Original Investigation

Genetic and Environmental Influences on the Developmental Course of Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Adolescence

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IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is conceptualized as a neurodevelopmental disorder that is strongly heritable. However, to our knowledge, no study to date has examined the genetic and environmental influences explaining interindividual differences in the developmental course of ADHD symptoms from childhood to adolescence (ie, systematic decreases or increases with age). The reason ADHD symptoms persist in some children but decline in others is an important concern, with implications for prognosis and interventions.

OBJECTIVE To assess the proportional impact of genes and the environment on interindividual differences in the developmental course of ADHD symptom domains of hyperactivity/impulsivity and inattention between ages 8 and 16 years.

DESIGN, SETTING, AND PARTICIPANTS A prospective sample of 8395 twin pairs from the Twins Early Development Study, recruited from population records of births in England and Wales between January 1, 1994, and December 31, 1996. Data collection at age 8 years took place between November 2002 and November 2004; data collection at age 16 years took place between February 2011 and January 2013.

MAIN OUTCOMES AND MEASURES Both *DSM-IV* ADHD symptom subscales were rated 4 times by participants' mothers.

RESULTS Estimates from latent growth curve models indicated that the developmental course of hyperactivity/impulsivity symptoms followed a sharp linear decrease (mean score of 6.0 at age 8 years to 2.9 at age 16 years). Interindividual differences in the linear change in hyperactivity/impulsivity were under strong additive genetic influences (81%; 95% CI, 73%-88%). More than half of the genetic variation was specific to the developmental course and not shared with the baseline level of hyperactivity/impulsivity. The linear decrease in inattention symptoms was less pronounced (mean score of 5.8 at age 8 years to 4.9 at age 16 years). Nonadditive genetic influences accounted for a substantial amount of variation in the developmental course of inattention symptoms (54%; 95% CI, 8%-76%), with more than half being specific to the developmental course.

CONCLUSIONS AND RELEVANCE The large genetic influences on the developmental course of ADHD symptoms are mostly specific and independent of those that account for variation in the baseline level of symptoms. Different sets of genes may be associated with the developmental course vs the baseline level of ADHD symptoms and explain why some children remit from ADHD, whereas others persist. Recent longitudinal imaging data indicate that the maintenance or increase in symptoms is underpinned by atypical trajectories of cortical development. This may reflect a specific genetic liability, distinct from that which contributes to baseline ADHD symptoms, and warrants closer follow-up.

JAMA Psychiatry. 2015;72(7):651-658. doi:10.1001/jamapsychiatry.2015.0469
Published online May 6, 2015.

Supplemental content at jamapsychiatry.com

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Attention-deficit/hyperactivity disorder (ADHD) is conceptualized as a neurodevelopmental disorder[1-3] under substantial genetic influences.[4,5] However, research modeling specifically the developmental course of ADHD symptoms is rare.[2] A better understanding of the developmental course of symptoms (ie, systematic decreases or increases with age) may inform clinicians on the clinical course of the condition[6,7] and prognosis[2,8]; it may also provide critical insights regarding the mechanisms underlying ADHD symptoms[2] and preventive interventions.[9] Although children experiencing a systematic decline or increase in symptoms with age show a differential long-term prognosis,[2,10,11] the origins of these interindividual differences in the developmental course of ADHD symptoms are largely unknown.[8] This study is the first, to our knowledge, to examine the respective impact of genetic and environmental influences on the developmental course of the ADHD symptom domains of hyperactivity/impulsivity and inattention, using a large population-based sample of twins followed up from childhood to adolescence.

In both clinical and population samples, the 2 symptom domains of ADHD, hyperactivity/impulsivity and inattention, have repeatedly demonstrated concurrent, predictive, and discriminant validity[1,6,12-14] and follow a different developmental course.[6,7,15] Whereas hyperactive/impulsive symptoms tend to decline steadily after early childhood,[6,15-17] inattention symptoms, after an initial increase in early childhood,[16] tend to be stable or follow a less pronounced decline.[2,6,15,18] Although these trends describe the mean change in symptoms with age, there is also substantial variation between individuals, eg, some children experience a steady decline in inattention symptoms with age, whereas symptoms persist or increase for others.[10,19] These interindividual differences reflect more than nonsystematic transient change or random noise. For example, population-based studies have shown that children with increasing levels of inattention were more at risk for long-term poor academic outcomes, even when controlling for baseline or mean levels of inattention.[10,11] Interestingly, a longitudinal imaging study in a clinical sample suggested that, independent of baseline symptom severity, interindividual differences in trajectories of cerebral cortical development in childhood and adolescence are associated with a differential clinical course (ie, remission vs persistence).[8] Taken together, these findings suggest that, independent of the baseline level of ADHD symptoms, the heterogeneity between individuals in the developmental course of symptoms may be underpinned by differences in cortical trajectories and associated with differential prognosis. However, the origins of the interindividual differences in ADHD symptoms (ie, why they persist in some children but decline in others) are still largely unknown.

Behavioral genetic designs can help in addressing this question. Extant longitudinal twin studies[4,5,20] have shown that genetic factors are largely responsible for the stability of ADHD symptoms (ie, genetic stability) but also that new genetic factors emerge at different developmental stages (ie, genetic innovation; for instance, different genetic variants may be associated with ADHD in childhood and adulthood[9,21,22]). Although the models used in these studies point toward the importance of genetic influences on the developmental course of ADHD, they focus on age-to-age change in ADHD symptoms. One approach to examine systematic long-term change in symptoms is modeling latent growth curve factors (intercept and slope).[23,24] The mean of these factors captures the sample average in the baseline level (the intercept) and the average systematic change over time (the slope, eg, an overall linear decrease in hyperactivity symptoms). The variance of these factors captures interindividual differences in baseline level and systematic change (ie, symptoms do not decline at the same pace for all children). With the twin design, the variance of these factors as well as their covariation can be decomposed into genetic and environmental influences. Phenotypic and imaging studies[8,10,11] suggest that the differential prognosis associated with interindividual differences in the developmental course of ADHD symptoms cannot be entirely explained by interindividual differences in the baseline level of symptoms. Such interindividual differences in the course of symptoms may reflect specific genetic liability.

Herein, we applied genetically informative growth curve models to a population-based sample of twins to examine the respective impact of environmental and genetic influences on interindividual differences in the baseline level and the developmental course of inattention and hyperactivity/impulsivity.

Methods

Participants

Participants were drawn from the Twins Early Development Study, a longitudinal study of twin pairs recruited from population records of twin births in England and Wales between January 1, 1994, and December 31, 1996.[25] The current study sample included a total of 8395 twin pairs for whom both twins had ADHD symptoms data for at least 1 assessment between ages 8 and 16 years. Data collection at age 8 years took place between November 2002 and November 2004; data collection at age 16 years took place between February 2011 and January 2013. The study sample is fairly representative of the UK population as compared with the data obtained by the Office of National Statistics (eAppendix 1 and eTable 1 in the Supplement). Ethical authorization was given by the Institute of Psychiatry Ethics Committee. Parents were given a letter describing the general purpose of the study and written consent was required. It was made clear that participation was voluntary and participants could withdraw from the study whenever they wished.

Measures

The *DSM-IV* ADHD symptom subscale, taken from the Conners' Parent Rating Scales-Revised,[26] was completed by mothers to assess inattentive and hyperactive/impulsive symptoms at the following mean ages of the participants: 7.9, 11.3, 14.1, and 16.3 years. As in the *DSM-IV*, the measure comprised 18 items (9 for hyperactivity/impulsivity and 9 for inattention). Each item was rated on a 4-point Likert scale ranging from 0 (not at all true) to 3 (very much true), leading to final scores ranging from 0 to 18. Standardized Cronbach α across the 4 ages ranged between 0.83 and 0.85 for hyperactivity/impulsivity and 0.90 and 0.92 for inattention. These scores measure population symptoms dimensionally and not the clinical disorder.

Table 1. MZ and DZ Correlations at Each Age[a]

Twins	Age, y 8	12	14	16
Hyperactivity score, correlation (95% CI)				
MZ	0.87 (0.85-0.89)	0.87 (0.84-0.89)	0.84 (0.81-0.87)	0.78 (0.74-0.82)
DZ	0.42 (0.39-0.46)	0.45 (0.42-0.49)	0.38 (0.32-0.43)	0.41 (0.37-0.45)
Inattention score, correlation (95% CI)				
MZ	0.79 (0.76-0.81)	0.75 (0.72-0.78)	0.77 (0.73-0.82)	0.71 (0.67-0.75)
DZ	0.29 (0.26-0.32)	0.33 (0.30-0.37)	0.33 (0.29-0.38)	0.33 (0.29-0.37)
Twin pairs, No.				
MZ	2345	2099	1285	1820
DZ	4314	3735	2076	3264
Total	6659	5834	3361	5084

Abbreviations: DZ, dizygotic; MZ, monozygotic.

[a] The total study sample number is superior to time-specific numbers as all twin pairs with 1 complete pair of data at 1 time or more were included in the latent growth model (eg, a pair of twins with missing value[s] at 8 years but available scores at 12 years was included). Data were complete at all 4 assessments for 2154 pairs, at 3 assessments for 2096 pairs, at 2 assessments for 1889 pairs, and at 1 assessment for 2256 pairs, summing to the total study sample number of 8395 twin pairs.

Statistical Analysis

All analyses were conducted separately for hyperactivity/impulsivity and inattention. All scores were regressed on sex and age prior to analyses.

A latent growth curve model was fitted to examine the developmental course of hyperactivity/impulsivity and inattention between ages 8 and 16 years. First, a phenotypic latent growth curve (ie, without genetic decomposition) was fitted to the data (detailed specifications can be found in Figure 3 of the article by Olsen and Kenny[27]). This model was used to determine the baseline level (intercept) and the growth factors (eg, linear slope) required to account for the observed hyperactivity/impulsivity and inattention scores across time. Second, the resulting best model was modified to include the genetic and environmental influences on the growth factors. Two sets of genetic models were considered, an ACE model (A indicates additive genetic influence; C, common or shared environment; and E, nonshared environment) and an ADE model (D indicates nonadditive or dominant genetic influence, which reflects effects of interactions between alleles at the same or different loci). These models also enabled the estimation of how much of the genetic and environmental influences on the developmental course (eg, linear slope) were shared with the baseline level (ie, intercept). The residuals (variance at each time not explained by the growth factors) were also decomposed into ACE and ADE factors.[24] See eAppendix 2 in the Supplement for details on the estimation and the interpretation of ACE and ADE models.

Model Fit and Estimator

For each model, we report χ^2, the Akaike information criterion, and additional approximate fit indexes (eTable 2 in the Supplement).[28] Full information maximum likelihood was used to deal with missing data. A maximum likelihood estimator with robust standard errors (MLR) and scaled test statistics were used to account for skewness, while 95% confidence intervals were obtained by bootstrapping (5000 repetitions). The structural equation modeling package lavaan version 0.5-16 was used for phenotypic and biometric models[29] and implemented within R software[30] version 3.02.

Results

Preliminary Analyses

Consistent with previous studies,[20,31] we detected no differences in genetic and environmental etiologies across boys and girls for symptom scores; therefore, sex differences were not considered in subsequent multivariate analyses. **Table 1** shows the number of complete monozygotic and dizygotic twin pairs and twin correlations at each age (complete descriptive statistics are shown in eTable 3 and eTable 4 in the Supplement). The monozygotic to dizygotic correlation ratios suggested that a model with additive genetic influence (ACE) was more appropriate for hyperactivity/impulsivity, whereas a model with dominance genetic effects (ADE) was more adequate for inattention (dizygotic correlations less than half of the monozygotic correlations at all ages). We fitted a standard Cholesky decomposition, as is commonly used on longitudinal data.[32] For hyperactivity/impulsivity scores, an ACE model indeed fitted the data better (results are presented in **Table 2**; fit indices are shown in eTable 2 in the Supplement). The influence of additive genetic influences was pervasive at all ages, explaining around 80% of the total variance at each age. From a longitudinal perspective, there was evidence for both (1) genetic continuity, for instance, genetic factors explaining hyperactivity/impulsivity at age 8 years still explained 28% of the total variance at age 16 years (A1 at 16 years, Table 2); and (2) genetic innovation, for instance, 27% of the variance at age 16 years was independent of genetic influences at previous ages (A4 at 16 years, Table 2). No evidence of shared environmental influences on hyperactivity/impulsivity emerged. Nonshared environmental influences were small and largely age specific. Results for inattention (**Table 3**) were different, as a model with nonadditive genetic effects fitted the data better. Between 37% and 49% of the variance at each age was explained by additive genetic influences, whereas between 28% and 42% was explained by nonadditive genetic effects.

Latent Growth Curve Models

In the phenotypic model, the score of hyperactivity/impulsivity decreased sharply and linearly, with a 3-point de-

Table 2. Cholesky Decomposition of Additive Genetic Influences, Shared Environmental Influences, and Nonshared Environmental Influences for Hyperactivity/Impulsivity Score From Ages 8 to 16 Years[a]

	Proportion (95% CI) by Assessment No.				
Age, y	1	2	3	4	Total
Additive genetic influences	A1	A2	A3	A4	Total a^2
8	**0.85 (0.80 to 0.89)**				**0.85 (0.80 to 0.89)**
12	**0.48 (0.43 to 0.53)**	**0.35 (0.30 to 0.39)**			**0.83 (0.76 to 0.87)**
14	**0.36 (0.32 to 0.41)**	**0.16 (0.12 to 0.21)**	**0.34 (0.29 to 0.39)**		**0.86 (0.83 to 0.89)**
16	**0.28 (0.23 to 0.32)**	**0.14 (0.09 to 0.21)**	**0.10 (0.05 to 0.15)**	**0.27 (0.20 to 0.32)**	**0.79 (0.71 to 0.85)**
Shared environmental influences	C1	C2	C3	C4	Total c^2
8	0.02 (0.00 to 0.07)				0.02 (0.00 to 0.07)
12	0.00 (−0.04 to 0.05)	**0.05 (0.01 to 0.10)**			**0.05 (0.01 to 0.10)**
14	0.00 (−0.01 to 0.01)	0.00 (0.00 to 0.01)	0.00 (−0.03 to 0.00)		0.00 (0.00 to 0.00)
16	0.00 (−0.02 to 0.06)	0.00 (−0.03 to 0.05)	0.02 (0.00 to 0.11)	0.00 (0.00 to 0.00)	0.03 (0.00 to 0.09)
Nonshared environmental influences	E1	E2	E3	E4	Total e^2
8	**0.13 (0.11 to 0.15)**				**0.13 (0.11 to 0.15)**
12	**0.03 (0.02 to 0.05)**	**0.09 (0.08 to 0.11)**			**0.13 (0.11 to 0.15)**
14	**0.02 (0.01 to 0.04)**	**0.02 (0.01 to 0.03)**	**0.10 (0.08 to 0.13)**		**0.14 (0.11 to 0.17)**
16	**0.01 (0.01 to 0.02)**	0.01 (0.00 to 0.03)	**0.03 (0.02 to 0.06)**	**0.12 (0.10 to 0.15)**	**0.18 (0.15 to 0.22)**

[a] The values presented are standardized components of variance. For instance, additive genetic influences explain 83% of the total variance at age 12 years, of which 48% comes from factor A1 that corresponds to age 8 years and 35% comes from factor A2 specific to age 12 years. Finally, $a^2 + c^2 + e^2 = 1$ at each age (last column). Significant paths are in bold.

Table 3. Cholesky Decomposition of Additive and Dominant Genetic Influences and Nonshared Environmental Influences for Inattention Score From Ages 8 to 16 Years[a]

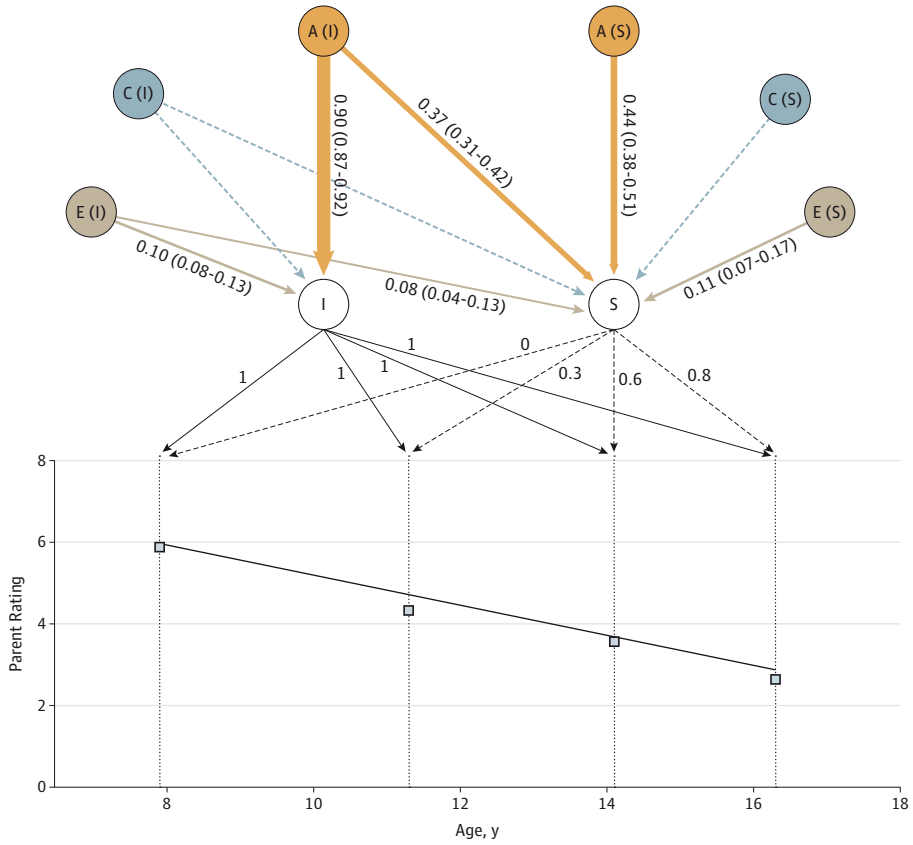
	Proportion (95% CI) by Assessment No.				
Age, y	1	2	3	4	Total
Additive genetic influences	A1	A2	A3	A4	Total a^2
8	**0.37 (0.24-0.50)**				**0.37 (0.24-0.50)**
12	**0.17 (0.07-0.29)**	**0.31 (0.26-0.36)**			**0.49 (0.37-0.61)**
14	**0.15 (0.04-0.29)**	**0.08 (0.02-0.14)**	**0.23 (0.15-0.31)**		**0.46 (0.30-0.62)**
16	**0.12 (0.03-0.27)**	**0.06 (0.01-0.10)**	**0.03 (0.00-0.08)**	**0.26 (0.19-0.31)**	**0.47 (0.33-0.60)**
Dominant genetic influences	D1	D2	D3	D4	Total d^2
8	**0.42 (0.28-0.56)**				**0.42 (0.28-0.56)**
12	**0.26 (0.14-0.39)**	0.03 (0.00-0.10)			**0.28 (0.16-0.41)**
14	**0.19 (0.07-0.34)**	**0.15 (0.04-0.29)**	0.00 (0.00-0.00)		**0.34 (0.17-0.52)**
16	**0.13 (0.03-0.27)**	**0.16 (0.05-0.30)**	0.00 (0.00-0.00)	0.00 (0.00-0.00)	**0.29 (0.14-0.44)**
Nonshared environmental influences	E1	E2	E3	E4	Total e^2
8	**0.21 (0.18-0.24)**				**0.21 (0.18-0.24)**
12	**0.04 (0.03-0.06)**	**0.18 (0.16-0.21)**			**0.23 (0.20-0.26)**
14	**0.03 (0.02-0.05)**	**0.03 (0.02-0.05)**	**0.14 (0.12-0.16)**		**0.20 (0.16-0.24)**
16	**0.02 (0.01-0.04)**	**0.03 (0.02-0.05)**	**0.05 (0.03-0.07)**	**0.14 (0.12-0.16)**	**0.24 (0.20-0.28)**

[a] The values presented are standardized components of variance. See Table 2 for an explanation of the values. Finally, $a^2 + d^2 + e^2 = 1$ at each age (last column). Significant paths are in bold.

crease from a score of 6.0 at age 8 years to a score of 2.9 at age 16 years (**Figure 1**). An ACE model (with additive genetic influence) fitted best (eTable 2 in the Supplement). Heritability of the baseline level (intercept) of hyperactivity/impulsivity was high: 90% (95% CI, 87%-92%) of the variance was explained by additive genetic influences. Interindividual differences in the linear systematic change (slope) of hyperactivity/impulsivity was also highly influenced genetically: 81% (95% CI, 73%-88%). Figure 1 shows that more than half of this influence was not shared with the genetic factors influencing the baseline level (ie, 44% specific to the slope and 37% shared with the intercept, summing to 81%). No shared environmental influences and little nonshared environmental influences were detected on either the intercept or the slope.

Results for inattention differed in 2 ways. First, in the phenotypic model, the significant linear decline was much less pronounced, with a 1-point decrease from a score of 5.8 at age 8 years to 4.9 at age 16 years (**Figure 2** and eTable 4 in the Supplement). The eFigure in the Supplement displays interindividual differences in the developmental course of symp-

Figure 1. Genetic and Environmental Influences on the Intercept and Slope of Hyperactivity/Impulsivity



Observed mean values of hyperactivity/impulsivity (squares) and model-fitted linear decrease (black line) are represented. The intercept (I), slope (S), and their loadings are indicated (slope loadings equal distance in years from the first measurement, divided by 10 to facilitate computations). The heritability (A), shared environment (C), and nonshared environment (E) standardized components of variance and 95% bootstrapped confidence estimates are provided for I and S (except for the nonsignificant dotted arrows). The width of the arrows is proportional to the effect.

toms: the distributions of the slopes for hyperactivity/impulsivity and inattention show that, although the slope was negative for inattention, a substantial minority of the sample had increasing levels of inattention, in contrast to hyperactivity/impulsivity. eTable 5 in the Supplement provides additional information on children with increasing inattention. A model including nonadditive genetic variance (ADE) fitted the model better (estimates are presented in Figure 2; fit indices are shown in eTable 2 in the Supplement). The nonadditive genetic component (D) explained more than half of the total variance of the baseline level (55%; 95% CI, 38%-74%) and 54% (95% CI, 8%-76%) of the slope, with 35% being specific to the slope and 19% shared with the intercept, summing to 54% (Figure 2). Additive genetic influences explained a substantial part of the variance of the baseline level but not of the slope.

The residuals were explained by the E term, including nonshared environmental influences as well as error variance (between 21% and 45%), with the rest being explained mostly by genetic influences. Detailed results are available in eTable 6 in the Supplement.

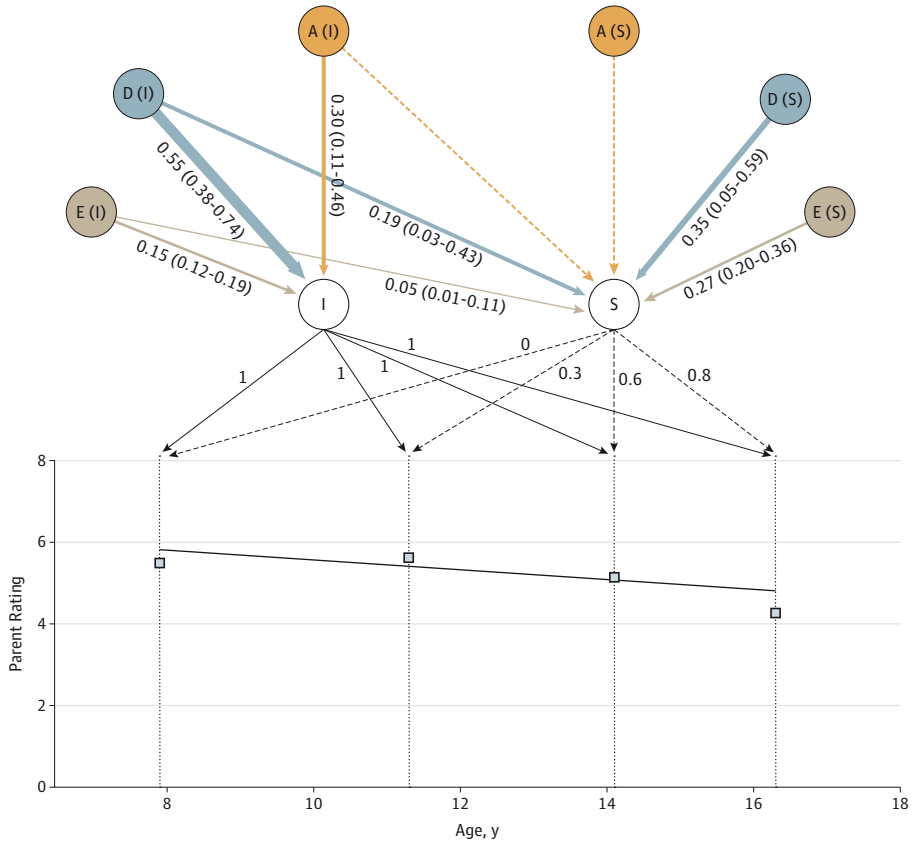
Discussion

This study examined the etiology of interindividual differences in the baseline levels and the developmental course of inattention and hyperactive/impulsive symptoms from childhood to adolescence. Interindividual differences in the overall decline in ADHD symptoms were explained by genetic and environmental influences that were largely distinct from those influencing the baseline level of symptoms. In addition, consistent with the literature, we found large genetic influences on ADHD symptoms with dominant and additive genetic influences for inattention symptoms and only additive genetic effects for hyperactive/impulsive symptoms.[33]

Developmental Course of Inattention and Hyperactivity/Impulsivity

At the phenotypic level, our results are consistent with clinical and population-based studies showing a substantial decrease in mean levels of hyperactive/impulsive symptoms with age.[6,15-17] As compared with hyperactivity/impulsivity, inattention symptoms have been found to follow a less pronounced decline or be stable with age.[2,6,15,18] In this study, we found that the decline in inattention symptoms was significant, even though it was clearly less pronounced than for hyperactivity/impulsivity. Although compatible with the extant literature, these findings may seem at odds with some recent population-based studies reporting increasing trajectories of inattention symptoms for subgroups of children.[10,17,19] This apparent inconsistency stems from interindividual differences in the developmental course of symptoms, which can be illustrated by the distribution of rates of change in this study: despite the mean decline, a substantial percentage of the

Figure 2. Genetic and Environmental Influences on the Intercept and Slope of Inattention



Observed mean values of inattention (squares) and model-fitted linear decrease (black line) are represented. The intercept (I), slope (S), and their loadings are indicated (slope loadings equal distance in years from the first measurement, divided by 10 to facilitate computations). The additive genetic influences (A), nonadditive genetic influences (D), and nonshared environment (E) standardized components of variance and 95% bootstrapped confidence estimates are provided for I and S (except for the nonsignificant dotted arrows). The width of the arrows is proportional to the effect.

sample had increasing levels of inattention (eFigure in the Supplement). The age at onset of ADHD—postponed from 7 to 12 years in *DSM-5*—remains a controversial topic[34] and may seem somewhat arbitrary in the face of the continuous change in symptoms described here. The increase in inattention symptoms for a subset of children in the population is consistent with the emergence of late-onset predominantly inattentive clinical cases, although evidence for late-onset cases is mixed.[34] Alternatively, together with the decline in hyperactive/impulsive symptoms, this increase in inattention is consistent with the observed shift with advancing age from combined ADHD to predominantly inattentive.[6]

Genetic Effects on the Developmental Course of ADHD Symptoms

Meta-analyses have documented cross-sectional structural brain differences (eg, in basal ganglia) between children with ADHD and typically developing children and have suggested change in ADHD-related structures with advancing age.[35,36] A recent longitudinal imaging study[8] showed that interindividual differences in cortical thinning in the cingulate gyrus and medial prefrontal cortex in childhood and adolescence were associated with the clinical course of ADHD. Specifically, thickening or minimal thinning of these cortical regions occurred exclusively among patients with ADHD whose symptoms had decreased by adulthood to a level below the diagnosis threshold. Moreover, cortical change was independent of baseline symptom severity, revealing a specific relationship between the trajectories of cerebral cortical development in these areas and prognosis. Taken together, these and our findings suggest that the parallel developmental processes at the cortical and phenotypic levels might reflect specific genetic influences, mostly independent from those underlying the baseline status. The hypothesis of a specific genetic liability underlying both developmental processes is only one possible account for the findings and does not exclude complex explanations involving, for instance, gene-by-environment interactions. To test this hypothesis, future research could aim to identify genetic variants associated with the developmental course of ADHD symptoms and verify how these variants associate with cortical development (ie, whether the genetic effect on the developmental course of ADHD symptoms is mediated by cortical development).

Genome-wide association studies have not been successful so far in identifying specific genetic variants associated with ADHD.[4] Our results show that some of these genetic variants should be expected to predict both the baseline status and the developmental course of ADHD symptoms, whereas others would predict only the latter. In other fields, studies have already uncovered genetic variants specifically associated with age-related systematic change (eg, obesity[37]). These studies[37-40] also demonstrated that genetic variants may remain unde-

tected when systematic change is not directly modeled. As such, when characterizing ADHD phenotype for genetic studies,[41] it appears crucial to adopt a developmental perspective. Longitudinal monozygotic twin studies have shown enduring differences in ADHD symptoms and comorbidity between discordant twin pairs.[42] However, identifying specific nonshared environmental factors contributing to these long-term differences has proven challenging, consistent with the general difficulty in identifying nonshared environmental influences.[43-45]

Limitations and Strengths

Mother ratings from childhood to adolescence constituted a coherent set of measures, which was essential to model systematic change with age. However, rater-related issues are important in twin studies and can influence heritability estimates and the type of genetic and environmental influences (eg, additive or dominant genetic effects).[5,20,33,41] Furthermore, recent studies have focused on the transition from childhood to adulthood.[5,20] Such studies present specific challenges as instruments and raters often change between childhood and adulthood. As such, although our cohort does not yet include adulthood data, it retains the following strengths: spanning a critical developmental period; distinguishing between both symptom domains (contrary to the aforementioned long-term studies); and using the same measure and the same rater throughout, which allowed us to fit a latent growth curve model. Given the common assumptions and limitations of twin models, caution must be applied when interpreting these findings (discussed further in eAppendix 2 in the Supplement). Finally, this study used dimensional measures of ADHD symptoms in a population-based sample. While this means that we captured interindividual differences across the population, our conclusions cannot be directly applied to clinical populations. The genetic etiology underlying clinical diagnoses of ADHD and ADHD symptoms in population-based samples may differ, although recent evidence points toward some overlap.[46,47]

Conclusions

A sharp general linear decrease in the levels of hyperactive/impulsive symptoms was observed from ages 8 to 16 years in this population-based sample of twins. A less pronounced decrease was observed for inattention symptoms. Important interindividual differences were detected (faster or slower decreases vs persistence, or even increases in inattention symptoms for a subset of children). These interindividual differences in the developmental course of symptoms were mostly explained by genetic influences, mostly independent from those influencing the baseline level of symptoms. Developmental models will be crucial in identifying genetic variants and specific environmental influences explaining why some children remit from ADHD, whereas others persist. The confirmation of large genetic influences on the developmental course of ADHD symptoms is important for both clinicians and patients. For clinicians, the maintenance or increase in symptoms (a decline being normative in the population) might represent a marker of vulnerability reflecting genetic liability and warrant closer follow-up. It also raises the question of the necessity to inform patients and their relatives about the higher risk of persistence in families of index cases with persistent symptoms.

ARTICLE INFORMATION

Submitted for Publication: October 21, 2014; final revision received February 3, 2015; accepted March 15, 2015.

Published Online: May 6, 2015. doi:10.1001/jamapsychiatry.2015.0469.

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Acquisition, analysis, or interpretation of data: Pingault, Viding, Galéra, Greven, Zheng, Plomin.
Drafting of the manuscript: Pingault, Viding, Rijsdijk.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Pingault, Rijsdijk.
Obtained funding: Pingault, Plomin.
Study supervision: Viding, Greven, Rijsdijk.

Conflict of Interest Disclosures: Dr Galéra reported receiving support from the industry to attend scientific congresses in the past. No other disclosures were reported.

Funding/Support: The Twins Early Development Study is supported by grant G0901245 (and previously G0500079) from the UK Medical Research Council. Dr Pingault is supported by Marie Curie Intra-European Fellowship 330699 from the European Commission. Dr Viding is supported by a Royal Society Wolfson Research Merit Award from the Royal Society and the Wolfson Foundation. Dr Plomin is supported by research professorship award G19/2 from the Medical Research Council and by advanced investigator award 295366 from the European Research Council.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We gratefully acknowledge the ongoing contribution of the participants in the Twins Early Development Study and their families.

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Supplementary Online Content

Pingault J-B, Viding E, Galéra C, et al. Genetic and environmental influences on the developmental course of attention-deficit/hyperactivity disorder symptoms from childhood to adolescence. *JAMA Psychiatry*. Published online May 6, 2015. doi:10.1001/jamapsychiatry.2015.0469.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Comparison of Study Sample With Initial Sample and UK Characteristics

Twin births between 1994 and 1996 were identified through birth records by the United Kingdom Office for National Statistics. A total of 16,810 families responded to the office to acknowledge their interest in taking part in the study. A first contact with these families was made by TEDS team when the twins were about 18 months. A total of 13,722 families returned data for this first contact. eTable 1 below shows the characteristics of these respondents. Of note is that these characteristics mirror closely data from the U.K. census data, so that TEDS families appear reasonably representative of the UK population. The characteristics of the 8,395 families included in the current study sample are presented in eTable1 and match closely with first contact characteristics. The biggest difference is maternal education, with 4.6 percentage points more of mothers with A-levels of education or higher in the study sample compared to the first contact sample. Further details on the sample and measures can be found in earlier publications.[1–4]

eAppendix 2. Estimation and Interpretation of Genetic and Environmental Components in ACE and ADE Models

This section presents some background for readers unfamiliar with behavioural genetics regarding the estimation of genetic and environmental influences in the classical twin design (CTD), as well as the interpretation and limitations of twin models. There is a vast literature on the topic that cannot be summarize here. We refer the readers to the following key references for additional consideration.[7–12]

Estimations of ACE and ADE univariate models

Behavioural genetics take advantage of differential genetic relationships between family members to estimate genetic and environmental influences on the variance of phenotypes. In the CTD, data of monozygotic twins (assumed to share 100% of their genes) and dizygotic twins (assumed to share 50% of their segregating genes on average) are used. The estimation of the genetic and environmental components of variance is based on the relative differences of the MZ and DZ twin within pair correlations (rMZ and rDZ) for a particular phenotype.

The different components that can be estimated in the CTD are:

- A, which represents additive genetic effects: the sum of the effects of the individual alleles at all loci that influence the trait. The genetic factors are assumed to correlate 1 in monozygotic twins and 0.5 in dizygotic twins (corresponding to 100% and 50% of shared genes).

- C, which represents the common or shared environment, defined as the environmental influences that make the twins reared in the same family similar. Because, by definition, the shared environment is the environment that is common between the two twins, shared environment factors correlate 1 between the two twins. C is assumed to have the same importance in monozygotic and dizygotic twins (i.e. similarity of MZ twins is not due to the fact that they share a higher proportion on environmental factors due to e.g. a more equal treatment based on their physical similarity).

- E, which represents the non-shared environment, i.e., the environment that make twins different. By definition, non-shared environmental factors are not correlated between the two twins. It is important to notice that E also includes measurement error.

- D, which represents non-additive genetic effects: the effects of the interactions of individual alleles either on the same or different loci that influence the trait. These genetic factors are assumed to correlate 1 in monozygotic twins (corresponding to 100% genes sharing) and 0.25 in dizygotic twins, based on the 25% chance of two siblings sharing 2 alleles Identical-by-Descent (alleles from the same parental origin).

A model with only additive genetic effects and E will predict an rDZ which is half the rMZ. The effects of C will increase the rDZ such that it is higher than .5*the rMZ, whereas the effects of D will decrease the expected rDZ such that it is lower than .5*rMZ. Since these situations are mutually exclusive, we cannot estimate both C and D in the CTD, but we fit the model (ACE or ADE) which is consistent with the observed correlations. When the correlations are consistent with an ACE model, we can use simple formulas to get an approximate value for A, C and E. For instance, let's assume that, for phenotype X, rMZ = .80 and rDZ = .50 the effects of A, C and E, referred to as a^2, c^2, and e^2 are calculated as follows:

a^2 = 2*(rMZ – rDZ) = 2*(.80 - .50) = 2*.30 = .60

The heritability of phenotype X is said to be .60, meaning that 60% of the variance can be explained by additive genetic effects. The formula can be understood as follows: because MZ and DZ twins only differ by the proportion of genes they share, the difference between MZ and DZ correlations is due to genetic effects. This difference (.30 here) corresponds to the difference in genetic relationships in MZ and DZ (100% & 50%). Therefore, multiplying this difference by 2 approximates the whole additive genetic influence on phenotype X.

c^2 = rMZ - a^2 = .80 - .60 = .20

Shared environmental influences on phenotype X equal 20%. The formula can be understood as follows: the reason why MZ twins are similar, which is manifested by the within pair correlation of .80, is because of genetic influences and shared environmental influences. Because we already calculated genetic influences, the shared environmental influences are therefore the rest of the correlation: rMZ minus genetic influences.

e^2 = 1 - rMZ = 1 - .80 = .20

Non-shared environmental influences are, by definition, what makes twin dissimilar. E is therefore calculated by subtracting the observed correlation (.80) to a perfect correlation of 1. Importantly, even if the true correlation in monozygotic twins was 1, the observed correlation

would be less than 1 because of measurement error. The CTD does not enable the distinction between true non-shared environment influence and measurement error.

These simple formulas only represent an initial approximation of the genetic and environmental effects. Structural Equation Modelling software is used to compute maximum likelihood estimates of the components based on the covariances and variances of the data, taking into account missing data.

The principle of the univariate models can be extended to include two or more phenotypes such that the MZ and DZ ratio of the cross-twin cross-phenotype correlations are used to estimate the genetic and environmental origins of the correlation between two phenotypes.

ACE and ADE models and the latent growth model.

In the present study, as described in the manuscript, the first step was to estimate a phenotypic latent growth model. This model yielded two important parameters: the intercept and the slope, which represent respectively the baseline level of the phenotype and the systematic change in that phenotype over time. Each of this parameter can be decomposed in a similar fashion to what was explained above using the within pair correlations in MZ and DZ twins. For instance, for the intercept, the MZ correlation was largely superior to the DZ correlation. The same set of rules can be applied with the only difference that they are applied to a latent factor (the intercept) rather than to a simple observed variable.

In addition, as mentioned above, the univariate model can be extended to a bivariate model, which is what we did here. Instead of two observed phenotypes, we used the two latent factors (intercept and slope) but the principles remain the same. The main aim was to verify whether some of the genetic influences detected for the slope were unique to the slope or if they were shared with the intercept (i.e. the same genes underlie both the baseline level and the systematic change in symptoms with age). Again, this is similar to a model with simple observed phenotypes, for instance to verify whether the genetic factors that underlie conduct disorders also influence addictions.

Assumptions and limitations of twin models

Several assumptions of twin models, if not met, may bias the estimates of genetic and environmental influences. These are discussed in detail elsewhere.[8,10,11] We mention below only the ones that may influence the present results.

A first set of assumptions, if not met, can bias the size of the different components, for instance:

- *Equal environment assumption.* The shared environment is assumed to have the same effect in MZ and DZ twins, i.e. to make MZ and DZ twins similar to the same extent. However, it is possible that parents, for instance, will treat MZ twins in a more similar fashion than DZ twins. If this was the case, this phenomenon would unduly increase the estimate of genetic effects, i.e. shared environmental effects would be counted as genetic effects. This assumption has been tested a number of time and seems to hold reasonably well for most traits.[7]

- *MZ twins share 100% of their genes.* Although the genetic material of MZ twins is almost identical, residual genetic differences still exist. Some important structural

differences have been found in some pairs of monozygotic twins.[13,14] If MZ twins are not 100% identical it means that some genes may contribute to differences in MZ twins. This, in turn, may underestimate genetic effects and overestimate the role of the non-shared environment. Although this is unlikely to have an effect at a population level, it cannot be excluded as yet. Of note is that genetic effects were already high in the present study, whereas the non-shared environmental influences were more limited.

Gene-environment correlations and interactions if present and not modelled may also add complexity to the interpretation of the estimates derived from twin models.

- The concept of *gene-environment correlation* relates to the fact that people are not randomly allocated to environment but, to a certain extent, their exposure to the environment varies according to the genetic make-up of their parents (passive rGE) or their own genetic make-up (active rGE). For instance, the behaviour of a hyperactive child may evoke harsh reactions from his/her parents. As such, the adverse environment – here harsh parenting – is partly dependent on the child's behaviour, which is itself partly dependent on his genetic make-up. Active rGE also explains why a lot of environmental measures are found to be heritable in genetically informative studies (e.g. life events like divorce). This does not obviously mean that genes have a direct physiological effects on these environments but rather that exposure to these environment is influenced by genes. The effects of un-modelled gene-environment correlations are included in the A parameter in the ACE model. However, this does not mean that genetic effects are overestimated but rather that some genetic effects included in the A are direct whereas others are indirect. For instance, some genetic variants have been shown to be associated with smoking severity. As such, these genetic variants have an effect on an environmental exposure, i.e. smoking severity. In turn, smoking causes lung cancer. When examining the heritability of lung cancer, the effect of those genes will be taken into account in the genetic estimate. However, these genetic variants do not affect the physiology of lung cells in a direct fashion, which is shown by the fact that they are not associated with cancer in non-smoking patient. Instead, they increase an environmental exposure that, in turn, causes cancer. In this case, the effect of these genetic variants is correctly classified in genetic effects as the ultimate origin of the cascade of events leading to cancer is genetic. However, the proximal cause of the cancer is rather environmental in origins. The twin model cannot distinguish between these genetic effects without measuring environmental factors that lie on the pathway from genes to phenotype. As such, it is important to keep in mind that part of the genetic effects detected in the present study may follow this indirect pattern of influence.

- *Gene-environment interactions* relate to the fact that sometimes the expression of genetic effects depend on the environmental exposure. For instance, susceptibility to skin cancer can be partly genetic in origin. However, these genetic variants will not express if there is no sufficient exposure to the sun, i.e. if the environmental exposure is not present. In other words, if only one factor – genes or the environment – is present, the disease will not manifest but it will if both of them are. Gene-environment interactions, if present and un-modelled, end up being represented in either genetic (A) or non-shared environment (E) estimates. If the interaction of genetic effects is with the non-shared environment (E), this will inflate the E estimate. Conversely, interactions of genetic influences with the shared environment (C), will inflate the genetic (A) estimate. Although these interaction effects

cannot be modelled in the classical twin design, other methods can give us a sense of their existence and if the assumption of additivity of A, C and E is reasonable or not.

In spite of their limitations, twin models, together with other designs in quantitative genetics, can still give us invaluable information on the genetic and environmental architecture of phenotypes and represent a helpful starting point for limiting the problem space when searching for likely developmental mechanisms (for a recent review, see[8]). This is all the more the case as many of the aforementioned assumptions and limitations can be addressed by using complementary research designs (including the DNA-based estimates of heritability based on Genome-Wide Complex Trait Analysis[15]).

eTable 1. Sample Characteristics

	Returned data (N families)	% White	% Mothers with A-levels or higher	% Mother employed	% Father employed	% Female	% MZ
UK census[1]	-	*93%*	*32%*	*49%*	*89%*	-	-
TEDS first contact	13,722	91.7%	35.5%	43.1%	91.6%	50.1%	33.2%
TEDS study sample	8,395	93.1%	40.1%	46.2%	93.0%	51.4%	34.7%

Note. [1]UK data from the 2000 General Household Survey[5] are used rather than more recent data because they provide more appropriate comparisons for TEDS twins who were born 1994-96. The % MZ data are from Imaizumi[6] because they are not available from UK census data. A-levels are the national educational exam taken at 18 years of age in the UK. MZ=monozygotic twins.

eTable 2. Fit Indices

For each model, we report the Akaike-Information Criterion (AIC) and the chi-square, as well as additional approximate fit indexes and three approximate fit indexes: CFI (Comparative Fit Index) for which values close to 1 indicate better fit; RMSEA (Root Mean Square Error of Approximation, and 90% Confidence Interval) and SRMR (Standardized Root Mean Square Residual) for which values close to 0 indicate better fit. No consensus exists on cut-off values for these indexes, but values close to .95 for CFI, 0.06 for RMSEA and 0.08 for SRMR have been suggested[16] to conclude that there is a relatively good fit between the model and the data.

		AIC	Chi Square	DF	pvalue	CFI	SRMR	RMSEA	RMSEA lower	RMSEA upper
Hyperactivity Impulsivity	Cholesky ACE	215218	85.377	54.000	0.004	0.997	0.046	0.012	0.008	0.015
	Cholesky ADE	215230	83.286	54.000	0.006	0.997	0.044	0.011	0.008	0.015
	LGC phenotypic	215447	210.593	65.000	0.000	0.986	0.055	0.023	0.021	0.026
	LGC ACE	215455	200.700	65.000	0.000	0.987	0.055	0.022	0.020	0.025
	LGC ADE	215475	211.385	65.000	0.000	0.985	0.055	0.023	0.021	0.026
Inattention	Cholesky ACE	232708	156.603	54.000	0.000	0.990	0.065	0.021	0.018	0.024
	Cholesky ADE	232619	112.280	54.000	0.000	0.995	0.048	0.016	0.013	0.019
	LGC phenotypic	233097	429.262	65.000	0.000	0.966	0.068	0.037	0.034	0.039
	LGC ACE	233199	458.148	65.000	0.000	0.963	0.077	0.038	0.035	0.040
	LGC ADE	233112	406.384	65.000	0.000	0.968	0.067	0.035	0.033	0.038

Note. The degrees of freedom (DF) for ACE and ADE models are equal. Therefore, the choice between ACE and ADE models for Cholesky models on the one hand and for LGC models on the other hand was based on the Akaike-Information Criterion (AIC), with lower values indicating better fit. Approximate fit indexes were useful to assess whether the phenotypic Latent Growth Model (LGC) fitted the model adequately. All indexes were in line with recommended cut-offs, showing that a linear growth model fitted the data adequately.

eTable 3. Correlation Table, Hyperactivity/Impulsivity Score

	DZ / MZ	TWIN 1				TWIN 2					
		4 years	7 years	12 years	16 years	4 years	7 years	12 years	16 years	MEAN (DZ)	SD (DZ)
TWIN 1	4 years	-	0.667	0.579	0.453	0.424	0.289	0.224	0.191	5.748	5.038
	7 years	0.703	-	0.681	0.581	0.280	0.452	0.271	0.254	4.281	4.318
	12 years	0.546	0.663	-	0.698	0.237	0.284	0.378	0.259	3.640	4.210
	16 years	0.488	0.596	0.647	-	0.172	0.234	0.267	0.409	2.763	3.692
TWIN 2	4 years	0.870	0.640	0.516	0.465	-	0.672	0.560	0.499	5.781	5.131
	7 years	0.632	0.868	0.595	0.506	0.698	-	0.694	0.595	4.357	4.492
	12 years	0.469	0.589	0.838	0.568	0.543	0.670	-	0.692	3.671	4.329
	16 years	0.439	0.524	0.595	0.784	0.479	0.566	0.674	-	2.662	3.595
	MEAN (MZ)	6.100	4.385	3.357	2.508	6.044	4.331	3.435	2.483		
	SD (MZ)	5.162	4.393	3.756	3.339	5.017	4.272	3.918	3.257		

Note. The table shows the observed Pearson pairwise correlations within and across time, within and between twins for MZ (lower part of the table) and DZ (upper part), as well as the observed means and standard deviations (SD). Values in grey are twin correlations at each time point: heritability and environmental estimates at each time point are based on the comparison of each pair of MZ and DZ correlations. Values in yellow represent the across time correlations for each twin, showing the phenotypic continuity in hyperactivity/impulsivity scores. Values in blue represent cross-twin cross-time correlations: the respective role of genes and the environment in explaining hyperactivity/impulsivity is estimated based on the comparison of these correlations between MZ and DZ.

eTable 4. Correlation Table, Inattention Score

	DZ / MZ	TWIN 1				TWIN 2					
		4 years	7 years	12 years	16 years	4 years	7 years	12 years	16 years	MEAN (DZ)	SD (DZ)
TWIN 1	4 years	-	0.656	0.562	0.493	0.291	0.211	0.169	0.168	5.529	5.238
	7 years	0.674	-	0.668	0.606	0.184	0.330	0.232	0.208	5.578	5.054
	12 years	0.535	0.704	-	0.697	0.194	0.231	0.333	0.231	5.157	5.045
	16 years	0.471	0.605	0.706	-	0.147	0.188	0.230	0.326	4.515	5.082
TWIN 2	4 years	0.786	0.565	0.448	0.425	-	0.642	0.560	0.491	5.515	5.195
	7 years	0.553	0.752	0.547	0.457	0.633	-	0.699	0.594	5.712	5.247
	12 years	0.438	0.600	0.775	0.539	0.523	0.684	-	0.708	5.424	5.389
	16 years	0.390	0.475	0.544	0.711	0.475	0.577	0.668	-	4.459	4.930
	MEAN (MZ)	5.455	5.683	4.946	3.867	5.423	5.500	4.838	3.831		
	SD (MZ)	5.133	5.028	4.803	4.542	5.008	4.815	4.770	4.372		

Note. See eTable2.

eTable 5. Characteristics of Children With Increasing Inattention vs Others

	Increasing inattention % or Mean (SD)	Other participants % or Mean (SD)	Effect sizes[1]	P-values
% Female	46.4	52.7	0.05	< .001
% White	93.6	92.9	0.01	= .17
% Mothers with A-levels or higher	39.4	41.4	0.02	=.03
% Mother employed	44.7	46.6	0.02	=.15
GCSE Maths	8.73 (1.47)	9.00 (1.47)	0.19	< .001
GCSE English	8.89 (1.34)	9.18 (1.29)	0.22	< .001
GCSE Science	8.88 (1.52)	9.17 (1.51)	0.20	< .001
G: 7 years	0.03 (0.98)	0.03 (0.99)	0.00	= .94
G: 9 years	-0.02 (1.02)	0.01 (0.99)	0.03	= .35
G: 10 years	-0.04 (1.01)	0.02 (0.99)	0.07	= .10
G: 12 years	-0.14 (1.05)	0.04 (0.98)	0.18	< .001
G: 14 years	-0.22 (1.05)	0.05 (0.98)	0.27	< .001
G: 16 years	-0.16 (0.96)	0.04 (1.00)	0.20	< .001
Conners Inattention Teachers				
14 Years	6.22 (6.66)	3.93 (5.41)	-0.40	< .001

Note. [1]Hedges g (an equivalent of Cohen d for unequal sample sizes) was used for socioeconomic status. For other variables a phi-coefficient is presented. See eTable 1 for an explanation of the first four variables. The General Certificate of Secondary Education (GCSE) is taken by more than 99% of pupils at the end of compulsory education, which is typically around the age of 16 years. English, mathematics and science are compulsory subjects. The grades were coded from 11 (the highest grade) to 4 (the lowest pass grade). G is a standardized score of general cognitive ability that was assessed at each age using a battery of parent-administered and phone- and web-based tests. At each testing age, individuals completed at least two ability tests, which assessed verbal and non-verbal intelligence. For additional details on these measures, see[17,18]. Results for the Conners inattention scale rated by teachers instead of mothers are also presented.

Comment: eTable 5 provides additional information on children with increasing inattention represented in eFigure 1 above. These children differed very little from other children on sex, ethnicity, maternal education and maternal employment, although they were slightly more likely to be males and to have less educated mothers. However, at the end of the follow-up, they had significantly lower educational achievement, as measured by GCSE at age 16 years. In addition, while they did not differ on general cognitive abilities at baseline, differences widened with age and very significant differences between the two groups were observed after age 12 years. These differences seem consistent with the existence of specific developmental processes that become evident with advancing age and concern inattention as well as other cognitive characteristics. Finally, the score on the Conners inattention scale rated by teachers at age 14 years was higher for children with increasing inattention.

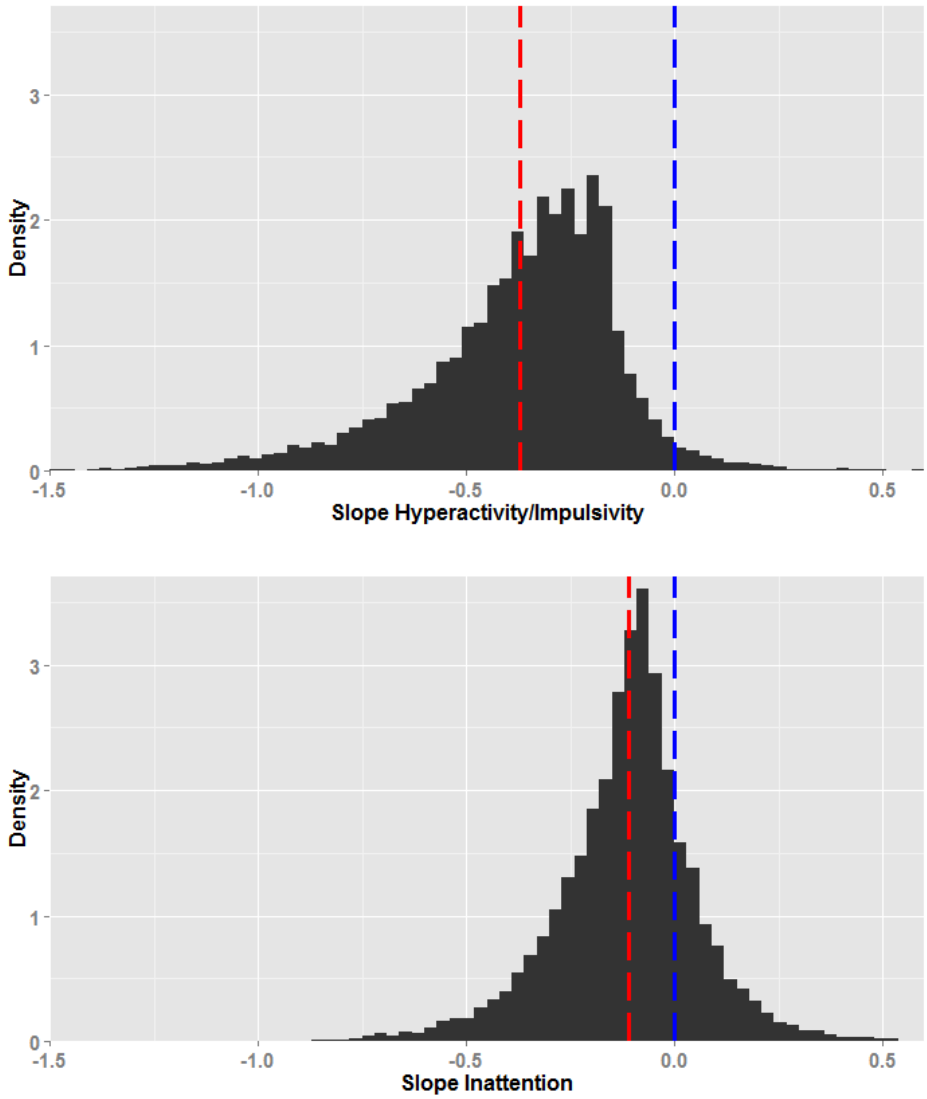
The results presented in eTable 5 are presented for descriptive purposes and caution should be applied when interpreting them. A latent growth model was used to model systematic change in a dimensional score of inattention. Systematic change – here the slope of inattention – was therefore modelled in a continuous fashion as represented in eFigure 1. Consequently, separating the sample into two sub-groups following different developmental trajectories based on the slope value is arbitrary as it cuts in a continuous distribution (here below and above 0). In addition, such a cut-off based on the slope does not take into account the baseline values (i.e. the intercept) to constitute the groups. Although outside the scope of the present study, more appropriate methods can be applied to examine sub-groups following different developmental trajectories.[19–21]

eTable 6. Genetic and Environmental Influences on the Residuals From the Latent Growth Models

RESIDUALS HYPERACTIVITY	Age	7.9	11.3	14.1	16.3
	Total	0.24	0.29	0.32	0.16
	A	.73 (.52-.85)	.63 (.49-.77)	.80 (.70-.85)	.41 (.00.-.70)
	C	.07 (.00-.23)	.15 (.04-.27)	.00 (.00-.28)	.14 (.00-.45)
	E	.21 (.15-.29)	.22 (.18-.27)	.21 (.15-.27)	.45 (.28-.66)
RESIDUALS INATTENTION	Total	0.26	0.33	0.30	0.22
	A	.66 (.49-.77)	.61 (.55-.66)	.72 (.58-.79)	.70 (.60-.79)
	D	.00 (.00-.52)	.00 (.00-.22)	.00 (.00-.36)	.00 (00-.49)
	E	.34 (.25-.45)	.39 (.34-.45)	.28 (.22-.35)	.30 (.21-.40)

Note. Latent growth factors – intercept and linear slope – explained a large amount of variance at each age, with remaining total residual variances between .16 and .33 (lines Total). These residual variances were decomposed into genetic and environmental influences: ACE decomposition for hyperactivity/impulsivity and the ADE decomposition for inattention.

eFigure. Distributions of the Slope for Hyperactivity/Impulsivity and Inattention



The Figure represents the distributions of the predicted linear slopes of hyperactivity/impulsivity and inattention symptoms. The red line represents the mean *yearly* slope, which is negative for hyperactivity/impulsivity (-0.37), meaning that, for each year during the 8 years follow-up, the mean score of Hyperactivity/impulsivity decreased by 0.37 point (the slope being -0.11 for inattention),. The blue line is zero so that participants on the right side of the blue line have a positive slope. As can be seen, this is much more frequent for inattention (≈ 20%) than for hyperactivity/Impulsivity (≈ 3%).

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