The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 59:3 (2018), pp 268–276 doi:10.1111/jcpp.12815

Comorbid symptoms of inattention, autism, and executive cognition in youth with putative genetic risk

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Background: Symptoms of autism spectrum disorder (ASD) and inattention (IA) are highly comorbid and associated with deficits in executive cognition. Cognitive deficits have been posited as candidate endophenotypes of psychiatric traits, but few studies have conceptualized cognitive deficits as psychiatric comorbidities. The latter model is consistent with a latent factor reflecting broader liability to neuropsychological dysfunction, and explains heterogeneity in the cognitive profile of individuals with ASD and IA. **Methods:** We tested competing models of covariance among symptoms of ASD, IA, and cognition in a sample of 73 youth with a known genetic mutation. **Results:** A common executive factor fit best as a cognitive comorbidity, rather than endophenotype, of the shared variance between measures of IA and ASD symptoms. Known genetic risk explained a third of the shared variance among psychiatric and cognitive measures. **Conclusions:** Comorbid symptoms of ASD, IA, and cognitive deficits are likely influenced by common neurogenetic factors. Known genetic risk in ASD may inform future investigation of putative genetic causes of IA. **Keywords:** ADHD; autism spectrum disorders; executive function; genetics; attention.

Introduction

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are two of the most common neurodevelopmental disorders, affecting approximately 2% and 7% of school age children, respectively (Blumberg et al., 2013; Willcutt, 2012). ASD is characterized by deficits in social communication and restricted and repetitive behaviors and interests, while hallmarks of ADHD are symptoms of inattention, impulsivity, and hyperactivity (APA, 2013). Despite these seemingly disparate symptom clusters, there is a high degree of comorbidity, such that 20%–50% of individuals with ASD show comorbid symptoms of ADHD (Di Martino et al., 2013; Simonoff et al., 2008; Sinzig, Walter, & Doepfner, 2009). Likewise, children with ADHD have persistent social difficulties (Arnett, MacDonald, & Pennington, 2013) and tend to score higher than average on behavioral questionnaires targeting core ASD symptoms (Reiersen, Constantino, Volk, & Todd, 2007).

Several theories have been proposed to explain comorbidity between ASD and ADHD, including the notion that executive dysfunction is a cognitive endophenotype reflecting neural atypicalities underlying both disorders (Charman et al., 2011; Ozonoff, Pennington, & Rogers, 1991; Rommelse et al., 2009). An endophenotype is a measurable construct that mediates the path from genetic risk to behavior (Gau & Shang, 2010), and as such serves as a proxy for neurodevelopmental differences that are more directly tied to genetic expression. Both ASD and the inattention (IA) symptom domain of ADHD have been well characterized with regard to cognitive deficits; executive functions (e.g. inhibition, planning, and flexibility) are repeatedly named as candidate cognitive endophenotypes of each disorder (Gau & Shang, 2010; Nydén, Hagberg, Goussé, & Rastam, 2011). Processing speed and inhibitory control are particularly strong predictors of IA when multiple cognitive factors are included in a model (McGrath et al., 2011). The literature is mixed as to whether a double dissociation exists regarding ASD and IA cognitive profiles. Several studies (Ozonoff & Jensen, 1999; Pennington & Ozonoff, 1996; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008) have reported that ASD is associated with planning and cognitive flexibility deficits, but intact inhibition and working memory. Adamo et al. (2014) found that variability in reaction time was specific to IA, with or without comorbid ASD. Van der Meer et al. (2012) reported that working memory and cognitive style of primary IA with comorbid ASD differed from primary ASD with comorbid IA. Still others have reported fewer distinctions between the two disorders (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Goldberg et al., 2005; Hill & Bird, 2006; Nydén, Gillberg, Hjelmquist, & Heiman, 1999).

Conflict of interest statement: See acknowledgements for disclosures.

Notable limitations to most of these studies have been (a) inclusion of only high functioning individuals with ASD, which may obscure important observations about comorbidity in this population; and (b) use of dichotomous diagnostic categories to characterize ASD and IA comorbidity, which decreases power to estimate covariance across continuous symptom dimensions. The current study addresses these gaps by measuring the covariance of continuous scales of ASD and IA symptoms. We focused on the IA symptom domain in ADHD due to its pervasiveness across development and stronger association with cognitive deficits (Lahey, Pelham, Loney, Lee, & Willcutt, 2005).

The concept of a general psychopathology factor, '*P*,' has been proposed to explain covariance across psychiatric traits (e.g. Caspi et al., 2014; Tackett et al., 2013). Like the general cognitive factor, *g* (Spearman, 1927), *P* is a latent factor that estimates shared variance across behavioral traits and is thought to reflect complex, underlying neurodevelopmental characteristics. Previous research indicates that *g* and *P* are correlated (Caspi et al., 2014), and variance in *P* can be partially accounted for by cognitive skills. For example, McGrath et al. (2016) demonstrated that shared variance among psychosis, mania, and autistic traits was partially explained by a common executive cognition factor. This model is consistent with a cognitive endophenotype model and indicates that measures of cognition are more closely tied to brain functions that give rise to the abnormal psychiatric phenotype.

In the present study, we propose an alternative model to explain the association between cognitive and psychiatric traits. In this model, *P* is an underlying, neurodevelopmental liability that influences the shared variance across all three cognitive and psychiatric traits, that is, ASD symptoms, IA, and cognition. Like the cognitive endophenotype model, this cognitive correlate model assumes that all three traits share common neurogenetic etiology. Unlike the cognitive endophenotype model, the correlate model does not place cognition as a mediator of the association between genetic and psychiatric expression. In practice, this means that an individual could show severe psychiatric traits with relatively intact cognitive skills. The correlate model is consistent with findings that executive cognition only accounts for 35% of the behavioral variance in ADHD symptoms (McGrath et al., 2011), executive deficits are neither necessary nor sufficient to cause ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), and only a portion of individuals with ASD have intellectual disability (Matson & Shoemaker, 2009).

A major limitation to testing cognitive endophenotype models of psychiatric comorbidity is a lack of clearly identified genetic risk. Known single-gene and copy number variation (CNV) mutations now account for approximately 10%–30% of autism diagnoses (Iossifov et al., 2012; Krumm et al., 2015), while in contrast, genome-wide association and candidate gene studies of ADHD have failed to identify any single genes with large effects (Neale et al., 2010; Todd et al., 2005). High heritability estimates (h^2 = .76; Faraone & Doyle, 2001) and high prevalence rates of IA are consistent with a polygenic etiology, that is, suggesting lack of putative single gene events. On the other hand, failure to identify single gene events may relate to a lack of routine clinical genetic testing with ADHD, as well as heterogeneity of the disorder, which dilutes power to identify putative genetic causes (Fair, Bathula, Nikolas, & Nigg, 2012; Karalunas et al., 2014). Although there is scant evidence for specific linkage loci or shared candidate genes across IA and ASD (Rommelse et al., 2009), pleiotropic effects for single nucleotide polymorphisms (SNPs) and large, rare CNVs at common genetic loci do support a high degree of overlapping genetic risk (Taurines et al., 2012). Comparisons of functional gene network analyses for each disorder implicate gene pathways involved in synaptogenesis and neuronal growth and differentiation (Gilman et al., 2011; Poelmans, Pauls, Buitelaar, & Franke, 2011). The growing list of known genetic events associated with ASD thus presents an opportunity to search for a subset of those genes that also confer risk for IA.

Current study

The current study aimed to clarify the origin of covariance among symptoms of ASD, IA, and executive dysfunction. Our sample was unique in that all individuals had a likely gene disrupting mutation (LGDM) on a gene that had previously been associated with ASD. In the current study, we hypothesized that a subset of disrupted genes in this sample was also associated with clinically Elevated IA symptoms and that this subset of genetic events would explain shared variance between symptoms of ASD and IA. Thus, the first goal was to test whether known genetic risk (defined as an event on the subset of genes associated with Elevated IA) could explain shared variance between symptoms of ASD and IA. Second, we tested alternative models that placed executive cognition as either (a) an endophenotype mediating the effect of genetic risk on shared variance between ASD and IA symptoms, or (b) a correlate of ASD and IA symptoms, with covariance across all three traits explained by genetic risk.

Methods

Procedures

Individuals aged 3–22 years old were recruited for participation following identification of an LGDM that has previously been associated with ASD (O'Roak et al., 2011, 2014). Enrollment exclusion criteria included known syndromic disorder associated with ASD (e.g. Fragile X). Fourteen individuals were unable to complete cognitive testing due to living outside the

United States (n = 5), failure to return behavioral questionnaires (n = 1), or behaviors that interfered with cognitive testing (n = 8). The final sample comprised 73 individuals (see Table 1 for participant demographics). Testing took place in the laboratory or in the participant's home over the course of 2 days. Parents completed questionnaires about their child's behavior and participated in interviews including the Autism Diagnostic Interview Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), the Vineland Adaptive Behavior Scales, 2nd Edition (Sparrow, Cicchetti, & Balla, 2005), and a family and medical history. Parents and participants age 13 and older provided written consent, and younger youth provided verbal or written assent, as developmentally appropriate. All procedures were in compliance with the University of Washington Institutional Review Board.

Autism diagnosis. A DSM-5 (APA, 2013) diagnosis of ASD was assigned based on clinical consensus of a licensed psychologist following administration of the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; Lord, Rutter, & DiLavore, 2012) and the ADI-R by clinicians demonstrating research reliability on these measures. Caregivers also completed the Social Responsiveness Scale, 2nd edition (SRS-2; Constantino & Gruber, 2005). The SRS-2 total T-score (M = 50, SD = 10) was used as a continuous measure of ASD symptoms, following previous findings that this measure is correlated with the ADI-R (Murray, Mayes, & Smith, 2011) and ADOS-2 (Pugliese et al., 2015). However, given debate regarding the specificity of elevated SRS-2 scores to ASD as opposed to other behavioral disorders (Hus, Bishop, Gotham, Huerta, & Lord, 2013a, 2013b), we henceforth refer to this measurement as SRS-2, rather than ASD.

Inattentive symptoms. As ADHD was not the primary focus of the recruitment study, a thorough diagnostic evaluation was not conducted. However, parents completed the Child and Adolescent Symptom Inventory – 5 (CASI-5; Gadow & Sprafkin, 2015), which includes explicit evaluation of the 18 DSM-5 ADHD symptoms. Additionally, caregivers completed the age appropriate version of the Achenbach Behavior Checklist (i.e. Child Behavior Checklist 1.5–5, Child Behavior Checklist 6–18, or Adult Behavior Checklist; Achenbach & Rescorla, 2000, 2001). The Achenbach checklists include an attention problems subscale that is predictive of DSM diagnoses of ADHD Primarily Inattentive and Comorbid subtypes (Eiraldi, Power, Karustis, & Goldstein, 2000; Ostrander, Weinfurt, Yarnold, & August, 1998). For the present study, Elevated IA was defined as six or more CASI-5 ADHD inattention symptoms *and* a clinically elevated Achenbach attention problems scale (T-score ≥70). The continuous measure of IA severity was defined as the mean of the CASI-5 inattentive severity and Achenbach attention problems T-scores.

Table 1 Participant demographics

	LGDM without IA Risk	IA Risk Gene	Total
N	26	47	73
Age in months (*SD*)	167 (51)	121 (56)	138 (58)
Female (%)	5 (19)	15 (32)	20 (27%)
Autism Spectrum Disorder (%)	26 (100%)	39 (83%)	65 (89%)
Elevated IA (%)	0	27 (57%)	27 (37%)
% Household Income ≤ $75,000	14	30	25
Full-Scale IQ (*SD*)	78 (26)	56 (25)	65 (27)
IA Severity (*SD*)	61 (8)	74 (9)	69 (11)
SRS-2 Severity (*SD*)	70 (11)	79 (12)	76 (12)
Adaptive Functioning (*SD*)	68 (14)	59 (14)	62 (15)

Elevated IA defined as six or more CASI-5 inattention symptoms and Achenbach Attention Problems T-score >70. IA and SRS-2 severity scales are T-scores with M = 50, SD = 10. Adaptive Functioning was measured with the Vineland Adaptive Behavior Composite Standard Score, M = 100, SD = 15. LGDM, likely gene-disrupting mutation.

Cognitive factors. The cognitive battery was designed to ascertain a broad range of cognition and included the Differential Ability Scales, 2nd Edition (Elliott, 2007), California Verbal Learning Test -2nd Edition and Child Versions (Delis, Kramer, Kaplan, & Ober, 1994, 2000), Expressive Vocabulary Test 2nd Edition (Williams, 1997), Peabody Picture Vocabulary Test, 4th Edition (Dunn & Dunn, 2007), and selected subtests from the Delis–Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001) and NIH Toolbox (Weintraub et al., 2013). Full-scale IQ was derived from the DAS-II general cognitive abilities composite. Exploratory and confirmatory factor analyses were used as complementary approaches to obtain theoretically and data-driven cognitive factors (see Table S1, Appendix S1, Table S2, and Figure S1). We found four latent factors: verbal memory, verbal fluency, visual-spatial processing, and common executive (CE). Similar to previous research (McGrath et al., 2016), CE was created as a broad factor reflecting inhibition, switching, and processing speed because we did not find support for distinction among these constructs in our analysis.

Genetic data. ASD-associated LGDMs were identified with family-based exome sequencing studies (Iossifov et al., 2014), or companion molecular inversion probe-based (MIP) targeted resequencing of potential ASD loci (O'Roak et al., 2011, 2014). Primary gene events in our sample spanned 31 genes and multiple effects, including frameshift, stop-gained, splice site acceptor, splice site donor, and missense (see Table S3).

Structural equation modeling. Confirmatory factor analysis and structural equation models were conducted in Mplus 7.31 (Múthen & Múthen, 1998–2012), which uses full information maximum likelihood (FIML) as a default approach to estimating models with missing data. Covariance coverage ranged from .37 to .95 for the cognitive and behavioral variables. The primary reason for missing data was inability of the participant to complete some component of psychometric testing. Model fit was evaluated using the following indices: Chi-square p > .05, Comparitive Fit Index (CFI) >0.95, and Standard Root Mean Residual (SRMR) <.08 (Loehlin, 2004). Nested models were compared using the Bayesian information criterion (BIC), with lower values indicating better fit (Jung & Wickrama, 2008).

Results

Rates of ASD and Elevated IA

Eighty-nine percent (n = 65) of our sample received an ASD diagnosis and of these, 31% (n = 20) also demonstrated Elevated IA symptoms. Seven participants showed Elevated IA but no ASD, and one participant had neither Elevated IA nor ASD. All eight participants without ASD had a diagnosis of intellectual disability or global developmental delay. Among the ASD-only group, IA severity was still higher than the normative population: M = 63.5, SD = 8.51 (t[44] = 10.65, p < .001).

IA risk genes

To examine associations between specific LGDMs and Elevated IA, we conducted exploratory analyses to look for patterns of Elevated IA within specific gene disruptions. Eleven of the 31 genes involved in LGDMs in our sample were associated with at least one participant with Elevated IA (Figure 1). We categorized those 11 genes as 'IA Risk Genes.' IA Risk Gene versus LGDM without IA Risk sample demographics are listed in Table 1. More than half the sample had an event on an IA Risk Gene (n = 47). Of those, only 57% (n = 27) actually showed Elevated IA (M = 79.28, SD = 6.39). However, the remaining 20 individuals with an IA Risk Gene event who did not cross the threshold for Elevated IA still had IA severity in the borderline range (M = 68.85, SD = 8.07), which was significantly higher than participants with an LGDM without IA Risk (M = 61.35, SD = 8.30; $t(44) = 2.26$, p = .029). Thus, our IA Risk Gene categorization was associated with greater risk of high IA.

IA and SRS-2 shared variance

The correlation between SRS-2 and IA severity was moderate in magnitude (r = .66, $p < .001$). We modeled a latent psychopathology factor, *P*, reflecting the shared variance between SRS-2 and IA, and tested a structural equation model with the dichotomous predictor IA Risk Gene (vs. LGDM without IA Risk) directly predicting *P*. The model explained 32% of variance in *P* (Figure 2A), indicating that an event on an IA Risk Gene explained about one third of the covariance between SRS-2 and IA severity.

CE as cognitive endophenotype

Prior to testing our endophenotype model, we aimed to determine that CE was in fact a candidate endophenotype of IA in our sample. We hypothesized that if CE is a cognitive endophenotype of IA, disruptions to IA Risk Genes would confer unique deficits on the CE factor, even among the group of individuals with an IA Risk Gene event who had subthreshold IA symptoms. Contrary to expectations, the IA Risk Gene group performed lower on all four cognitive factors ($p \leq .001$; Table 2). This remained true even when we dropped individuals who had Elevated IA from the analysis (p's < .05), indicating that disruption to an IA Risk Gene was associated with greater risk of broad cognitive impairment, regardless of IA symptom severity.

Next, we compared individual path models in which the effect of IA Risk Gene on *P* was mediated by each of the four cognitive factors (Figure S2) to test for specificity of the CE factor. The models each showed excellent fit (chi-square $p > .05$, CFI > .98,

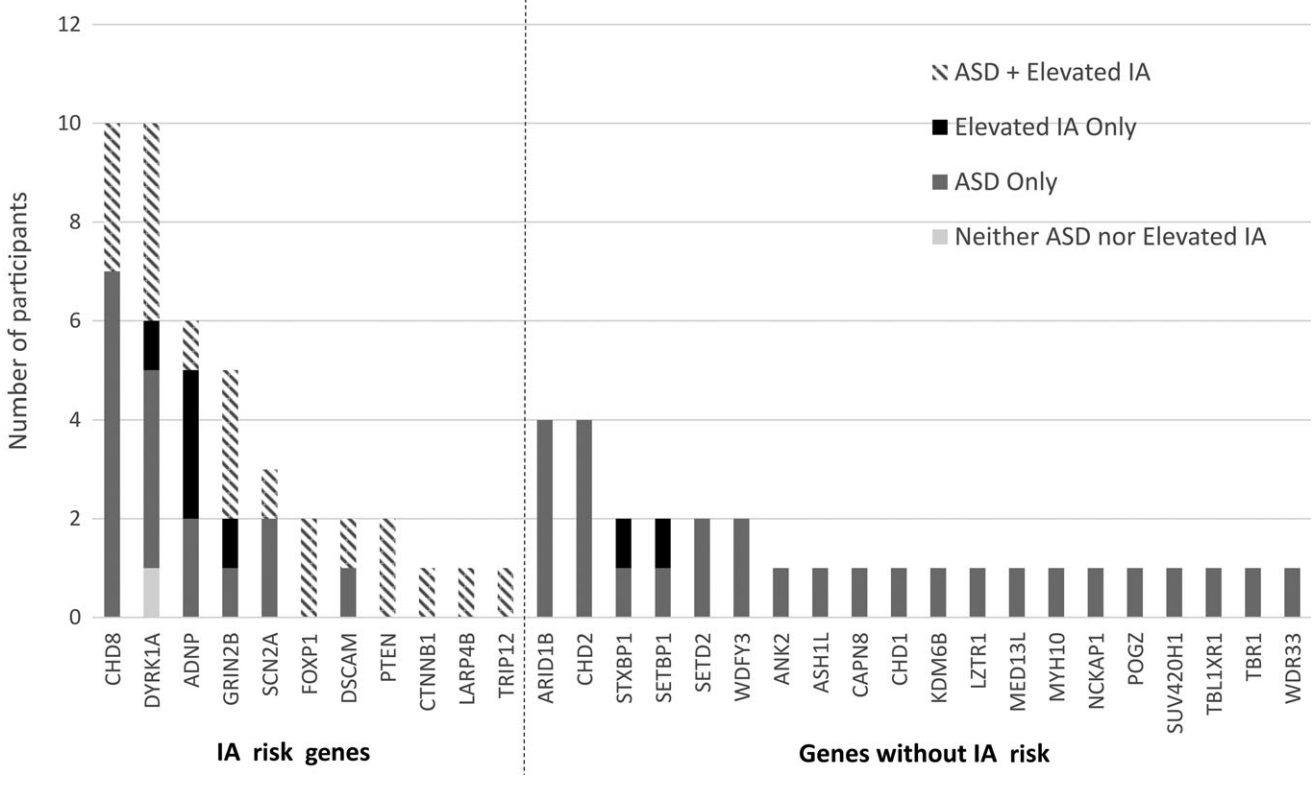

Figure 1 Number of individuals with ASD and/or Elevated IA by primary affected gene. Eleven IA Risk Genes were defined as those with any individuals with ASD+ Elevated IA (slanted stripe) or Elevated IA only (solid black). Some individuals had mutations on additional genes (see Table S1)

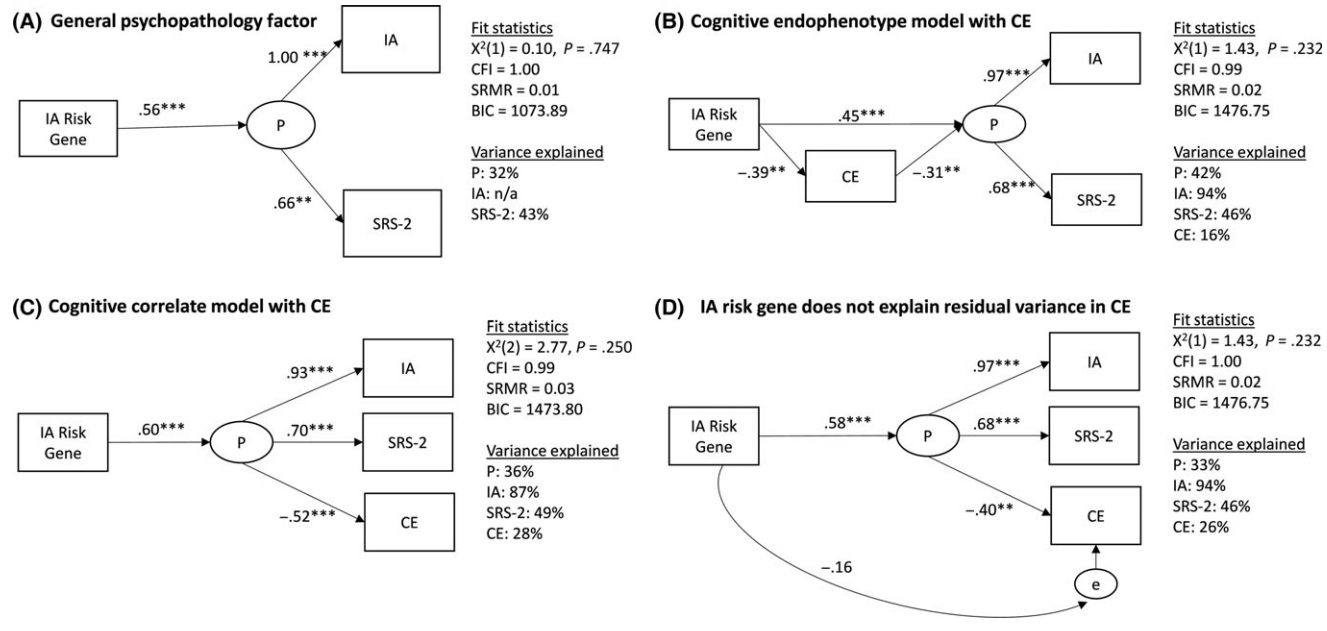

Figure 2 (A) IA Risk Gene categorization explains *P*, a latent variable reflecting shared variance between IA and SRS-2. (B) Common executive mediates the association between genetic risk and *P*. (C) IA Risk Gene categorization explains shared variance among IA, ASD and CE. (D) IA Risk Gene categorization does not explain residual variance in CE when CE is explained by *P*. IA Risk Gene = 1, LGDM without IA Risk = 0. Path weights are standardized Beta coefficients. ***$p < .001$; **$p < .01$. Note that in Model A, the residual variance of IA severity is set to zero

Table 2 Cognitive factor scores of participants with and without IA Risk Gene events

	LGDM without IA Risk (n = 26)	IA Risk Gene (n = 47)	t (71)
Verbal memory *M* (*SD*)	1.25 (13.94)	−10.96 (11.39)	4.05***
Verbal fluency *M* (*SD*)	1.69 (16.64)	−12.89 (17.60)	3.46**
Visual-Spatial *M* (*SD*)	3.18 (15.58)	−14.71 (14.18)	4.98***
Executive control *M* (*SD*)	0.25 (3.86)	−2.87 (3.36)	3.61**

Two-tailed p value: ***<.001, **<.01. LGDM, likely gene-disrupting mutation.

SRMR <.03). The CE factor explained the greatest amount of variance in *P* (42%), although the visual-spatial and verbal fluency factors were also good predictors, explaining 38% and 40% variance, respectively. However, given substantial literature pointing to unique deficits in CE-related tasks in youth with symptoms of IA and ASD, we elected to focus on CE in subsequent models.

Cognitive endophenotype versus cognitive correlate models

The question of whether CE constitutes an endophenotype, versus correlate, of the covariance between SRS-2 and IA can be uniquely addressed in our sample where we have high confidence in the genetic etiology of the ASD symptoms. To this end, we next compared the results of the cognitive endophenotype model (Figure 2B) to a cognitive correlate model (Figure 2C), wherein *P* reflected the shared variance among IA, SRS-2, and CE. Both models had excellent fit; however, the BIC was slightly lower for the cognitive correlate model, indicating better fit. IA Risk Gene explained 36% of the variance in *P* in the cognitive correlate model, suggesting more than one-third covariance across all three traits can be explained by known genetic risk in this sample. Moreover, when we added a direct effect from genetic risk to the residual variance in CE (Figure 2D), the path was not statistically significant, indicating that all of the effect of IA Risk Gene on CE is accounted for by *P*. In other words, the genetic risk in this model is only associated with CE to the extent that CE covaries with IA and SRS-2. Altogether, these models suggest deficits in CE are not an endophenotype, but rather reflect comorbidity with IA and SRS-2 in our sample of individuals with LGDMs.

Discussion

We examined evidence for shared genetic risk associated with SRS-2 and IA comorbidity using a sample of youth with a known LGDM previously associated with ASD. Consistent with prior research that has used a behavior-based approach to associate particular gene disruptions with ASD (O'Roak et al., 2011), we categorized a subset of 11 genes based on their association with Elevated IA in our sample. These IA Risk Genes accounted for 32% of the shared phenotypic variance between SRS-2 and IA, and 36% of the shared variance among SRS-2, IA, and CE. Across all models, a greater proportion of IA was explained

than SRS-2 severity, suggesting that there are additional, unmeasured genetic, and environmental risk factors that influence SRS-2 symptoms. Individuals with an event on one of the IA Risk Genes showed greater cognitive impairment and higher IA severity, whether or not their IA symptoms crossed the research diagnostic threshold. This might imply that the IA Risk Genes constitute genes of greater global impact on neurodevelopment; however, LGDMs without IA Risk in this sample were also strongly associated with intellectual disability in this and previous datasets (e.g. ARID1B; McRae et al., 2017). Altogether, IA Risk Genes appear to reflect unique neurodevelopmental liability related to IA.

Given the heterogeneity of genetic events associated with ASD, a logical model of SRS-2 and IA covariance is one in which multiple gene variants converge on a cognitive endophenotype, such as CE, which serves as a proxy for atypical neurodevelopment resulting from shared genetic risk. However, prior studies are inconclusive regarding common cognitive deficits across ASD and ADHD diagnoses, and our results suggest that CE deficits may be better conceptualized as a comorbid trait. In our cognitive correlate model, covariance across SRS-2, IA, and CE was explained by disruption to IA Risk Genes, while residual variance for each trait was presumably explained by additional, unmeasured genetic, and environmental factors. This is not to imply that a deficit in CE represents a separate clinical disorder; the near ubiquity of CE deficits in neurodevelopmental disorders argues against its validity as a standalone diagnosis. Instead, the cognitive correlate model supports the notion of trait covariance over categorical comorbidity. Notably, the cognitive endophenotype model also demonstrated good fit to the data and LGDM are rare, particularly in ADHD. Thus, future research should also aim to test these competing models using behavioral genetic approaches, such as twin analyses.

Our study applied the concept of *P,* a general psychopathology factor that has gained increasing support in the literature as an explanation for high rates of comorbidity among childhood-onset disorders (Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011). Historically, *P* represents vulnerability to all psychiatric traits, but in the current study, *P* only captured shared variance across IA, SRS-2, and CE. Thus, it is unclear to what extent *P* in our study reflects a unique comorbidity, as opposed to one aspect of an overarching general psychopathology factor. Future studies should aim to include additional comorbidities, such as anxiety and depression, as well as additional cognitive deficits, to test the specificity of the IA and SRS-2 overlap.

The current study contributes to a growing body of research indicating that comorbidity is the rule, rather than the exception, in neurodevelopmental disorders (Van Steensel, Bögels, & de Bruin, 2013). At the same time, clinical services are becoming highly specialized, and families endure extremely long wait times for a diagnosis of ASD only to be sent elsewhere for further evaluation of ADHD, anxiety, depression, and learning disorders (Austin et al., 2016; Gordon-Lipkin, Foster, & Peacock, 2016). The notion of a common psychopathology factor, whether explained by a single gene event or polygenic factors, introduces a conflict between specialized versus comprehensive treatment centers for children with neurodevelopmental disorders. The current results imply that even within specialized services, clinical practice should be comprehensive, and emphasize trait continua over diagnostic classification, in line with research initiatives such as the NIMH research domain criteria (RDoC; Insel, 2014).

Use of the SRS-2 as a measure of ASD symptom severity may be considered a limitation in the current study due to prior documentation of elevated SRS-2 scores among youth with ADHD and other behavioral challenges (Hus et al., 2013a; Reiersen et al., 2007). The SRS-2 contains eight items (out of 65) that appear to overlap with ADHD symptom criteria, such as 'seems more fidgety in social situations' and 'stares or gazes off into space.' However, Reiersen et al. (2007) found that individuals with ADHD still demonstrated elevated symptoms on the SRS-2 when these items were removed, indicating that ADHD symptoms were not driving this result. A lack of normative data for those subscales precluded their use in the current study; however, future research could benefit from use of scales that are more independent from one another.

The present study was unique in that we included participants with a broad range of IQ. However, our low-IQ group showed high correlations among the cognitive factors. Relatedly, we were unable to identify distinct executive function factors in our CFA (consistent with some prior research even among youth with average intellectual functioning, i.e. McGrath et al., 2016; Miyake et al., 2000) and verbal fluency and visual-spatial factors also showed excellent fit as cognitive endophenotypes; thus, our results may not be specific to CE. Previous research supports a common intelligence factor, g, that explains a great deal of variance in cognitive performance and is highly correlated with *P* (Caspi et al., 2014); thus, these limitations likely reflect true covariance across cognitive measures in individuals with neurodevelopmental symptoms.

Relatedly, our sample did not contain a sufficient number of participants to test the structural equation models separately within an average-range FSIQ group. Among individuals with average-range FSIQ, the putative genetic event may be less impactful, allowing for greater effects of other genetic and environmental factors on development. High-IQ individuals warrant further study to investigate protective factors or specific genetic variants that relate to better outcomes.

In the current study, we characterized gene groups according to behavioral expression. Notably, many of our affected gene groups only included a single participant (n = 17/31), so there is likely a degree of error to classification of our IA Risk Genes. Moreover, although all gene variants were likely disruptive, they were not identical across individuals even within a common gene group. The presence of additional 'secondary' genetic hits, such as single nucleotide and copy number variants, was not considered, and such events are highly implicated in both ASD and ADHD (Taurines et al., 2012). The resulting IA Risk Gene group did not clearly correspond to known ontological subtypes, such as genes involved in chromatin modification (Iossifov et al., 2014); enhanced understanding of gene ontology will facilitate more targeted modeling of genetic risk in the future.

Interestingly, we identified seven individuals with Elevated IA but not ASD in our sample. Currently, an ADHD diagnosis alone does not prompt genetic testing in clinical settings, and candidate gene studies of ADHD have not yielded putative causal genetic variants of large effect (Neale et al., 2010; Todd et al., 2005). Our results suggest genes involved in putative genetic events previously associated with ASD may be worthwhile targets in future studies of ADHD. Along that line, all individuals with LGDM without IA Risk Gene events received a diagnosis of autism, while only 83% of the IA Risk Gene group received that diagnosis. Thus, genes in our LGDM without IA risk group may confer specific risk for core ASD symptoms and warrant further attention.

Conclusions

A subset of known genetic mutations associated with both ASD and Elevated IA explained a substantial portion of the covariance across SRS-2 and IA symptom severities. Associated cognitive deficits associated with are most likely correlates, influenced by common neurodevelopmental vulnerability, rather than endophenotypes mediating the effect of genetic expression on behavior. Known genetic risk in ASD may inform future investigation of putative genetic causes of ADHD.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Confirmatory factor models for the cognitive factors.

Figure S2. Comparison of cognitive endophenotype (mediation) models using each of the cognitive factors.

Appendix S1. Additional information.

Table S1. Confirmatory factor analysis sample demographics.

Table S2. Cognitive measures included in the exploratory factor analysis.

Table S3. Individual gene events.

Acknowledgements

This research was supported in part by grants from the National Institutes of Health: R01MH101221 to E.E.E. and R01MH100047 to R.A.B. The authors thank the individuals and their families for participation in this study. E.E.E. is an investigator of the Howard Hughes Medical Institute on the scientific advisory board (SAB) of DNAnexus, Inc. The other authors have declared that they have no competing or potential conflicts of interest.

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Key points

- ASD and inattention problems are highly comorbid.
- Putative genetic mutations account for shared variance between symptoms of autism and inattention.
- Cognitive deficits associated with autism and ADHD may be better conceptualized as comorbidities, rather than endophenotypes.
- Genetic events associated with ASD may provide leads for investigating the genetic etiology of ADHD.

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Accepted for publication: 3 August 2017
First published online: 18 September 2017