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Genetic and Environmental Links Between Motor Activity Level and Attention Problems in Early Childhood

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Abstract

Cross-lagged biometric models were used to examine genetic and environmental links between actigraph-assessed motor activity level (AL) and parent-rated attention problems (AP) in 314 same-sex twin pairs (MZ=145, DZ=169) at ages 2 and 3 years. At both ages, genetic correlations between AL and AP were moderate ($r_{a2}=.35$; $r_{a3}=.39$) indicating both overlap and specificity in genetic effects across the two domains. Within- and across-age phenotypic associations between AL and AP were entirely due to overlapping genetic influences. There was a unidirectional effect of AL at age 2 predicting later AP. For AP, genetic and environmental influences from age 2 were transmitted to age 3 via stability effects and from AL. For AL, across-age effects were transmitted only via stability. These results suggest that overactivity in late infancy may impact the later development of problems related to inattention, and that genetic factors explain the association between the two domains.

Factor analytic studies of attention deficit/hyperactivity disorder (ADHD) symptoms suggest that ADHD can be best viewed as extremes on the two continuous dimensions of hyperactivity/impulsivity and attention problems (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007; Nikolas & Burt, 2010; Willcutt et al., 2012). Research with children in middle childhood and adolescence finds that although the two dimensions are distinct, they are highly correlated and this association is largely due to genetic effects that are common to both phenotypes (Greven, Asherson, Rijdsdijk, & Plomin, 2011; Greven, Rijdsdijk, & Plomin, 2011; Larsson, Lichtenstein, & Larsson, 2006; McLoughlin et al., 2007). Little is known, however, about the etiological factors that link the two domains in early childhood.

The majority of research on ADHD has been conducted with school-age children (Willcutt et al., 2012). Nonetheless, it appears that ADHD can be identified in very young children. Both the prevalence and behavioral profiles of ADHD in toddlers and preschoolers are similar to that of older children (Byrne, DeWolfe, & Bawden, 1998; Lavigne et al., 1996). Moreover, although stability of specific sub-types are moderate (Lahey, Pelham, Loney, Lee, & Willcutt, 2005), diagnoses of ADHD in young children show substantial stability, with

approximately 70% of children continuing to meet criteria 7 years later (Law, Sideridis, Prock, & Sheridan, 2014). The preschool period may be an important time for intervention, hence it is critical to understand the extent to which hyperactivity and attention problems share etiological pathways both within and across age as it may inform about early developmental processes underlying ADHD.

Parent reports of hyperactive behavior problems in young twins (i.e., ages 1 to 3 years) consistently yield evidence of genetic influences, with heritability estimates explaining as much as 80% of the variance (Derks, Hudziak, van Beijsterveldt, Dolan, & Boomsma, 2004; Ilott, Saudino, Wood, & Asherson, 2010; Price, Simonoff, Waldman, Asherson, & Plomin, 2001; Saudino, Carter, Purper-Ouakil, & Gorwood, 2008). Longitudinal analyses suggest that the phenotypic stability in hyperactive behavior problems across early childhood is largely due to genetic effects that persist across age; however, there is also evidence of genetic change as indicated by genetic effects that are age-specific (Ilott, Saudino, & Asherson, 2010; Price et al., 2005). Less is known about the etiology of individual differences in attention problems in early childhood. To our knowledge there are no behavioral genetic studies of *problematic* attention (i.e., symptoms of dysfunctional attention) in this developmental period, but there are studies of attentional *competency*—usually assessed as the trait of attention/persistence within a temperament framework. These studies find that variations in early attention/persistence are genetically influenced and that genetic factors contribute to stability across age (Braungart, Plomin, DeFries, & Fulker, 1992; Petrill & Deater-Deckard, 2004; Saudino et al., 2008; Saudino & Cherny, 2001). There are also hints of genetic change, but this is complicated because evidence of genetic change coincides with changes in the measures used to assess attention/persistence (Saudino & Cherny, 2001). Overall, these findings for attention/persistence in early childhood suggest that early attention problems will also show a pattern of genetic effects, however, this is an empirical question that has gone unanswered. We explore this question by looking at sources variation in symptoms of problematic attention, as opposed to attentional competencies, in a sample of twins assessed at ages 2 and 3 years.

Hyperactivity and inattention are moderately correlated in young children (Gray, Carter, Briggs-Gowan, Jones, & Wagmiller, 2014) indicating that there is some overlap in the factors that influence both dimensions. Although genetic and environmental sources of covariance have not been explored in young children, as indicated earlier, hyperactivity and attention problems in middle childhood and adolescence are genetically linked. Multivariate behavioral genetic analyses exploring genetic and environmental contributions to the covariance between hyperactivity and attention problems suggest that approximately 50–60% of the genetic effects covary across phenotypes (Eaves et al., 2000; Greven et al., 2011; Larsson et al., 2006; McLoughlin, Rijdsdijk, Asherson, & Kuntsi, 2011; McLoughlin et al., 2007). Thus, in older children there is evidence of both genetic overlap and genetic specificity across the two ADHD dimensions.

The fact that hyperactivity and attention problems are related and have some common genetic underpinnings raises questions about causation and direction of effects. It is possible that the phenotypic and genetic associations arise simply because of pleiotropy (i.e., genes that influence multiple phenotypes). However, it is also possible that one phenotype

influences the other. For example, restlessness or over activity may be a consequence of having problems with attending, or conversely, it could be that being overactive makes it harder to pay attention. The two population-based studies that have looked at causal effects between hyperactivity and attention problems have produced conflicting results. When rated by teachers, hyperactivity and attention problems in children in kindergarten to 5th grade did not predict each other across two 1-year intervals once stability was taken into account (Burns & Walsh, 2002). In contrast, parent ratings of hyperactivity and attention problems across a 4-year interval spanning middle-childhood and adolescence showed a unidirectional pattern with hyperactivity predicting later attention problems (Greven et al., 2011). The cross-lagged effect was modest, explaining .64% of variance ($b=.08$), nonetheless, this study provides novel evidence that hyperactivity in middle childhood may impact the development of adolescent inattentiveness.

There are several possible explanations for the discrepancies between studies. First, the developmental periods (within childhood vs across childhood and adolescence) and length of intervals (1 year vs 4 years) differed across samples. Thus, the different results might arise because the cross-lagged effect of hyperactivity on attention problems emerges only later in development. Second, raters differed across studies and it may be that teachers and parents provide different perspectives of behavioral problems related to ADHD. Indeed, behavioral genetic research looking at the genetic overlap between parent and teacher ratings of inattention and hyperactivity has found that while there is some common variance between raters, there are also substantial rater-specific variances suggesting that teachers observe significantly different aspects of ADHD behaviors in the classroom (McLoughlin et al., 2011). A related issue has to do with the consistency of raters across age. In Burns and Walsh (2002) raters (i.e., teachers) and in some instances, measures, differed across age which could attenuate longitudinal cross-lagged associations. On the other hand, in Greven et al. (2011) both domains were rated by the same parent across age and consequently, the significant longitudinal cross-lagged association could reflect methodological overlap or halo effects.

The present study is the first to address these gaps in the literature by using a longitudinal, multi-method approach to examine links between hyperactivity and attention problems in early childhood. Biometric cross-lagged models were used to explore the direction of effects underlying the association between actigraph-assessed motor activity level (AL) and parent ratings of attention problems in twins at ages 2 and 3 years. In addition, we explored genetic and environmental sources of stability across age, and sources of covariance between AL and attention problems both within and across age. Examining these associations across early childhood may better inform about the direction of causal influences and the etiological factors that underlie them. Moreover, our use of actigraphs allows for a direct measure of motor activity and eliminates the potential problem of associations arising due to methodological overlap or halo effects. Although our focus is on AL and not hyperactivity specifically, high levels of motor activity are included in 4 of the 6 hyperactive symptoms in the DSM V (Sarver, Rapport, Kofler, Raiker, & Friedman, 2015). In addition, a high AL in early childhood is predictive of later ADHD symptoms (Campbell, Ewing, Breaux, & Szumowski, 1986; Marakovitz & Campbell, 1998). More important to the present study, actigraph measures of motor AL in both early and middle childhood are significantly

associated with parent ratings of hyperactivity and this association is largely due to genetic effects that covary across phenotypes (Ilott et al., 2010; Wood, Rijdsdijk, Saudino, Asherson, & Kuntsi, 2008).

Based on prior research with older children, we made a number of predictions about the interrelations between AL and attention problems in early childhood. First, we predicted that the two behavioral domains would be phenotypically associated both within and across age. Given the conflicting research about cross-lagged associations, we did not have a strong a priori hypothesis about direction of effects, but rather sought to clarify existing findings by addressing methodological issues related to raters in the previous research. Second, we predicted that, as with AL in the current sample (see Saudino, 2012), attention problems in early childhood would be genetically influenced, and that there would be evidence of genetic change in attention problems across age. Finally, we predicted that genetic factors would largely explain any observed covariance between AL and attention problems.

Methods

Sample

The Boston University Twin Project (BUTP) sample was recruited from birth records supplied by the Massachusetts Registry of Vital Records. Twins were selected preferentially for higher birth weight and gestational age. No twins with birth weights below 1750 grams or with gestational ages less than 34 weeks were recruited into the study. Twins were also excluded if they had a health problem that might affect motor activity (e.g., club foot) or had chromosomal abnormalities. Three hundred and fourteen same-sex pairs of twins (145 MZ, 169 DZ) participated in the age 2 assessments, and 304 of these twin pairs (141 MZ, 163 DZ) returned for the age 3 assessments (96.8% retention rate). Race was generally representative of the Massachusetts population (85.4% White, 3.2% Black, 2% Asian, 7.3% Mixed, 2.2% Other). Socioeconomic status according to the Hollingshead Four Factor Index (1975) ranged from low to upper middle class (range=20.5–66; $M=50.9$, $SD=14.1$). Zygosity was determined via DNA analyses using DNA obtained from cheek swab samples. In the cases where DNA was not available ($n=3$), zygosity was determined using parents' responses on physical similarity questionnaires which have been shown to be more than 95% accurate when compared to DNA markers (Price et al., 2000).

Procedure Overview

Twins were assessed within approximately 2 weeks of their second and third birthdays. At each age, the procedure consisted of two 1-hour visits, 48-hours apart, to the laboratory. At the initial visit, informed consent from parents was obtained. Prior to attaching the actigraphs (see below), children were told that they would be wearing “bracelets” on all 4 limbs but were unaware that these devices measured AL. After attachment of the actigraphs, one twin was assessed within a standardized test situation, while the other twin was assessed within a laboratory play situation. The order of situations was counterbalanced across first- and second-born twins. The test situation involved administration of the Mental Scale of *Bayley Scales of Infant Development–Second Edition* (Bayley, 1993). The play situation comprised activity and inhibitory control episodes (arc of toys, corral of balls, workbench,

fidget video, dinky toys, snack delay, gift) from the *Laboratory Temperament Assessment Battery–Preschool Version* (Goldsmith, Reilly, Lemery, Longley, & Prescott, 1995). At the second visit, situations were reversed for each twin, actigraphs removed, and questionnaires and cheek scrapings collected. Twins were assessed by different testers, however, within age for each twin the tester was the same across the two laboratory situations.

Measures

Mechanical assessment of motor AL.—AL was assessed with the Minimitter actical (actigraph). This device is a miniature omnidirectional accelerometer that has been designed to detect low frequency (0.5–3.2 Hz) G-forces (0.05–2.0 Hz) within the range of normal human movement (Heil, 2006). Activity (i.e., physical movement exceeding the device's threshold) is sampled 32 times per second (32Hz) and is expressed as activity counts representing the frequency and amplitude of acceleration events occurring over each 1-minute measurement epoch during which the device was worn (Actical Physical Monitoring System Instruction Manual, 2005). Activity counts correspond to changes in physical activity energy expenditure (Heil, 2006).

Four randomly-selected actigraphs were assigned to each twin, one for each limb. Assignment of actigraph to limb was also random. Actigraphs were attached by means of tyvek® adhesive or plastic snap wristbands. Arm attachment, at the wrist, was on the dorsal aspect of the forearm proximal to the radial carpal joint. Leg attachment, at the ankles, was superior to the lateral malleoli. The children wore the actigraphs continuously during the two 1-hour lab visits at each age. To adjust for minor variations in the total time that each instrument was worn within the laboratory, the number of activity units was converted to a rate per minute real time. Arm and leg activity counts were highly correlated (Age 2 $r=.69$, $p<.001$; Age 3 $r=.73$, $p<.001$), and composite actigraph scores reflecting overall motor activity were calculated by averaging the four limb actigraph scores. Because actigraph scores correlated substantially across the lab and play situations (Age 2 $r=.64$, $p<.001$; Age 3 $r=.58$, $p<.001$), and prior analyses found that the same genetic effects influenced both situations (Saudino & Zapfe, 2008) measures were combined across situations to create an overall laboratory measure of actigraph AL.

Parent reports of Attention Problems.—Parents (94% mothers) rated attention problems at ages 2 and 3 years on the *Child Behavior Checklist/1½ - 5* (CBCL, Achenbach & Rescorla, 2000). The Attention Problems scale consists of 5 items (can't concentrate, can't pay attention for long; quickly shifts from one activity to another; wanders away; can't sit still restless or hyperactive; poorly co-ordinated/clumsy). Parents were asked to indicate on a 3-point scale how well each item described their children's behavior within the past 2 months (0 = "not true of their child", 1 = "somewhat or sometimes true", 2 = "very true or often true"). Previous research has shown that this measure is a valid and reliable measure of attention problems in toddlers (Mahone & Pritchard, 2014). Internal consistency, as assessed by Cronbach's alpha in the present sample, was .67 at age 2 and .69 at age 3.

Data Transformation

Consistent with prior research (Saudino & Eaton, 1991; Saudino & Eaton, 1995; Wood, Saudino, Rogers, Asherson, & Kuntsi, 2007), actigraph scores at both ages were positively skewed and were square-root transformed to create a more normal distribution (see Eaton, McKeen, & Saudino, 1996). Attention problems were also positively skewed and were normalized via square-root transformation. Because twin covariances can be inflated by variance due to sex, all scores were residualized for sex effects (see McGue & Bouchard, 1984).

Twin Design

The twin design decomposes the observed (i.e., phenotypic) variance of a variable into additive genetic (A), shared (C) and nonshared (E) environmental variance components. *Heritability*, the genetic effect size, is the proportion of phenotypic variance that can be attributed to genetic factors. If genetic influences are important to a behavior, genetically identical monozygotic twins (MZ) who share 100% of their genes should be more similar in behavior than dizygotic twins (DZ) who share on average, only 50% of their segregating genes. *Shared environmental variance* is familial resemblance that is not explained by genetic variance and comprises environmental influences that are shared by family members such as family demographics, one's rearing neighborhood, shared friends, family resources, etc. If shared environments are important to individual differences in the behavior under study, they should enhance the similarity of family members. *Nonshared environmental variance* is a residual variance that includes environmental influences that are unique to each individual. These unique environmental influences operate to make members of the same family different from one another. Possible sources of nonshared environmental variance include differential parental treatment; relationships with friends, peers and teachers; and nonsystematic factors such as accidents, illness and measurement error (Plomin, Chipuer, & Neiderhiser, 1994).

Cross-Lagged Analysis

Biometric cross-lagged models (Burt, McGue, Krueger, & Iacono, 2005) were used to examine genetic and environmental sources of: a) variance at each age; b) covariance between AL and attention problems within each age; and c) on the transmission of effects between and within variables across age (i.e., stability and cross-lagged effects, respectively). The model, depicted in Figure 1, constrains all cross-age associations (i.e., b_{11} , b_{22} , b_{12} , b_{21}) to function as phenotypic partial regression coefficients. The paths leading from the phenotype at age 2 to the same phenotype at age 3 (b_{11} and b_{22}) index the stability of the phenotype controlling for any prior association with the second phenotype. The cross-lagged paths (b_{12} and b_{21}) reflect the effects of one behavior at age 2 on the other behavior at age 3 and allows us to partial out the impact of traits across age independent of both their preexisting relation at the earlier age and of stability effects. For example, path b_{12} reflects the influence of AL at age 2 on attention problems at age 3 above and beyond their prior association at age 2. Variances of AL and attention problems at age 2 are decomposed into their genetic, shared environmental, and nonshared environmental components. The path estimates a_1 , c_1 , e_1 and a_2 , c_2 , e_2 are standardized partial regression coefficients indicating

the relative influences of the latent variables A_1 , C_1 , and E_1 and A_2 , C_2 , and E_2 on each phenotype at age 2 and the square of these paths represent genetic and environmental variances. The genetic correlation at age 2 (r_{a1}) indicates the extent to which the genetic effects on AL and attention problems correlate independent of the heritability of each phenotype. The genetic factors that influence two phenotypes can covary perfectly even when the genetic contributions to the phenotypic variances are modest. Therefore, r_{a1} can be 1.0 when the heritability of each measure is low. Conversely, two phenotypes may be highly heritable, but if there is no genetic overlap, the genetic correlation would be zero. A similar logic applies to the shared environmental correlation (r_{c1}) and nonshared environmental correlation (r_{e1}). The effects at age 3 (right side of Figure 1) are residual effects that are independent of age 2. Thus, a_3 , c_3 , e_3 and a_4 , c_4 , e_4 estimate the relative influences of the latent variables A_3 , C_3 , and E_3 and A_4 , C_4 , and E_4 on the phenotypes that are specific to age 3. These novel age 3 effects reflect change. The genetic and environmental correlations at age 3 (r_{a2} , r_{c2} , r_{e2}) index genetic and environmental overlap of these novel effects across the phenotypes.

Using this model, the overall genetic and environmental variances for both AL and attention problems at age 3 can be decomposed into four different components that inform on the extent to which the two phenotypes influence each other across age: (1) *stability effects*: genetic and environmental influences specific to AL at age 2 that are transmitted to AL at age 3 (e.g., genetic effects= $b_{11}^2 \times a_1^2$); (2) *cross-lagged effects*: genetic and environmental influences specific to the attention problems at age 2 that are transmitted to AL at age 3 (e.g., genetic effects= $b_{21}^2 \times a_2^2$); (3) *common effects from age 2*: the genetic and environmental effects common to both AL and attention problems at age 2 that are transmitted to AL at age 3 (e.g., genetic effects= $2 \times [b_{11} \times a_1 \times r_{a1} \times a_2 \times b_{21}]$); and (4) *residual effects*: unique genetic and environmental effects on AL at age 3 (e.g., genetic effects= a_3^2) (Larsson, Viding, Rijdsdijk, & Plomin, 2008). The age 3 variances for the attention problems are similarly decomposed.

Models were fit to raw data using a maximum likelihood pedigree approach implemented in Mx structural equation modeling software (Neale, Boker, Xie, & Maes, 2006). This approach allows the inclusion of participants with incomplete data. The overall fit of a model can be assessed by calculating twice the difference between the negative log-likelihood ($-2LL$) of the model and that of a saturated model (i.e., a model in which the variance/covariance structure is not estimated and all variances and covariances for MZ and DZ twins are estimated). The difference in $-2LL$ is asymptotically distributed as χ^2 with degrees of freedom equal to the difference in the number of parameters in the full model and that in the saturated model. A reduced model, in which all nonsignificant parameters were dropped, was compared to the full model in which all parameters were estimated. The relative fit of the reduced model was determined by the chi-square difference (χ^2) between the full model and the reduced model and corresponding change in degrees of freedom (df). A nonsignificant change in chi-square between the full and reduced model indicates that the parameters can be dropped from the model without a significant decrement in overall model fit.

Results

Phenotypic and Twin Correlations

Table 1 presents the phenotypic correlations indexing the associations between AL and attention problems within and across age as well as the stability of each domain. AL and attention problems were moderately correlated at both ages and across age. The age-to-age correlations were high for both AL and attention problems, indicating that both domains were stable. Twin intraclass and cross-correlations are presented in Table 2. In all cases the MZ correlations were greater than the DZ correlations, suggesting genetic contributions to the variances of each variable and covariances between variables.

Model-fitting

Table 3 presents the model-fit statistics. In the full model shared environmental influences on AL and attention problems at both ages, shared and nonshared environmental correlations at both ages, and the cross-lagged path from attention problems at age 2 to AL at age 3 were estimated as near zero and were nonsignificant as indicated by confidence intervals that included zero. A model fixing these parameters to zero did not fit significantly worse than the full model. This best-fitting reduced model is presented in Figure 2.

Phenotypic Stability and Cross-lagged Effects

There was substantial stability in both AL and attention problems across age. Submodels that dropped stability paths (i.e., b_{11} or b_{22}) resulted in a significant decrement in fit (see Table 3). Estimates of variance at age 3 due to stability across age can be obtained by squaring the partial regression coefficients for the respective paths (see also Total Variances for stability effects in Table 4). Stability effects explained 15.4% of the variance in AL at age 3 and 20.4% of the variance for attention problems at age 3.

It was not possible to drop the cross-lagged path from AL at age 2 to attention problems at age 3 (i.e., b_{12}) without worsening the fit of the model. Although AL at age 2 contributes significantly to attention problems at age 3, consistent with prior research, the effect was modest (i.e., explaining only .64% of the variance). Attention problems at age 2 did not significantly impact AL at age 3. The confidence interval for the b_{21} path estimate included zero and fixing this path to zero did not result in a poorer fit of the model. Thus, for AL, effects from age 2 are transmitted to age 3 via only stability, whereas for attention problems, age 2 effects are transmitted to age 3 via stability and cross-lagged (i.e., from AL) effects.

Genetic and Environmental Influences on AL and Attention Problems at Age 2

The genetic and environmental contributions to AL and attention problems at age 2 are the squared path values of the latent variables A_1 , E_1 and A_2 , E_2 in Figure 2. These values represent the percentage of variance due to genetic and nonshared environmental effects, respectively. Genetic factors explained 73.3% of the variance in AL and 73.2% of the variance in attention problems. Nonshared environmental influences accounted for the remaining 27% of the variance in both AL and attention problems. There was significant genetic covariance (r_{a1} in Figure 2) between AL and attention problems indicating that approximately 35% of the same genetic effects overlap across the two domains. Neither the

shared nor nonshared environmental correlations were significant, thus, only genetic factors significantly contribute to the phenotypic correlation between AL and behavior problems at age 2.

Genetic and Environmental Influences on AL and Attention Problems at Age 3

Genetic influences accounted for approximately 60% (CI: 52%–67%) of the variance in AL and 51% (CI: 40%–60%) of the variance in attention problems at age 3 (see “Total Variances” in Table 4). The remaining variance was due to nonshared environmental influences and accounted for 40% (CI: 33%–48%) of the variance in AL and 49% (CI: 40%–62%) of the variance in attention problems.

These estimates of total genetic and nonshared environmental variances on AL and attention problems at age 3 include effects that are transmitted from age 2 and novel effects at age 3. Table 4 presents the separate contributions of stability effects, cross-lagged effects, and common effects from age 2; and residual effects to the variances of each phenotype at age 3. The total variance is the sum of the component variances. Because effects are standardized, total variance for each phenotype at age 3 sum to 1 (slight deviations are due to rounding). The total genetic variance for a phenotype at age 3 reflects the proportion of total variance that is due to all four genetic sources of variance. Total environmental variances are similarly derived.

As indicated earlier, for AL only stability effects are transmitted from age 2 and these accounted for 15.4% of the total variance in AL at age 3. This stability is largely due to genetic influences. Genetic effects accounted for 73.3 % (i.e., $.1126/.1536 = 73.3\%$) of the stable variance in AL, although there were also modest nonshared environmental contributions to stability (i.e., $.0410/.1536 = 26.7\%$). These genetic effects from age 2 that persist across age explain 18.7% of the genetic variance at age 3 (i.e., $.1126/.602$). Similarly, stable nonshared environmental effects account for 10.3% of the nonshared environmental variance at age 3 (i.e., $.041/.398$). Most (84.6%) of the variance in AL at age 3 is independent of age 2 and reflects developmental change in AL. These novel effects are depicted as the paths on the right side of the model in Figure 2 and are listed as “Residual effects” in Table 4. There were significant and substantial genetic and nonshared environmental residual effects on AL at age 3. Approximately 48.9% of the total variance and 81.3% ($.4894/.6020$) of the genetic variance on AL at age 3 was due to genetic effects specific to age 3. New nonshared environmental effects explained 35.7% of the total variance and 89.7% of the nonshared environmental variance.

For attention problems at age 3, effects from age 2 are transmitted via stability, cross-lagged, and common effects. Stability effects accounted for 20.4% of the variance in attention problems at age 3. Again, genetic effects explained most of the stable variance (i.e., $.1492/.2039 = 73.2\%$) with modest, but significant, nonshared environmental contributions (i.e., $.0547/.2039 = 26.8\%$). Although significant, the cross-lagged effects from AL at age 2 explained less than 1% of the variance in attention problems at age 3. When cross-lagged effects were further decomposed into their genetic and environmental components, no single effect was significant. Common effects reflecting the covariation between AL and attention problems at age 2 explained approximately 2% of the variance in attention problems at age 3.

and this was due to genetic effects common to both phenotypes. Despite the continuities across age, most of the variance in attention problems at age 3 (77.1%) is independent of age 2. Residual effects explained approximately 66.0% (i.e., .3347/.507) of the genetic variance and 88.6% (i.e., .4366/.493) of the nonshared environmental variance at age 3. Thus, both attention problems and AL show substantial genetic and environmental change across age. Once again, only genetic factors contributed to the covariance between AL and attention problems. As indicated in Figure 2, the novel genetic effects that emerge at age 3 are moderately correlated across phenotypes ($r = .36$). The full genetic correlation between AL and attention problems at age 3, including covariance transmitted from age 2, was .39 (CI: .26-.51).

Discussion

The association between activity level and attention problems is well documented (Foley, McClowry, & Castellanos, 2008; Konrad, Gunther, Heinzel-Gutenbrunner, & Herpertz-Dahlmann, 2005; Reichenbach, Halperin, Sharma, & Newcorn, 1992), but little is known about the etiological factors that link the two domains across early childhood. The present multi-method study provides novel evidence of links between actigraph-assessed motor AL and parent ratings of attention problems at both ages 2 and 3 years and across age. This cross-age effect is unidirectional in that AL at age 2 significantly predicted later attention problems at age 3, however the reciprocal effect for attention problems was not significant. The present study also provides novel evidence of substantial genetic influences on attention problems in early childhood. Moreover, the associations between AL and attention problems, both within and across age, are entirely due to genetic influences.

Our finding of a unidirectional relation where activity level contributed to later attention problems is consistent with Greven et al. (2011) who found that hyperactivity in middle childhood predicted attention problems in adolescence, but not the other way around. It is noteworthy that in both studies the significant cross-lagged path was estimated at .08 indicating hyperactivity accounts for less than 1% of the total variance in attention problems. Thus, although modest, the effect has replicated in both direction and magnitude in different samples, across different ages, and using different methodologies. This replication adds some resolution regarding factors that can account for the lack of agreement between the two prior cross-lagged studies. Because the cross-lagged results replicated when we used a multi-method approach (i.e., actigraphs for activity level and parent ratings for attention problems), it suggests that the cross-lagged effect found by Greven et al. using only parent ratings is not simply due to shared method variance or halo effects. Nor is the effect specific only to later development. The same pattern of effects in early childhood and in adolescence makes it less likely that the null finding for Burns and Walsh (2002) in middle childhood is due to developmental changes in the trajectories of cross-lagged effects (Greven et al.). While it is possible that there is something unique about middle childhood, based on these findings, we suggest that the failure to find that hyperactivity predicts later attention problems in the Burns and Walsh study is attributable to their use of teacher ratings. It may be that within the classroom setting hyperactivity does not predict attention problems, however, it is also possible that measurement noise resulting from the different raters, and in some instances different measures, across age attenuated longitudinal prediction of attention

problems. Research in middle childhood using parental ratings of attention problems are needed to more fully address issues of developmental trajectory and rater effects in this developmental period.

The contribution of high activity to later attention problems in early childhood may explain developmental shifts in ADHD symptoms and subtypes. In preschool and early school-aged children, hyperactive problems are more prominent than attention problems in both clinical and nonclinical samples, but by adolescence, ADHD is more characterized by problems of inattention (Larsson et al., 2006). Although most contemporary models of ADHD view hyperactivity as a secondary consequence of underlying cognitive deficits including attentional processes (Alderson, Rapport, Kasper, Sarver, & Kofler, 2012; Rapport et al., 2009), it appears that, at least to some extent, hyperactivity may play a role in the development of attention problems. Our young sample shows that the onset of this directional influence begins as early as late infancy. Admittedly, the cross-lagged effect is small, but it represents effects that are independent of both the preexisting covariance between activity and attention problems at age 2 and the stability of each domain, and as such, reflects novel “causal” effects across only the interval studied. That is, any prior predictive effects would have contributed to the covariance between variables at age 2 and would be transmitted via stability effects. It is possible, therefore, that although the effects are small across any single interval, they may build upon prior effects and their impact accumulate across time. This incremental influence of activity on attention problems could explain the pattern of higher within- and across-age correlations found by Greven et al. (2011) in their adolescent sample.

The present study also provides novel evidence of genetic influences on attention problems in early childhood. Prior behavioral genetics research in this developmental period has focused on attentional competencies assessed within a temperament framework rather than on problems with inattention. This is likely a consequence of a lack of available measures (i.e., the earlier version of the CBCL for ages 2 and 3 did not include an attention problems scale). However, although related, temperament and behavior problems are independent constructs (Lemery, Essex, & Smider, 2002) and thus, there is a need to understand the factors that influence individual differences in early attention problems as well as competencies. The findings for attention problems in early childhood are consistent with longitudinal studies of older children in several ways (e.g., Greven et al., 2011; Hay, Bennett, McStephen, Rooney, & Levy, 2004; Larsson et al., 2006). First, genetic effects are substantial, explaining between one-half to two thirds of the variance in attention problems. Second, shared environmental influences were nonsignificant and the environments that impact attention problems are of the nonshared variety. Third, continuity in attention problems is due primarily to genetic effects that persist across age. Fourth, although there is genetic continuity, there are also novel genetic influences that emerge from one age to the next. In fact, more than half of the genetic variance at age 3 was independent of those effects that operated at age 2. Finally, nonshared environmental influences on attention problems contribute only modestly to age-to-age stability and are largely age specific. Thus, development in attention problems is characterized by genetic continuity and both genetic and nonshared environmental change. A similar pattern emerged for activity level (see Saudino, 2012 for a detailed discussion of continuity and change in AL for this sample).

Genetic and nonshared environmental sources of change (e.g., novel influences at age 3 that are independent of those at age 2) have implications for researchers searching for specific genes or environments that influence attention problems or activity level. While there are some genetic effects that may persist across age, there are also age-specific effects, hence the age of the sample will be an important consideration for molecular genetics researchers. To some extent, genes that influence attention problems or activity at one age will differ from those that operate at another. This is even truer for nonshared environmental influences which are almost entirely unique to each age. Nonshared environmental influences are environments or experiences that are specific to the individual and make family members different. Identifying the precise nonfamilial environmental factors that influence developmental change in attention problems and activity level is an important goal for future research. Once again, however, age will be a critical factor as nonshared environments that influence these behaviors will differ across age.

At both ages, there was moderate genetic overlap between activity level and attention problems indicating that roughly a third of the genetic influences are common to both domains. These estimates of genetic covariance between actigraph-assessed activity and parent-rated attention problems are only slightly lower than those from studies with older children that have relied solely on parent ratings (Greven et al., 2011; McLoughlin et al., 2007). Thus, it would appear that prior findings of substantial genetic links between hyperactivity and attention problems are not simply an epiphenomenon of method covariance. As is the case with hyperactivity and attention problems in older children, it is these overlapping genetic influences that largely explain the phenotypic correlation between actigraph-assessed activity level and attention problems in our sample. That is, the reason why the two domains are related is because of common genetic underpinnings. One implication of this is that molecular genetics findings for one domain can inform about possible genes that may influence the other.

In addition to signaling genetic overlap, our moderate genetic correlations between activity and attention problems also indicate that there is substantial genetic specificity across the two domains in early childhood. Again, this mirrors research with older children and adolescents (Greven et al., 2011; McLoughlin et al., 2007). To some extent, hyperactivity and attention problems are etiologically distinct (Nikolas & Burt, 2010) which may explain their differential associations with neuropsychological outcomes (e.g., general cognitive ability, working memory) and other areas of functional impairment such as academic and social problems (Willcutt et al., 2012). The finding of genetic heterogeneity between activity level and attention problems at ages 2 and 3 years provides unique support for a multidimensional structure of ADHD symptoms in early childhood. The factor structure of ADHD in young children is not well-studied, but phenotypic research with preschoolers ages 3 to 5 years suggests that early hyperactivity and inattention symptoms may be less differentiated than for older children (Willoughby, Pek, Greenberg, & the Family Life Project, 2012). The present results, however, reveal differentiation at the level of genetic etiology. Thus, as with older children, activity levels and attention problems in young children are correlated but distinct behaviors.

The limitations of this study should be acknowledged. First, our findings refer to continuously-distributed behaviors of motor activity level and attention problems in a population-based sample rather than clinical ADHD subtypes. It is possible that analyses using clinical diagnoses of hyperactivity and attention deficits might yield different results, however, this is unlikely given that both twin and molecular genetic studies provide strong support for the hypothesis that the clinical diagnosis of ADHD is best viewed as the extreme of a behavior that varies genetically throughout the entire population rather than as a categorical disorder (Chen et al., 2008; Levy, Hay, McStephen, Wood, & Waldman, 1997; Price et al., 2001). Second, we assessed motor activity levels not hyperactive behavior problems. This approach allowed us to objectively measure a key component of the ADHD-HI subtype and thereby circumvent issues of rater effects or method covariance. Prior research has found that children who are more motorically active are rated as having more hyperactive behavior problems (Ilott et al., 2010; Marakovitz & Campbell, 1998; Schaughency & Fagot, 1993; Wood et al., 2008) and those diagnosed with ADHD tend to show higher motor AL when compared to other diagnostic groups or control children (Hall, Halperin, Schwartz, & Newcorn, 1997; Halperin et al., 1993; Matier-Sharma, Perachio, Newcorn, Sharma, & Halperin, 1995). However, although there is a clear relation between motor AL and hyperactivity, mechanical measures of AL do not address impulsivity. Despite this, our findings are remarkably consistent with prior research in older samples using parent-report measures of hyperactivity that include impulsive symptoms. Nonetheless, these results may not fully extrapolate to hyperactive behavior problems or ADHD as these two latter domains encompass behaviors beyond simple motor activity level. Third, the CBCL attention problems measure includes two items that are motoric in nature (i.e., “can’t sit still restless or hyperactive” and “poorly co-ordinated/clumsy”) raising the possibility that the association between our actigraph measure of activity and the CBCL is due to both indexing physical activity to some extent. To explore this, we created a revised CBCL attention problems scale with the 3 remaining items. Although the reliability of this reduced scale was poor (age 2 $\alpha=.57$; age 3 $\alpha=.59$), the correlations between the actigraph AL and the reduced CBCL attention problems scale were essentially unchanged both within and across age (i.e., the largest difference was the correlation between attention problems and activity level at age 2, which was .26 using the full CBCL scale and .28 with the reduced scale). Thus, it does not appear that the associations between actigraph activity and attention problems as measured on the CBCL is driven by the two motoric items. Finally, our sample of just over 300 twin pairs is relatively small and consequently, some confidence intervals are broad and we lacked the power to decompose the cross-lagged path from AL to attention problems into its genetic and environmental components. For this reason, we focus on the overall pattern of results, rather than specific parameter estimates.

The limitations notwithstanding, the present study has much to contribute to the understanding of the influences that underlie links between activity levels and attention problems and has the potential to inform about early risk factors in the development of ADHD. ADHD and related behaviors in early childhood have been understudied (Willcutt et al., 2012; Willoughby et al., 2012) and as a consequence, there are gaps in our knowledge about the structure, developmental course, and developmental pathways of ADHD symptoms. The present data begins to address these gaps by indicating that activity level and

attention problems—two behavioral dimensions that are related to ADHD—are genetically related in early childhood. These genetic links between domains involve both stable and newly developing genetic effects. In addition to being linked within age, the two phenotypes are also linked across age with the direction of effects going from activity level at age 2 to attention problems at age 3. Thus it appears that overactivity in late infancy can impact the later development of problems related to inattention. Although there is some genetic overlap between activity level and attention problems, there are also genetic and nonshared environmental effects unique to each domain indicating differences between the two phenotypes at the level of underlying etiology.

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Research Highlights

- This study provides novel evidence of substantial genetic influences on attention problems in early childhood.
- Further, this study reveals genetic links between motor activity level (AL) assessed via actigraphs and parent-rated attention problems both within and across ages 2 and 3 years.
- The cross-age effect is unidirectional with AL at age 2 predicting attention problems at age 3.
- Although the associations between AL and attention problems are entirely due to genetic influences, there are also genetic and environmental effect specific to each behavior.

Figure 1. A path diagram of the cross-lagged model shown for one twin.

Latent factors appear in circles (i.e., A for genetic factors, C for shared environments, and E for nonshared environments), while observed (measured) variables appear in rectangles. Latent factors of the older age represent residual variances specific to age 3. Standardized path estimates for the latent factors are indicated by lowercase letters (e.g., a_1 , c_1 , e_1). Cross-age stability is represented by b_{11} and b_{22} , while b_{12} and b_{21} indicate cross-lagged effects. Double-headed arrows linking two latent factors represent genetic, shared environmental, or nonshared environmental correlations (i.e., r_{a1} , r_{c1} , r_{e1} , and r_{a2} , r_{c2} , r_{e2}).

Figure 2. Standardized parameter estimates (and 95% confidence intervals) from the best-fitting cross-lagged model.

Path estimates of genetic (A) and nonshared environmental (E) influences on activity level and attention problems at age 2 represent the genetic and environmental contributions to the total variance. The effects at age 3 are residual effects that are independent of age 2. All paths are significant at $p < .05$.

Table 1

Phenotypic Correlations (95% CI) Between Activity Level and Attention Problems Within and Across Age

	Age 2		Age 3	
	Activity Level	Attention Problems	Activity Level	Attention Problems
Activity Level Age 2	1			
Attention Problems Age 2	.26 (.17-.34)	1		
Activity Level Age 3	.45 (.37-.52)	.17 (.08-.26)	1	
Attention Problems Age 3	.21 (.12-.29)	.51 (.44-.57)	.26 (.17-.34)	1

Note. All correlations are significant at $p < .05$.

Table 2

Twin Intraclass and Cross Correlations (95% CI) Between Activity Level and Attention Problems Within and Across Age

	Age 2				Age 3			
	Activity Level		Attention Problems		Activity Level		Attention Problems	
	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ
Age 2								
Activity Level	.73 (.56-.78)	.38 (.25-.50)						
Attention Problems	.22 (.12-.31)	.09 (–.02-.19)	.74 (.64-.79)	.39 (.26-.50)				
Age 3								
Activity Level	.43 (.35-.51)	.28 (.17-.39)	.14 (.05-.24)	.08 (–.03-.18)	.68 (.59-.74)	.47 (.33-.59)		
Attention Problems	.19 (.10-.28)	.01 (–.10-.12)	.52 (.43-.59)	.22 (.11-.32)	.27 (.17-.35)	.08 (–.03-.19)	.70 (.61-.76)	.10 (–.05-.25)

Note. MZ monozygotic twins, DZ dizygotic twins. Intraclass correlations are bolded.

Table 3

Fit Statistics for Cross-lagged Models

	Overall Fit of Model ^a							Relative Fit of Model ^b		
Model	-2LL	df	χ^2	df	p	AIC	RMSEA	χ^2	df	p
Saturated	8459.616	2353								
Full	8573.813	2403	114.197	50	.000	14.197	.064			
Drop b_{11}	8648.657	2404	189.041	51	.000	87.041	.092	74.844	1	.000
Drop b_{22}	8686.201	2404	226.585	51	.000	124.585	.105	112.388	1	.000
Drop b_{12}	8577.680	2404	118.064	51	.000	16.064	.065	3.867	1	.049
Drop b_{21}	8575.466	2404	115.850	51	.000	13.850	.064	1.653	1	.199
Drop all nonsignificant paths	8582.766	2412	123.150	59	.000	5.150	.059	8.953	9	.442

Note. -2LL=Likelihood Statistic. χ^2 =Chi-square fit statistic. df=Degrees of freedom. AIC=Akaike's Information Criterion. RMSEA=Root Mean Square Error of Approximation.

^aOverall fit of the model is determined by the difference in -2LL of the model and that of a saturated model.

^bRelative fit of the model determined by the χ^2 difference (χ^2) between full cross-lagged model and reduced model. Best fitting model indicated in bold.

Table 4

Genetic, Shared and Nonshared Environmental Influences on Activity Level and Attention Problems at Age 3 from Best-fitting Model

	Total variances	A	C	E
<u>Activity level at age 3</u>				
Total variances due to	1.000	.6020	-	.3980
1. Activity level at age 2 (Stability effects)	.1536	.1126 (18.7%)	-	.0410 (10.3%)
2. CBCL Attention problems at age 2 (Cross-lagged effects)	-	-	-	-
3. Common effects at age 2	-	-	-	-
4. Residual effects at age 3	.8464	.4894 (81.3%)	-	.3570 (89.7%)
<u>CBCL Attention problems at age 3</u>				
Total variances due to	1.000	.5070	-	.4930
1. CBCL Attention problems at age 2 (Stability effects)	.2039	.1492 (29.4%)	-	.0547 (11.1%)
2. Activity level at age 2 (Cross-lagged effects)	.0064	.0047 (0.9%)	-	.0017 (0.3%)
3. Common effects at age 2	.0184	.0184 (3.6%)	-	-
4. Residual effects at age 3	.7713	.3347 (66.0%)	-	.4366 (88.6%)

Note. A = Genetic influences; C = shared environmental influences; E = Nonshared environmental influences. Percentages of genetic/shared environmental/nonshared environmental influences due to four sources are provided in parenthesis. Bold text denotes effects that are significant at $p < .05$.