12759826]
46. MacAllister WS, Bender HA, Whitman L, et al. Assessment of executive functioning in childhood epilepsy: the Tower of London and BRIEF. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2012; 18(4):404–415. [PubMed: 21961902]

Clinical Guidance

- Comprehensive evaluations of children with ASD may benefit from the inclusion of assessment of EF, as deficits in EF may be appropriate targets for treatment, given their impact adaptive functioning.
- Given that parent-reported EF weaknesses are evidenced in preschool-aged children and are related to adaptive functioning, assessment of EF may also be warranted for children in this age group.
- EF deficits are evident on both questionnaires and tests, with questionnaire data related to adaptive functioning after controlling for IQ. Further research is needed to delineate the nature of the relationships between performance on tests of EF, IQ, and adaptive functioning.
- Unaffected relatives did not display impairments in EF, suggesting that EF impairments may not relate to risk factors for ASD that run in families but rather may be associated with factors relevant to the expression of the illness.

Table 1

Executive Functioning in Probands and Unaffected Siblings on Behavior Rating Inventory of Executive Functioning (BRIEF) and Behavior Rating Inventory of Executive Functioning - Preschool (BRIEF-P)

BRIEF	Probands (n=65)			Proband comparison to normative data		Unaffected siblings (n=76)			Unaffected sibling comparison to normative data	
	M	SD	Percent T ≥ 65	*t*	*p*	M	SD	Percent T ≥ 65	*t*	*p*
Behavior Regulation Index	69.28	13.79	67.8	11.27	.000**	48.57	11.77	11.7	1.18	>.05
Metacognition Index	65.63	11.80	55.4	10.68	.000**	51.89	13.89	16.9	1.04	>.05

BRIEF-P	Probands (n=44)			Proband comparison to normative data		Unaffected siblings (n=41)			Unaffected sibling comparison to normative data	
	M	SD	Percent T ≥ 65	t	*p*	M	SD	Percent T ≥ 65	t	*p*
Inhibitory Self-Control Index	63.14	14.11	52.3	6.18	.000**	45.46	11.69	7.3	2.49	.017
Flexibility Index	62.91	14.78	43.2	5.80	.000**	44.49	11.59	2.4	3.05	.004*
Emergent Metacognition Index	65.23	16.52	47.7	6.11	.000**	45.29	10.61	2.4	2.84	.007*

Note: M = mean; T = t-score; *t* = t-test statistic.

* p<.01

** p<.001, when compared to a population mean of 50.

Table 2

Executive Functioning on Delis-Kaplan Executive Functioning System (D-KEFS)

	Probands (n=35-39)		Percent of probands with ss ≤5	Biological Parents (n=335)		Unaffected Siblings (n= 57)	
	M	**SD**		**M**	**SD**	**M**	**SD**
Conceptual Flexibility Factor	8.04**	3.17	25.7	11.44**	2.77	9.87	2.69
Monitoring Factor	9.06	3.57	15.4	12.11**	3.24	11.30*	2.94
Inhibition Factor	8.19**	3.01	15.4	11.08**	1.94	10.15	2.26

Note: M = mean; ss =scaled score.

* $p \leq .01$

** $p \leq .001$ when compared to population mean of 10

Table 3

Correlations Between Full Scale IQ and Executive Functioning and Adaptive Functioning Measures

	Proband Full Scale IQ		Unaffected Sibling Full Scale IQ		Parental Full Scale IQ	
	r	*p*	*r*	*p*	*r*	*p*
D-KEFS Conceptual Flexibility	**.764**	**<.001**	**.604**	**<.001**	**.584**	**<.001**
D-KEFS Inhibition	**.601**	**<.001**	**.373**	**<.01**	**.469**	**<.001**
D-KEFS Monitoring	.379	.017	.244	.075	**.297**	**<.001**
BRIEF Behavioral Regulation Index	.036	.775	−.120	.338		
BRIEF Metacognition Index	−.143	.255	−.139	.266		
BRIEF-Preschool Inhibitory Self Control Index	−.173	.264	−.061	.749		
BRIEF-Preschool Flexibility Index	−.231	.131	−.176	.353		
BRIEF-Preschool Emergent Metacognition Index	−.315	.038	−.146	.433		
VABS-II Communication	**.358**	**<.001**	.218	.035		
VABS-II Socialization	.141	.080	.001	.990		
VABS-II Daily Living Skills	**.368**	**<.001**	.064	.539		

Note: significant relationships are indicated in bold. BRIEF = Behavior Rating Inventory of Executive Functioning; D-KEFS = Delis-Kaplan Executive Functioning System; *r* = Pearson correlation; VABS-II = Vineland Adaptive Behavior Scales- Second Edition.

Table 4

Questionnaire-Based Executive Functioning Difficulties Predict Adaptive Skills

	Variables in Equation	*F*	R^2	β	*T*	*p*
Socialization						
Step 1. Model Summary		26.461	.342			.000
	BRIEF Metacognition Index			−.584	−5.144	.000
Communication						
Step 1. Model Summary		19.478	.276			.000
	Full Scale IQ			.526	4.413	.000
Step 2. Model Summary		13.047	.150			.000
	Full Scale IQ			.509	4.743	.000
	Age			−.387	−3.612	.001
Step 3. Model Summary		9.225	.091			.000
	Full Scale IQ			.457	4.536	.000
	Age			−.324	−3.185	.003
	BRIEF Metacognition Index			−.313	−3.037	.004
Daily Living Skills						
Step 1. Model Summary		11.643	.186			.001
	Full Scale IQ			.431	3.412	.001
Step 2. Model Summary		11.433	.152			.000
	Full Scale IQ			.363	3.103	.003
	BRIEF Metacognition Index			−.395	−3.381	.001

Note: *F* indicates *F*-value at step 1; R^2 indicates R^2-value at step 1. β = standardized regression coefficient; BRIEF = Behavior Rating Inventory of Executive Functioning; *t*=test statistic.