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Regular Article

Single nucleotide polymorphism heritability and differential patterns of genetic overlap between inattention and four neurocognitive factors in youth

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Abstract

Theoretical models of attention-deficit/hyperactivity disorder implicate neurocognitive dysfunction, yet neurocognitive functioning covers a range of abilities that may not all be linked with inattention. This study (a) investigated the single nucleotide polymorphism (SNP) heritability (h^2_{SNP}) of inattention and aspects of neurocognitive efficiency (memory, social cognition, executive function, and complex cognition) based on additive genome-wide effects; (b) examined if there were shared genetic effects among inattention and each aspect of neurocognitive efficiency; and (c) conducted an exploratory genome-wide association study to identify genetic regions associated with inattention. The sample included 3,563 participants of the Philadelphia Neurodevelopmental Cohort, a general population sample aged 8–21 years who completed the Penn Neurocognitive Battery. Data on inattention was obtained with the Kiddie Schedule of Affective Disorders (adapted). Genomic relatedness matrix restricted maximum likelihood was implemented in genome-wide complex trait analysis. Analyses revealed significant h^2_{SNP} for inattention (20%, SE = 0.08), social cognition (13%, SE = 0.08), memory (17%, SE = 0.08), executive function (25%, SE = 0.08), and complex cognition (24%, SE = 0.08). There was a positive genetic correlation (0.67, SE = 0.37) and a negative residual covariance (−0.23, SE = 0.06) between inattention and social cognition. No SNPs reached genome-wide significance for inattention. Results suggest specificity in genetic overlap among inattention and different aspects of neurocognitive efficiency.

Keywords: adolescence, GCTA, genetics, heritability, inattention, neurocognitive functioning

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Individual differences in neurocognitive skills predict symptom presentation in individuals with attention-deficit/hyperactivity disorder (ADHD; Adalio, Owens, McBurnett, Hinshaw, & Pfiffner, 2018), and theoretical models of ADHD regularly implicate neurocognitive dysfunction as a predisposing factor (Barkley, 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Diamond, 2005). The observed and theoretical comorbidity between ADHD and neurocognitive dysfunction has stimulated investigations into the utility of measures of neurocognitive dysfunction to serve as endophenotypes (i.e., phenotypes that are more proximal to the etiology of a clinical disorder and influenced by common genes that reflect susceptibility for the disorder; Gottesman & Gould, 2003) for ADHD. In fact, neurocognitive processes (e.g., working memory, inhibition) are highlighted by the National Institutes of Mental Health Research Domain Criteria Initiative (RDoC) as endophenotypes that may be particularly useful for clarifying the mechanisms that underlie psychiatric disorders (Karalunas, Bierman, & Huang-Pollock, 2016).

The multifaceted nature of both ADHD and neurocognition complicates the study of neurocognitive dysfunction in ADHD, as there may be deficits in some but not all of the neurocognitive functions and patterns that are specific to different ADHD presentations such as inattentive (ADHD-I), hyperactive impulsive (ADHD-HI), and combined (ADHD-C). As a result, studies of the overlap between ADHD and neurocognitive function require a nuanced approach to clarify the specificity of comorbidity among ADHD and neurocognitive dysfunction. Further, different presentations of neurocognitive dysfunction may emerge for the dimensional (i.e., symptom count) versus categorical (i.e., diagnostic) classification of inattention. Although the use of categorical diagnoses is crucial for prioritizing individuals that are most in need of intervention, levels of inattention are variable within the population and it is important to understand how those varying levels relate to other outcomes, such as

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neurocognitive dysfunction. The utility of symptom counts vs. categorical diagnoses has been demonstrated for dimensional behaviors (Knopik et al., 2005; Levy, Hay, McStephen, Wood, & Waldman, 1997) including inattention (Bidwell et al., 2007). An exploration of the latent structure of inattention in a general population sample revealed that inattention problems have a dimensional latent structure (Marcus & Barry, 2011). This is consistent with the dimensional nature of many psychiatric conditions, including ADHD (Bidwell et al., 2017). Given the multidimensional and developmental nature of inattention, examining dimensions of behaviors rather than categories may be most useful in determining the etiology of inattention (Nikolas & Burt, 2010) and its overlap with neurocognitive functioning. To this end, the current study takes a dimensional perspective to evaluate inattention by using factor analysis to capture the shared variance among symptoms of inattention (rather than diagnostic cutoffs) and examines the genetic overlap between inattention and four aspects of neurocognitive functioning in youth: social cognition, memory, executive function, and complex cognition.

Neurocognitive Dysfunction in ADHD-I and Dimensional Assessment of Inattention

Behaviorally, children with ADHD-I often exhibit inattention, disorganization, and social passivity or social isolation (Hinshaw, 2002). The neurocognitive characteristics of children with ADHD-I subtype include slow orientation and responding to stimuli in their surroundings and challenges with memory search and retrieval (Solanto et al., 2007). Investigations of the neural mechanisms that underlie inattention in ADHD-I suggest that there are deficits in automatic perceptual processes (e.g., visual orienting to novel stimuli) that are mediated by the posterior attentional system (Posner & Petersen, 1990) as well as in the mediation of perceptual input processes via the arousal system (Tucker & Williamson, 1984). Further, children with ADHD-I recruit attentional alerting and/or orienting processes less efficiently than children with ADHD-C do in the context of inhibitory control tasks (Solanto et al., 2009). Consequently, in terms of performance on neurocognitive tasks, children with inattention would be expected to present with slower processing speed and slower reaction time, particularly in the context of cognitive load. However, *neurocognitive functioning* covers a wide range of abilities, which may or may not all be linked with inattention, underscoring the value of assessing the associations between inattention and multiple aspects of neurocognitive function. Further, despite prior evidence that inattention and neurocognitive function are associated, the factors that link these constructs in a pediatric sample remain undetermined. Genetically informed designs can be leveraged to investigate the sources of individual differences (i.e., genetic and environmental) in inattention and neurocognitive functioning and the sources that are common to both.

Genetic Influences on Inattention and Neurocognitive Functioning

There is evidence that individual differences in both clinical and dimensional levels of inattention emerge from a multilocus genetic basis that includes additive genetic effects (i.e., genes acting additively with each other both within and between loci [Hill, Goddard, & Visscher, 2008]), nonadditive genetic effects (i.e., interactions among alleles at the same or different loci [Pingault et al., 2015]), and nonshared environmental influences (i.e., environments unshared by family members that contribute to familial dissimilarity). Twin studies of both clinical and nonclinical levels of inattention reveal high heritability estimates (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007; Peng et al., 2016; Sherman, Iacono, & McGue, 1997; Willcutt, Pennington, & DeFries, 2000). For example, attention problems in middle childhood were highly heritable (77% for girls and 83% for boys) based on additive genetic effects (Groot, De Sonneville, Stins, & Boomsma, 2004). A meta-analysis of twin studies of the genetic and environmental influences on ADHD symptom dimensions of inattention revealed a high broad heritability estimate (71%), with the presence of dominant genetic influences and additive genetic influences ranging from 46–77% depending on the sex, age, and informant (Nikolas & Burt, 2010). Heritability may also be estimated by evaluating the additive genome-wide effects of single nucleotide polymorphisms (SNPs). As is consistent with other complex traits (Cheesman et al., 2017), the SNP-based heritability (h^2_{SNP}) estimates of inattention are lower than twin-based estimates. For example, a recent study of adult self-reported frequency of inattentive symptoms showed a moderate h^2_{SNP} of 44% (Bidwell et al., 2017).

Twin and family studies also consistently reveal genetic influences on individual differences in aspects of neurocognitive functioning. For example, individual differences in inhibitory control were approximately 50% heritable (Polderman et al., 2009; Polderman et al., 2007) and neural correlates of response inhibition in adolescence are also genetically influenced (Anokhin, Golosheykin, Grant, & Heath, 2017). Heritability estimates of set-shifting ranged from 50–80% in adolescence and adulthood (Anokhin, Heath, & Ralano, 2003; Friedman et al., 2008). Additive genome-wide effects of SNPs explain modest to moderate variance in aspects of neurocognitive functioning. For example, a prior study that also examined data from the same sample that was used in this study found that common SNPs explained 36% of the variance in general cognitive functioning, 12% in memory, 15% in social cognition, and 46% in reasoning and executive function (Robinson et al., 2014). Measures of neurocognitive ability tend to be positively associated both phenotypically and genetically, although not perfectly (Davies et al., 2016), underscoring the usefulness of evaluating the overlap between inattention and neurocognitive functions separately.

Shared Genetic Effects Among Inattention and Neurocognitive Functioning

Twin and family studies provide evidence that the co-occurrence of inattention and neurocognitive dysfunction is partially attributable to common genetic influences. Common genes link different aspects of neurocognitive functioning and ADHD, including verbal working memory (Bidwell, Willcutt, DeFries, & Pennington, 2007; Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005), abstract problem solving (Bidwell et al., 2007), interference control (Bidwell et al., 2007; Doyle et al., 2005; Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Meulen, & Buitelaar, 2003), processing speed (Bidwell et al., 2007; Doyle et al., 2005), verbal learning (Seidman, Biederman, Monuteaux, Weber, & Faraone, 2000), intellectual ability (Faraone et al., 1993; Kuntsi et al., 2003), and academic skills (Doyle et al., 2005; Gayán et al., 2005; Willcutt, Pennington, Olson, & DeFries, 2007). However, there is variability in the magnitude of genetic overlap,

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Table 1. Descriptive statistics and tetrachoric correlations among inattention symptoms ($n = 3,719$)

		Correlations				
Item	% endorsed	1	2	3	4	5
1. Trouble paying attention or keeping your mind on your school, work, chores, or other activities	34.6	—				
2. Problems following instructions and often fail to finish school, work, or other things you meant to get done	28.0	.93	—			
3. Dislike, avoid, or put off school or homework (or any other activity requiring concentration)	34.4	.84	.85	—		
4. Lose things you needed for school or projects at home; make careless mistakes in school work or other activities	33.6	.83	.83	.81	—	
5. Trouble making plans, doing things that had to be done in a certain kind of order, or that had a lot of steps	22.7	.84	.87	.76	.81	—
6. People tell you that you did not seem to be listening when they spoke to you or that you were daydreaming	29.7	.89	.87	.79	.80	.82
Variable	Mean	*SD*		Minimum		Maximum
Total inattention symptoms endorsed	1.81	2.25		0		6

underscoring the value of evaluating associations between inattention and different aspects of neurocognitive functioning. Molecular genetic investigations have identified specific genes that link ADHD-I/nonclinical inattention symptoms and various aspects of neurocognitive dysfunction (e.g., Luca et al., 2007). For example, a region on chromosome 3q13 is associated with both ADHD inattention symptoms and multiple neurocognitive measures including inhibitory control, set-shifting, planning/organization, verbal learning, working memory, and arithmetic and reading skills (Doyle et al., 2008). Additionally, there is evidence for an association of the dopamine receptor D1 gene with symptoms of inattention in families that were specifically selected for reading problems (Luca et al., 2007). Importantly, genetic overlap between aspects of neurocognitive functioning and inattention is partial, not complete, and the magnitude of genetic overlap with inattention varies by neurocognitive phenotype. For example, two aspects of cognitive functioning (i.e., reaction time variability and commission errors on the go/no-go and fast tasks) showed moderate (0.64) and low (0.11) genetic overlap with inattention in youth (Kuntsi et al., 2014).

Current Study

Evidence from prior research indicates that inattention and neurocognitive functioning are associated at the phenotypic level and common genetic influences contribute to both inattention and neurocognitive dysfunction. Neurocognitive functioning covers a wide range of abilities, and some of them may or may not be linked with inattention. A systematic examination of the association between inattention and multiple aspects of neurocognitive function is needed but has not been completed to date. To our knowledge, there have been no studies of the genetic overlap between symptoms of inattention and multiple aspects of neurocognitive functioning as measured by the additive effects of SNPs in a pediatric sample. As such, the goals of the current study were to (a) investigate the h^2_{SNP} of inattention and aspects of neurocognitive efficiency (memory, social cognition, executive function, and complex cognition) based on additive genome-wide effects; (b) examine if there were shared genetic effects among inattention and each aspect of neurocognitive efficiency; and (c) conduct an exploratory genome-wide association study (GWAS) to identify the genetic regions that are associated with inattention.

Method

Sample

The participants were children and adolescents ages 8 to 21 years that were enrolled in the Philadelphia Neurodevelopmental Cohort (PNC; Satterthwaite et al., 2016), a large-scale, NIMH-funded collaboration between the Center for Applied Genomics at the Children's Hospital of Philadelphia and the Brain Behavior Laboratory at the University of Pennsylvania. Consent/assent was obtained for the children to participate in genomic studies of complex pediatric disorders. The participants completed clinical assessments including a structured neuropsychiatric interview and review of electronic medical records. The participants also completed a comprehensive computerized neurocognitive battery and self- and parent-reports of behaviors (e.g., ADHD symptoms) were obtained. For more complete descriptions of the study, see Calkins et al. (2015) and Gur et al. (2012).

The participants received a severity rating for medical condition based on parent report (for children 17 or younger) or self-report (for participants ages 18 to 21) and electronic medical records, ranging from 1 (*none or minor*) to 4 (*severe*). Consistent with other studies of the same sample (e.g., Robinson et al., 2014) those with a medical rating of 4 were excluded from the analyses, as physical symptoms may have affected their task performance. Individuals with invalid neurocognitive tests were marked as missing.

Measures

Inattention

Participants (for participants ages 18+) or their parent (for participants under age 18) reported on six inattention questions that were drawn from the Kiddie Schedule for Affective Disorders and Schizophrenia (shortened) interview (Merikangas, Avenevoli, Costello, Koretz, & Kessler, 2009). The inattention items (Table 1) assessed the presence of inattentive behaviors across activities that demand attention (e.g., school work, making plans) and across

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Table 2. Model results (standardized factor loadings, standard errors, and *p* values) from the full sample confirmatory factor analysis of inattention symptoms ($n = 3{,}719$)

Item	*B*	*SE*	*p*
1. Trouble paying attention or keeping your mind on your school, work, chores, or other activities	.958	.005	<.001
2. Problems following instructions and often fail to finish school, work, or other things you meant to get done	.965	.005	<.001
3. Dislike, avoid, or put off school or homework (or any other activity requiring concentration)	.878	.009	<.001
4. Lose things you needed for school or projects at home; make careless mistakes in school work or other activities	.881	.009	<.001
5. Trouble making plans, doing things that had to be done in a certain kind of order, or that had a lot of steps	.893	.009	<.001
6. People tell you that you did not seem to be listening when they spoke to you or that you were daydreaming	.914	.007	<.001

Note: Model fit—RMSEA = .036, 90% CI [.027, .046]; CFI = .999; χ^2 (9) =52.905, $p = <.001$.

contexts (e.g., "Did you often have trouble paying attention or keeping your mind on school, work, chores, or other activities that you were doing?"). The items were coded as 0 = *no* (*unaffected*), 1 = *yes* (*affected*). To our knowledge, the reliability and validity of the six-item assessment for inattention has not been tested in the PNC sample, but Cronbach alpha for inattention in the current study was .90.

Neurocognitive Functioning

The Penn Computerized Neurocognitive Battery (CNB) was used to conduct 12 tasks that reflect four domains of neurocognitive functioning (Gur et al., 2012; Moore, Reise, Gur, Hakonarson, & Gur, 2015). Each of four neurocognitive domains were assessed with three tasks. *Social cognition* evaluated emotion identification, emotion intensity differentiation, and age differentiation with the Penn Emotion Identification Test, Penn Emotion Differentiation Test, and the Penn Age Differentiation test, respectively. *Memory* reflected episodic memory for verbal material, faces, and shapes and was assessed with the Penn Word Memory Test, Penn Facial Memory Test, and the Visual Object Learning Test, respectively. *Executive function* evaluated abstraction and mental flexibility, vigilance and visual attention, and working memory with the Penn Conditional Exclusion Test, Penn Continuous Performance Test, and the Penn Letter N-Back Test. *Complex cognition* reflected verbal, nonverbal, and spatial reasoning, assessed with the Penn Verbal Reasoning Test, Penn Matrix Reasoning Test, and the Penn Line Orientation Test. The CNB demonstrates adequate psychometric properties in the PNC sample (Moore et al., 2015), and Cronbach's alphas for the neurocognitive measures in the present study were acceptable (i.e., Memory = .91; Social Cognition = .97; Executive Function = .90; Complex Cognition =.90).

Moore and colleagues (2015) evaluated the neuropsychological theory that was used to construct the CNB by confirming the factor structure of the tests that compose it within the PNC sample. The authors compared the fit of a correlated traits model and a bifactor model and advise researchers to use the correlated traits model if the investigators use CNB subscale scores. As such, the current study sought to confirm the four-factor correlated model (Moore et al., 2015).

Data Analysis

Derivation of Phenotypes

Exploratory and confirmatory factor analyses were conducted in Mplus Version 8 (Muthén & Muthén, 1998–2017). Missing data were handled with full information maximum likelihood estimation. Model fit was assessed with the confirmatory fit index (CFI) and the root mean square error of approximation (RMSEA), where better fit is indicated by CFI > .90 and RMSEA < .05 (Noar, 2003).

Inattention

To derive a continuous dimension of inattention problems that captures the shared variance among available inattention symptoms, we conducted a factor analysis of the inattention items. This approach has also been applied using externalizing items within the PNC data (Shanmugan et al., 2016). First, the sample was split into random halves to conduct the exploratory and confirmatory factor analyses (EFA and CFA, respectively). Weighted least-squares mean variance estimation was used for analyzing the binary inattention items. An exploratory factor analysis of data from half of the sample ($n = 1{,}858$) revealed a single dimension of inattention with the following model fit statistics: χ^2 (9) = 15.281, $p = .084$; RMSEA = .019. All of the items had high factor loadings, ranging from .876 to .971. The single dimension was confirmed by conducting a CFA of the second half of the sample data ($n = 1{,}861$), with model fit statistics, χ^2 (9) = 48.107, $p < .001$; RMSEA = .048, 90% CI [.035, .062]; CFI = .999, and again with the full sample. The inattention items and model results from the full sample CFA are presented in Table 2. The model fit statistics and parameter estimates for the split-half EFA and CFA are presented in Supplemental Table 1. Based on the confirmation of a single factor solution in the CFA, the factor scores from the one factor solution were extracted to be used in the genetic analyses.

Neurocognitive Functioning

For neurocognitive functioning, a CFA using maximum likelihood estimation was conducted with data that were collected from 3,571 individuals who completed the CNB. Consistent with Moore et al.'s (2015) approach, raw accuracy and speed data from the CNB were transformed into standard scores (*z*-scores) by using the sample mean and standard deviation for each measure. Median speed was multiplied by -1, with higher scores indicating faster response times and better performance on both measures. Efficiency scores were calculated to reflect the sum of the standardized scores on speed and accuracy, and they were used as is advised by Moore and colleagues. Further, considering that the focus of our study was to examine inattention, with ADHD hypothesized and shown to impair speed-accuracy tradeoff optimization (Mulder et al., 2010), we focused on an average of speed and accuracy. The factor structure (see Figure 1) yielded factor loadings that were similar to those reported by Moore

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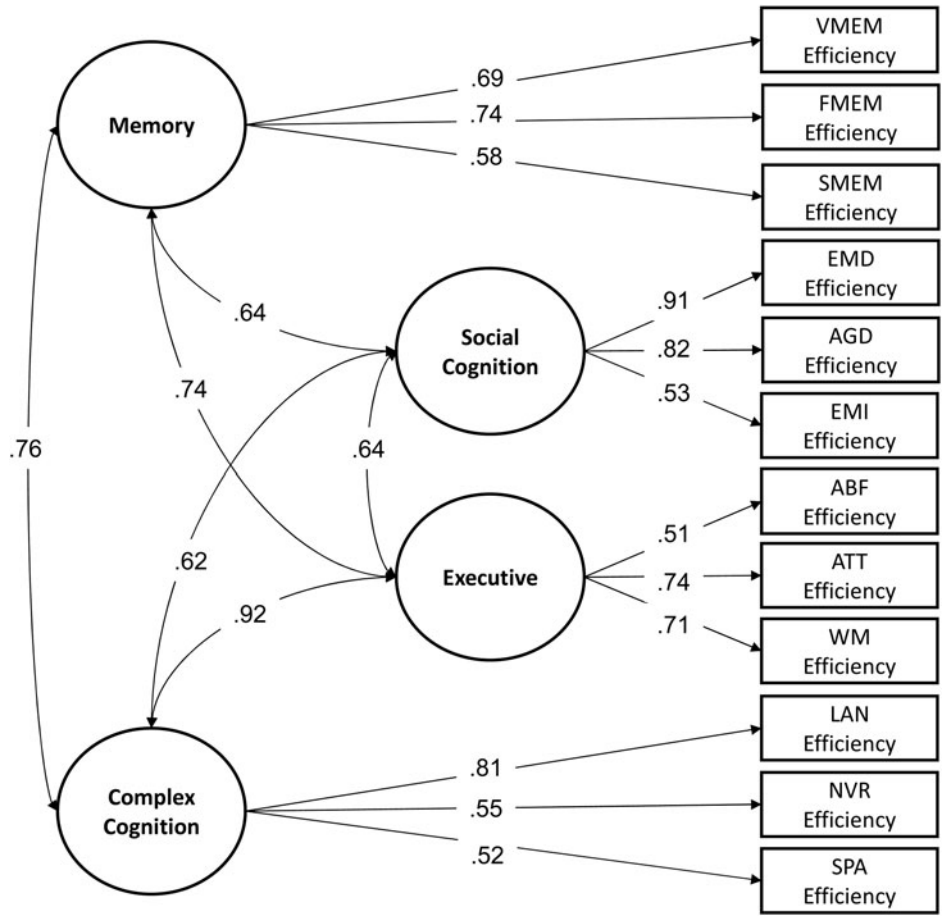

Figure 1. Confirmatory correlated-traits model of CNB efficiency scores.

et al. (2015). Support for the correlated four-factor model was also demonstrated by the model fit statistics, χ^2 (66) = 16,205.418, p < .001; RMSEA = .097, 90% CI [.093, .101]; CFI = .900.

Genotyping, Quality Control, and Genetic Imputation

The SNP & Variation Suite (version 8.4.4), PLINK (version 1.9; Purcell et al., 2007), and R (version 3.1.1) were used for all of the genetic data management. Genomic data were drawn from the Neurodevelopmental Genomics: Trajectories of Complex Phenotypes Study through the National Center for Biotechnology Information's Database for Genotypes and Phenotypes (dbGAP, Study Accession: phs000607.v3.p2). A large sample of youth who had been genotyped previously and data from several Illumina platforms were pooled (Illumina Human610 Quad v1, Human Hap550 v1.1, Human Hap550 v3.0, Human 1M-Duo, Human OmniExpress-12 v1.0). We conducted a principle components analysis within each sample by using the 1000 Genomes Project (1KG) Phase III (Version 5) reference panel (Auton et al., 2015) to determine genetic ancestry and perform strand alignment. A total of 4,296 individuals of European ancestry (EA) were identified and selected for imputation by using a pipeline that minimizes effects due to population stratification by screening based on alignment with the 1KG reference samples of Utah residents of northern and western European ancestry. For a detailed outline of this protocol, see Brick, Keller, Knopik, McGeary, & Palmer, 2019. Briefly, each sample was genetically imputed by using the 1KG reference panel and ShapeIT phasing with Minimac3 via the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!pages/home). Following imputation, markers that were not biallelic, were not autosomal, or had a poor imputation quality score (r^2 < 0.30) were removed. Next, markers that had a call rate < 99%, low minor allele frequency (<1%), or failed the Hardy–Weinberg equilibrium test (p < 0.0001) were removed and samples with < 90% missing data were removed, resulting in a total of 5,360,405 SNPs. A genetic relationship matrix was computed by using the genome-wide complex trait analysis software tool (version 1.25.3) to control for cryptic relatedness (Yang, Lee, Goddard, & Visscher, 2011). A total of 3,991 unrelated individuals of EA were retained for analysis. See Supplemental Table 2 for a summary of the markers that were removed at each step of the quality control procedure.

SNP-based Univariate and Bivariate Heritability Estimates

Genetic analyses were conducted on the subsample of 3,563 youth of EA (50% female; mean age = 13.7, standard deviation = 3.65) that had available genetic data, valid CNB data, and data on inattention symptoms. Genomic-relatedness-based restricted maximum likelihood, implemented in genome-wide complex trait analysis software (Yang et al., 2011), was used to estimate the h^2_{SNP} of each construct. That is, the phenotypic variance in inattention and each neurocognitive factor was decomposed into the additive effects of genotyped and imputed SNPs. Additionally, we conducted regression analyses to determine whether h^2_{SNP} estimates for inattention varied by chromosome and longer chromosomes accounted for more variance in inattention. These analyses were followed with a mixed-linear-model-based association analysis (Yang, Zaitlen, Goddard, Visscher, &

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Table 3. Univariate SNP-heritability (h^2_{SNP}), phenotypic correlation (r_p), and genetic correlation (r_g) estimates for inattention and neurocognitive domains ($n = 3,563$)

Trait	h^2_{SNP}	*SE*	*p (one-tailed)*	r_p with inattention	r_g with Inattention	*SE*	*p (one-tailed)*	*p (two-tailed)*
Inattention	.20	.08	.005	—	—	—	—	
Memory	.17	.08	.012	−.07***	0.23	0.38	0.26	0.52
Social Cognition	.13	.08	.034	−.05**	0.67*	0.37	0.009	.018
Executive Function	.25	.08	<.001	−.08***	0.20	0.34	0.26	0.52
Complex Cognition	.24	.08	<.001	−.08***	0.20	0.35	0.27	0.54

Note: *SE* = standard error. ***$p < .001$ **$p < .01$.

Price, 2014) to identify loci that were significantly associated with inattention. In the mixed linear model based association analyses, false discovery rate ($q < 0.05$) was used to correct for multiple testing (Benjamini & Hochberg, 1995). Bivariate genomic-relatedness-based restricted maximum likelihood was used to determine the additive genetic correlation ($r_{G\text{-}SNP}$) between inattention and each of the four neurocognitive factors. The $r_{G\text{-}SNP}$ estimate (ranging in value from -1.0 to 1.0) reflects the extent to which the same gene loci influence both outcomes. The two-tailed *p* values were derived by using the change in log-likelihood when the $r_{G\text{-}SNP}$ is fixed to zero, which is distributed as a chi-square statistic. All of the analyses controlled for sex and age.

Results

Prevalence of Inattention Symptoms and Associations With Neurocognitive Functioning

The percentages of endorsement for each inattention question and the correlations among the inattention items are presented in Table 1. The most commonly endorsed (34.6%) item was "Trouble paying attention or keeping your mind on your school, work, chores, or other activities." Associations among the inattention items were uniformly high, ranging from .76 to .93 (see Table 1). The factor scores between inattention and each aspect of neurocognitive function were negatively associated (r_P ranged from -.05 to -.08; Table 3), indicating that, phenotypically, higher levels of inattention were associated with lower neurocognitive efficiency across each domain.

Univariate and Bivariate SNP-Heritability Estimates

The SNP-based heritability estimates and genetic correlations are presented in Table 3. Modest genetic influences were observed for inattention (.20, $SE = 0.08$), memory (.17, $SE = .08$), social cognition (.13, $SE = .08$), executive function (.25, $SE = .08$), and complex cognition (.24, $SE = .08$). The examination of the additive genetic effects by chromosome indicated that several chromosomes (chromosomes 1, 3, 4, 8, 10, 13, and 14) significantly contributed to the total additive genetic variance in inattention (see Supplemental Figure 1). Longer chromosomes did not account for more genetic variance ($B = <.001$; $p = .10$). The bivariate analyses revealed a moderate positive genetic correlation between inattention and social cognition, ($r_{G\text{-}SNP} = .67$, $SE = .37$, $p < .01$) and a negative residual covariance ($r_E = -.23$, $SE = 0.06$). The genetic correlations between inattention and memory, executive function, and complex cognition were not significant (Table 3).

Exploratory GWAS

For inattention, no markers were significant at the GWAS level of $p < 10^{-8}$. One region on chromosome 16 (16:75216240) reached $p < 10^{-6}$, and 82 markers reached $p < 10^{-5}$. No markers passed the false discovery rate threshold (Benjamini & Hochberg, 1995). See Figure 2 for the Manhattan plot of the GWAS *p* values. The top hits and associated *p* values are presented in Supplemental Table 3. The GWAS results are available from the authors upon request.

Discussion

The goal of this study was to use data from a large pediatric sample to conduct a genetically informed study of the associations between inattention and four neurocognitive efficiency factors (memory, social cognition, executive function, and complex cognition) to uncover potentially heterogeneous neurocognitive impairments that are associated with inattention. The findings revealed that inattention and the neurocognitive efficiency variables were each modestly heritable and that there was a moderate, positive genetic correlation between inattention and only one aspect of neurocognitive efficiency, social cognition. The genetic correlations among inattention and neurocognitive efficiency in memory, executive, and complex cognition were not significant.

Consistent with research that has uncovered large gaps between the h^2_{SNP} and twin heritability for complex childhood traits such as cognitive abilities and behavior problems (Cheesman et al., 2017), the h^2_{SNP} of inattention that was observed in this study (i.e., 20%) falls towards the lower end of the estimates that have been reported from twin/family studies (Nikolas & Burt, 2010), which may be reflective of broad- rather than narrow-sense effects. The h^2_{SNP} estimate obtained herein is also lower than the h^2_{SNP} of 44% that was observed for the frequency of inattentive symptoms in a community sample of adults (Bidwell et al., 2017). One explanation for the different magnitude of genetic effects is differences in methodology. In the current study, the measure of inattention did not necessarily reflect the clinical levels of inattention that are observed in ADHD diagnoses. Instead, it may have reflected a normative level of inattention that is qualitatively different. Another plausible explanation for the differing magnitudes of genetic influence is the implication of evaluating heritability based on the additive effects of SNPs when nonadditive genetic effects have been observed in twin studies of inattention. If nonadditive genetic effects are important in the etiology of inattention, it is reasonable that these h^2_{SNP} estimates would be lower than those that have been observed in twin studies. The difference between the h^2_{SNP} estimate for inattention in this study and that of Bidwell et al. (2017) may be due to the developmental

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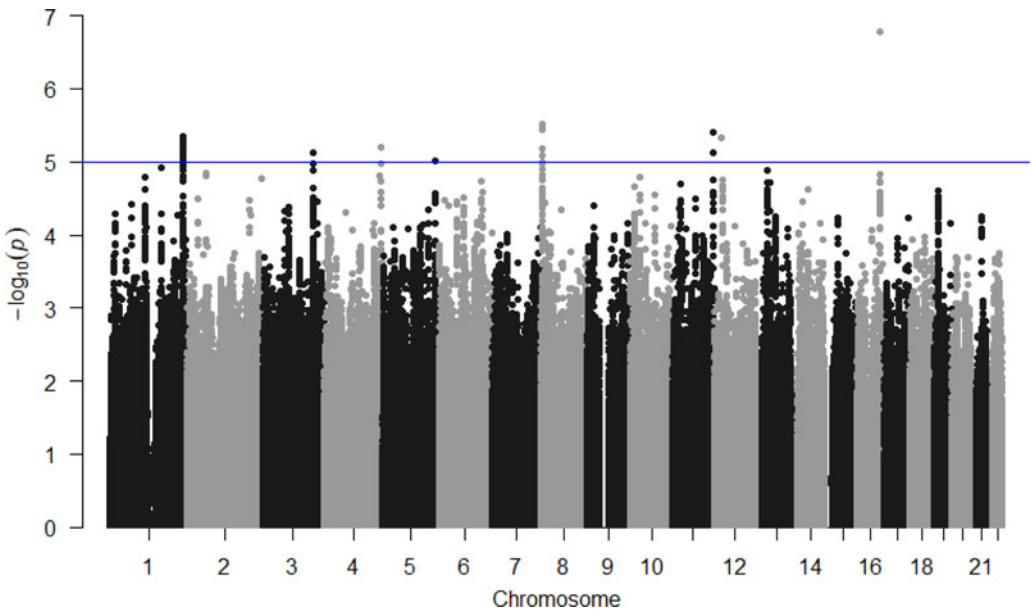

Figure 2. Manhattan plot for inattention by chromosome ($n = 3{,}563$).

course of inattention symptoms over time and the fact that this study evaluated inattention in youth. The symptoms of ADHD (Faraone, Biederman, & Mick, 2006) and inattention decline over age (Biederman, Mick, & Faraone, 2000), so heritability estimates may also follow this pattern and fluctuate with time. Additionally, the inclusion of more items (nine items vs. six included here) and items that capture different aspects of inattention by Bidwell et al. (2017) may contribute to the different magnitudes of h^2_{SNP}. For example, the Adult ADHD Self-Report Scale (Kessler et al., 2005) that was used by Bidwell et al. (2017) includes an item that asks explicitly about the frequency that the individual experiences distraction due to an activity or stimulus in their surroundings. The items included in this study obtained information about more concrete activities (e.g., related to school work or task completion), which may be more developmentally appropriate for this age range but, nonetheless, could contribute to the variation in heritability estimates.

Chromosome 1 accounted for the largest amount of the total observed genetic variance in inattention and the results of the mixed-linear-model-based association analysis revealed that 10 of the top 20 top hits were located on chromosome 1. Other molecular genetic studies have implicated chromosome 1 in the genetic architecture of ADHD. For example, a quantitative trait loci linkage scan revealed that there was a common locus at chromosome 1p36 that influenced both parent and teacher reports of ADHD symptoms (Zhou et al., 2008). Regions on chromosomes 7, 8, and 11 were also identified in a meta-analysis of GWAS studies of childhood ADHD (Neale et al., 2010). Although none of the SNPs reached genome-wide significance, five of the top 10 hits in the present study were on chromosome 8. For inattention specifically, consistent with the present findings, GWAS studies have failed to yield significant genome-wide effects (e.g., Ebejer et al., 2013). The strongest effect in the gene-based test was for G-protein coupled receptor 139 on symptoms of inattention (6.40×10^{-5}). Therefore, an ongoing effort is required to identify genes that underlie the heritable component of inattention (Neale et al., 2010). Future work could expand on these findings by estimating the heritability of more specific genomic regions such as candidate SNPs based on chromosomal or gene-based regions of interest for inattention. These analyses focused on autosomal variants due to the lack of any prior evidence of sex-specific effects. Therefore, genetic information common across males and females was explored while controlling for sex effects. Future research may consider exploring the role of the X chromosome in inattention and its covariance with neurocognitive efficiency.

The genetic effects that were observed for the four aspects of neurocognitive efficiency are of similar magnitudes to those that were identified in a prior study that used data from the same sample (Robinson et al., 2014). However, it is important to note that the measurement of neurocognitive function in this study differed slightly from that in the previous study. Robinson et al. (2014) used principle components analysis to extract three components of neurocognitive functioning (i.e., reasoning and executive function, social cognition, and memory). In contrast, the decision to model the four-factor structure of neurocognitive functioning that was used in the current study was based on a recent theoretically based and psychometrically rigorous investigation into the factor structure of the CNB (Moore et al., 2015). Based on Moore et al. (2015), we separated the reasoning and executive function component that was derived in Robinson et al. (2014) into two separate factors, executive function and complex cognition. It was important to keep executive function and complex cognition separate in this study, as the primary goal was to evaluate differential patterns of overlap between inattention and aspects of neurocognitive efficiency, and the executive function and complex cognition factors assess different aspects of neurocognitive function.

The positive genetic correlation between inattention and social cognition, though in need of replication, suggests that the same genetic loci influence both inattention and social cognition. In interpreting this finding, it is important to consider two points: (a) the possible consequences of using efficiency scores for the neurocognitive functioning variables; and (b) the levels of inattention that were captured in this study are not necessarily maladaptive or at a clinical categorical threshold.

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Regarding the first point, it may be the case that a modest amount of inattention facilitates social cognitive *efficiency*. It is reasonable that, in terms of speed/accuracy, social cognitive processing that is "not too slow" and "just accurate enough" may be more related to inattention than are fast/inaccurate and slow/accurate processing. Additionally, although evidence suggests that individuals with ADHD may demonstrate deficits in emotion perception compared with those without (Bisch et al., 2016), studies of typically functioning individuals show that conditions that promote inattention (i.e., distributed focus) result in better attention to happy faces than to sad faces (Srinivasan & Gupta, 2010; Srinivasan & Hanif, 2010). Therefore, the type of emotion that is being identified may interface with level of attention, allowing for the possibility that modest levels of inattention could be adaptive under prescribed situations. Future research that is directed at disentangling different symptomology profiles will shed light on the potential positive influence of moderate levels of inattention. Additionally, future studies could integrate other variables (e.g., personality, psychopathology) to probe mechanistic hypotheses.

Further, there was a negative phenotypic correlation between inattention and social cognition but a positive genetic correlation between the two constructs. It has been shown that a phenotypic correlational structure can be quite different from the underlying genetic and environmental structure (Cloninger, 1987; Heath & Martin, 1990; Knopik, Heath, Bucholz, Madden, & Waldron, 2009; Stallings et al., 1996). Because phenotypic correlations reflect both the correlation of additive genetic and environmental effects (i.e., environmental represents any effects that are not additive genetic), differences between phenotypic and genetic correlations must be explained by the relationship between genetic and environmental effects (Sodini et al., 2018). Therefore, certain traits have environmental effects that act in the opposite direction to the genetic effects (Hadfield et al., 2007). In this case, the genetic loci that were associated with increases in inattention were also associated with increased social cognitive efficiency as measured here, but environmental factors operated differently across the two traits, influencing the association such that the phenotypic correlation became negative.

Although inattention was associated with all of the aspects of neurocognitive efficiency at the phenotypic level, these associations were not largely explained by common genetic effects. This finding is not consistent with a study of young twins that determined that the association among inattention and two aspects of neurocognitive functioning (reaction time variability and commission errors) was, in part, attributable to common additive genetic effects (Kuntsi et al., 2014). Further, while there is evidence that a region on chromosome 3q13 is associated with both ADHD inattention symptoms and multiple neurocognitive measures (Doyle et al., 2008), at the level of h^2_{SNP}, the additive effects of SNPs did not explain the phenotypic correlations among the constructs. Again, this may be due to the multifaceted nature of neurocognitive functioning and the possibility that there are differential patterns of genetic overlap between inattention and aspects of neurocognitive functioning. For example, there is evidence that shared genetic variability between reading difficulties and ADHD inattention symptoms is largely independent from genes that contribute to individual differences in general cognitive ability (Paloyelis, Rijsdijk, Wood, Asherson, & Kuntsi, 2010).

Furthermore, there is evidence that child-specific environmental factors also contribute to the covariation between reading difficulties and inattention symptoms (Paloyelis, et al., 2010) and it is possible that common environmental influences rather than genetic effects explain the phenotypic overlap among inattention and neurocognitive efficiency. Prior evidence implicates processing speed and memory search and retrieval impairments in children with ADHD-I (Adalio et al., 2018). Therefore, we would expect children with inattention to perform more poorly on the executive function factor in particular. We observed a phenotypic association that aligned with this hypothesis, but the association was not explained by shared genetic effects. This may be because the genetic link between processing speed and inattention may be most salient for children with the most severe levels of inattention and our sample reflected those with dimensional levels of inattention. Therefore, these results indicate that the symptoms of inattention that are observed in general populations do not necessarily conform to the pattern of overlap between inattention and neurocognitive functioning that is observed in clinical populations. Another possibility is that inattention and neurocognitive efficiency are associated due to common additive genetic effects, but these effects could not be detected due to the relatively low h^2_{SNP} estimates for all of the variables. It will be important for future research to continue to explore the genetic and environmental sources of overlap among dimensional measures of inattention and various aspects of neurocognitive functioning, as the patterns of overlap may vary by measurement of both inattention and neurocognitive functioning as well as by the aspect of neurocognitive functioning under question.

The results of this study should be interpreted in light of the following considerations. First, although this study benefited from a large sample size, we were not powered to stratify the analyses by age or sex effects. The inclusion of participants across a relatively wide age range may introduce variation in h^2_{SNP} estimates. Investigations of genetic influences on neurocognitive functioning and inattention across development poses challenges due to the interplay between developmental and genetic factors (Anokhin et al., 2017). The heritability of inattention is relatively stable across adolescence (Anokhin et al., 2017; Larsson, Lichtenstein, & Larsson, 2006), whereas the heritability estimate of at least one aspect of neurocognitive functioning, set-shifting, increases across early adolescence (Anokhin, Golosheykin, Grant, & Heath, 2010). Future studies may consider evaluating whether the univariate h^2_{SNPs} and magnitude of genetic overlap among inattention and neurocognitive functions vary with age. Second, there were insufficient items (three) to obtain a reliable measure in this sample, but it would be of interest to determine if a similar pattern of findings emerges for dimensional measures of hyperactivity. Third, although Cronbach's alpha was acceptable in this study, to our knowledge the reliability and validity of the six-item assessment for inattention has not been demonstrated in the PNC sample and future studies are needed to validate this measure against typical assessments. Further, larger samples are needed to estimate several of these effects with sufficient confidence in future studies. Given that the standard errors for the genetic correlations are large, these findings should be considered to be preliminary, and they require replication. Finally, the present study used data only from individuals of European descent, and the extent to which these findings would generalize to other ancestral populations is unknown.

We must also consider potential bias in the results due to the reporting of inattention. The accuracy of youth self-report of ADHD symptoms as an identifier of ADHD is a longstanding debate. However, mounting empirical research suggests that parents and teachers are more accurate raters of ADHD symptoms

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than youth are, whereas in late adolescence and adulthood, self-reports of ADHD symptoms align with parent and partner ratings (Biederman et al., 2007). Discrepancies by reporter may be because youth and adults may have different thresholds for considering certain symptoms to be clinically significant (Achenbach et al., 1987) or that youth reports reflect an absence of self-awareness that may lead to a false negative report of ADHD by the youth (Biederman et al., 2007). Consequently, for youth under the age of 18, we used parent reports of their child's inattentive behavior, whereas for children aged 18 years or older we used self-report measures. There is evidence that aggregate ratings by parents and teachers are more accurate than parent report of child behavior alone (Narad et al., 2015). Therefore, it may be preferable for future studies to obtain both parent and teacher reports of child inattention to capture symptomology across raters and contexts. While the approach that was used in the current study is developmentally sensitive, the use of different reporters of inattention may limit the conclusions that can be drawn across ages.

Conclusion

The present study used a molecular genetic approach to evaluate the overlap among symptoms of inattention and a series of neurocognitive efficiency variables within a pediatric sample. The analyses revealed significant h^2_{SNP} for inattention, memory, social cognition, executive function, and complex cognition. Further, these findings provide preliminary evidence for a positive genetic and negative environmental correlation between inattention and social cognition. The observed phenotypic associations between inattention and efficiency in memory, executive function, and complex cognition were not explained by common SNPs that operate across the constructs. These findings underscore the value of assessing normative levels of inattention in genetically informed studies of general population samples as well as the usefulness of exploring the breadth of aspects of neurocognitive functioning, as the patterns of genetic overlap may not be universal across constructs.

Supplementary Material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579419001573.

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Conflict of Interest. The authors declare no conflict of interest.

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