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A Twin Study of the Relationships among Inattention, Hyperactivity/Impulsivity and Sluggish Cognitive Tempo Problems

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Abstract We investigated the etiological relationships between the three ADHD dimensions of Inattentive Problems (INP), Hyperactivity-Impulsivity Problems (HIP) and Sluggish Cognitive Tempo (SCT) as measured by the CBCL 6–18 questionnaire. Multivariate models were applied to 398 twin pairs (374 boys and 422 girls) aged 8 to 17 years (M=13.06, SD=2.59) belonging to the population-based Italian Twin Registry. The INP, HIP and SCT problem scores were moderately-to-substantially (range 0.29–0.47) intercorrelated. The best fitting model showed that these 3 dimensions are correlated both at the genetic (correlations' range: 0.65–0.83) and the environmental (correlations: 0.29 and 0.44) levels, but they are also distinct. While SCT showed moderate heritability and large non-shared environmental influences, variance for both INP and HIP was substantially explained by genetic influences. We also found evidence of negative sibling interaction for INP, implying that a given behavior in one twin leads to an opposite behavior in the co-twin. Our results support at the etiological level the findings of previous psychometric and longitudinal studies of ADHD, which yielded evidence of the 3 distinct—albeit correlated—problem dimensions of inattentiveness, hyperactivity-impulsivity, and sluggish cognitive tempo.

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Attention Deficit Hyperactivity Disorder (ADHD) is a common, complex and heritable disorder. According to the current nosographical systematization in the DSM IV-TR (American Psychiatric Association 2000), ADHD is characterized by 2 main dimensions: hyperactivity-impulsivity and inattention problems. Accordingly, the DSM-IV recognizes 3 relatively distinct subtypes, namely: hyperactive/impulsive, inattentive and combined.

Although the dimensions of ADHD are generally recognized as valid and clinically meaningful, some researchers have found that they are amenable to better specification. Particularly, the Inattentive Type can be phenotypically heterogeneous (Carlson and Mann 2002; Lahey et al. 1994), as it encompasses a "sluggish cognitive tempo" (SCT; Barkley 2011; Carlson and Mann 2002; Hartman et al. 2004; McBurnett et al. 2001) component, which is characterized by hypoactivity and lethargy, daydreaming, mental confusion or fogginess, staring and slow motor speed or movements. On the other hand, SCT symptoms have been found to yield poor negative predictive power towards an ADHD diagnosis (Frick et al. 1994). While this may have conspired against the inclusion of an explicit SCT dimension into the DSM-IV ADHD operational criteria, a disregard of SCT may cause greater ADHD heterogeneity in general, and diminished diagnostic clarity among children belonging in the ADHD inattentive group (Hartman et al. 2004).

The first study to empirically support SCT within ADHD was that of Lahey et al. (1988): by an exploratory factor analysis they isolated a SCT factor characterized by a pattern of inconsistent alertness and orientation, confusion, physical underactivity, daydreaming, and lack of mental alertness. They also reported evidence in favor of psychometric independence

of SCT from the hyperactivity/impulsivity and inattention/disorganization factors.

There is additional recent empirical support for the internal validity of the SCT factor: confirmatory factor analyses have shown that the SCT items load on a factor that is distinct from those of inattention and hyperactivity (Barkley 2011; Garner et al. 2010; Hartman et al. 2004). Different studies -one in community, (Hartman et al. 2004) and two in clinical (Bauermeister et al. 2011; Garner et al. 2010) samples of children and adolescents- provided evidence for the psychometric validity of the SCT construct. These studies showed that the best fitting model for ADHD symptoms was consistently a three factor model which encompassed the SCT, inattentive and hyperactive dimensions. In these studies the SCT and the inattention factor were highly correlated, while the SCT-hyperactivity/impulsivity correlation was weaker (Garner et al. 2010; Hartman et al. 2004). Barkley (2011) performed a confirmatory factor analysis of ADHD symptoms in a sample of adults, providing results that were again consistent with a three factor solution. Thus, the presence of 3 distinct, albeit psychometrically correlated factors-inattentive, hyperactive and SCT- in ADHD can also hold true longitudinally. Other psychometric investigations, however, were able to replicate the 3 factors solution in boys only, while in girls the SCT factor was subsumed within the inattentive subtype (Todd et al. 2004). A recent meta-analysis (Willcutt et al. 2012) again supports a tridimensional conceptualization of ADHD: although SCT items and DSM-IV inattention symptoms are highly correlated, both exploratory and confirmatory factor analyses indicated that at least a subset of SCT items do not load on either inattention or hyperactivity factors.

While the main goal of these studies was to determine how many factors are needed to best capture the covariation of inattentive, hyperactive-impulsive and SCT symptoms in children, genetically-informed designs can address the issue of independence/unitariness of these 3 dimensions at an etiological level (Hewitt 1993). Several twin studies have investigated the etiology of ADHD subtypes (Levy et al. 2006; Nikolas and Burt 2010), but they were exclusively focused on the two dimensions of inattention and hyperactivity. No univariate/multivariate genetically-informed study is available on SCT and its etiological relationships to inattention and hyperactivity. Overall, the available twin studies show that while the heritability for both inattention and hyperactivity is high, the role of shared environment appears negligible, and that of non-shared environment is moderate (Nikolas and Burt 2010). According to a review chapter on the genetics of ADHD (Derks et al. 2009) the heritability of ADHD ranges between 35 % and 89 %, for hyperactivity it ranges between 42 % and 100 %, and for attention problems it ranges between 39 % and 81 %.

Indeed, analyses of cross-sectional data of hyperactivity-impulsivity and inattentiveness suggest that their association is largely attributable to shared genetic influences, although there are additional genetic influences that are unique to each of these two dimensions (Greven, Rijsdijk and Plomin 2011). Cross-lagged twin data analyses showed that the association of inattention and hyperactivity over time is influenced by stable, as well as by newly-developing, genetic factors (Greven et al. 2011). A study by Hay et al. (2004) coupled cross-sectional and longitudinal behavioral genetic analyses of inattention and hyperactivity-impulsivity, and found that a large proportion of the consistency in ADHD behavior from childhood to early adolescence is attributable to genetic influences.

Moreover, several genetically-informed studies of ADHD and related phenotypes reported negative sibling interaction (Rietveld et al. 2003a; Silberg et al. 1996). Sibling interaction is present when twins influence each other's behavior. This can occur in the form of sibling "competition/contrast" or "co-operation", depending on whether the presence in the family of a high-scoring sibling inhibits, or facilitates the development of similar behavior by other siblings. This can result in greater similarity between the twins, as one twin imitates his/her cotwin's behavior (co-operation), or less similarity, as one twin attempts to individuate from his/her cotwin (competition or contrast) (Boomsma 2005).

Twin studies that have investigated the etiology of ADHD (Eaves et al. 1997; Nadder et al. 2001; Price et al. 2001; Rietveld et al. 2003a; van Beijsterveldt et al. 2004) have mostly found 'contrast effect' (Nadder et al. 2001; Price et al. 2001; Rietveld et al. 2003b; van Beijsterveldt et al. 2004), implying that high levels of ADHD behavior in one child leads to lower ADHD levels in the other sibling.

However, Simonoff et al. (1998) found a contrast effect in hyperactivity for maternal but not teacher ratings, suggesting that contrast effects may indeed be better thought as a form of rater bias in maternal ratings of hyperactivity. Other twin studies have found that contrast effects on parental ratings may be stable rather than age-specific (Plomin et al. 1993).

While psychometric approaches are important in stating the degree of phenomenological dependence/independence between phenotypes, behavioral genetic approaches can establish the nature of the co-aggregation of behavioral traits. Thus, while genetically-informed studies alone are not sufficient to reconceptualize the complex issue of ADHD classification, they can indicate whether, and to what extent, behavioral covariation is attributable to common biological mechanisms, or to what extent environmental influences shape these interrelationships.

It could be argued that a very strong (~1.00) etiological correlation between different ADHD dimensions/subtypes would speak against valid multidimensionality even in the presence of relative psychometric independence. Moderate environmental/genetic correlations would instead indicate

that, while some genetic and environmental factors are shared between ADHD dimensions, some other etiological factors are unique for each ADHD dimension, so that psychometric and etiological distinctiveness correspond to some extent.

Also, it should be remembered that twin studies of the general population are mostly based upon dimensional, rather than categorical, approaches: by definition, clinical cases are a minority of subjects in such studies. While there are clear conceptual differences between the categorical and dimensional methods, rigorous analyses (van den Oord et al. 2003) yield no evidence of qualitatively distinct processes generating abnormality as compared to normal variation for behavioral and emotional problems in children and adolescents.

Moreover, some studies have explored this issue empirically (Thapar and Stergiakouli 2008) and found that the genetic contribution to normal variation and to extreme ADHD scores is essentially the same, implying that ADHD whether defined dimensionally or categorically remains substantially heritable and that the same underlying liability can be assumed for all these phenotypic definitions.

The present study had three principle aims. First, we were interested in assessing the strength of the relationship between inattention, hyperactivity/impulsivity and SCT. Second, we analyzed the etiology of this co-occurrence. Third, we assessed whether sibling interaction explains part of the variance for hyperactivity, impulsivity and SCT.

Methods

Participants

A nationwide database of all "possible twins" in the Italian general population was set up in 2001 (Stazi et al. 2002) using the personal identification number "codice fiscale" (CF, or fiscal code) (Moruzzi et al. 2011; Ogliari et al. 2006; Spatola et al. 2007). In 2003, all subjects who were likely to be parents of twins born between 1986 and 1995 and were resident in the Northern Italian provinces of Milano and Lecco were contacted by mail and invited to participate in the study. Of 2,015 contacted families, 973 (48 %) confirmed the presence of a twin pair among their children; 707 of these 973 families agreed to be involved in twin surveys of various types, and 407 of these families agreed to participate in the present psychometric survey, yielding a participation rate for this study of 57.5 %. All respondents to this survey were mothers. The mean age of children and parents did not differ between families who agreed to participate in the psychometric survey versus the remaining families (M=13.06, SD=2.59 vs. M=13.1, SD=2.31, p=0.62 for children; M=46.06, SD=0.23 vs. M=46.71, SD=0.35, p=0.10 for parents). Moreover, the educational level and percentage of full-time employment were similar for mothers of participating and non-participating twins (17.7 % versus 16.3 %, p=0.65 for mothers with and without a university degree, respectively; 54 % and 52 %, p=0.10, for mothers with and without full-time employment, respectively,) These figures closely reflect those available for the northwestern Italian population (ISTAT 2003). As 9 of the 407 twin pairs were excluded owing to missing data on zygosity, the final sample for the present study consists of 398 pairs aged 8–17 years (mean age 13.06+2.59). The procedures of this study were approved by the ethical committees of the participating institutions and since all participants were minors at the time of the study, parents signed a declaration of consent.

We use the parent-rated Goldsmith questionnaire (Goldsmith 1991) to determine zygosity, accordingly the sample included 144 monozygotic (MZ) pairs (74 male and 70 female) and 254 dizygotic (DZ) pairs (53 male, 81 female, 120 opposite sex). The MZ/DZ same sex/DZ opposite sex ratio was 1.1/1.0/0.9 which is close to the expected 1/1/1 population distribution. Recent data (van Beijsterveldt et al. 2004) show an accuracy of zygosity determination of over 94 % when using the algorithm employed to score the responses by this questionnaire.

Measures

ADHD and Sluggish Cognitive Tempo Problems The presence of ADHD problems and SCT problems were evaluated, respectively, by the Child Behavior Checklist (CBCL) 6–18 DSM-oriented Attention-Deficit/Hyperactivity (ADH) scale, (Achenbach et al. 2003) and by the CBCL SCT scale (Achenbach et al. 2008). The CBCL is one of the most widely-used instruments to asses child and adolescent behavioral problems in both epidemiological and clinical samples (Achenbach and Rescorla 2001). It encompasses 118 items that describe common and specific behavioral and emotional problems, and three competence scales that cover competencies and adaptive functioning. Through factor analysis, an empirically-based taxonomy has been developed from the CBCL (Achenbach and Rescorla 2001), which has yielded internalizing and externalizing broad band dimensions. The CBCL 6–18 encompasses six DSM-oriented scales that have been developed in search of better correspondence to DSM-IV categories (Achenbach et al. 2003).

The CBCL SCT scale (Achenbach et al. 2008) includes four items ("confused or seems to be in a fog", "daydreams or gets lost in his/her thoughts", "stares blankly" and "underactive, slow moving, or lacks energy").

Similar to previous studies that have employed the CBCL (e.g., Becker et al. 2012), we divided the CBCL DSM Oriented Scales (DOS) ADH items into inattentive ("fails to finish things he/she starts", "can't concentrate, can't pay attention for long", "inattentive or easily distracted") and

hyperactive/impulsive ("can't sit still, restless, or hyperactive", "impulsive or act without thinking", "talks too much" and "unusually loud"), to build an inattentive problem (INP) subscale and an hyperactivity/impulsivity problem (HIP) subscale. The INP and HIP subscales were then employed to analyze their causal relationships to each other, as well as their causal relationships to the SCT subscale.

While to the best of our knowledge there is no published factorial analysis of CBCL-derived HIP, INP and SCT items, Hartman et al. (2004) were able to show 3 relatively well-separated ADHD SCT, INP and HIP dimensions by factor analyzing items of the CBCL SCT scale and items of the Disruptive Behavior Rating Scale. Moreover, the CBCL SCT scale has been employed by several previous studies investigating the SCT construct (Carlson and Mann 2002; McBurnett et al. 2001).

We have adopted the CBCL6-18 SCT, inattentive, and hyperactivity/impulsivity problem scales assuming that they were sufficiently reflective of the corresponding 3 domains of ADHD symptoms. While relatively new, there is growing evidence that the DOS scales predict DSM-IV childhood disorders, including ADHD, satisfactorily (Krol et al. 2006; Nakamura et al. 2009).

Statistical Analyses

The descriptive statistics of SCT, INP and HIP were calculated for individuals divided by sex and zygosity.

Structural Equation Modeling of Twin Data Phenotypic correlations (with 95 % CI) were calculated in the Mx program (Neale et al. 2003) using a saturated model, including sex and age as covariates in the model of the means. This model estimated the within-subject phenotypic correlations, the cross-twin/within-trait correlations (between twin 1 and twin 2 for the same trait) and cross-twin/cross-trait correlations (between one trait in a twin and the other trait in the co-twin) in MZ and DZ twin pairs for the INP, HIP and SCT scales. Prior to model fitting, all variables were log transformed to reduce skewness and approximate a normal distribution. An assumption of Structural Equation Modelling (SEM) is that the data are normally distributed (Derks et al. 2004): failure to correct for non-normality may lead to biased parameter estimates and incorrect likelihood ratio tests. The analyses were repeated even with non-transformed variable to check for possible differences.

The difference in phenotypic correlations across twin pairs of different zygosity provides a first indication of which factors are important for the variation of the traits, as well as of the presence of different forms of sibling interaction. Typically, MZ correlations twice the DZ correlations indicate the effects of additive genetic factors; DZ correlations greater than one-half the MZ correlations suggest that the environment shared by the twin pairs is influencing the trait. If the DZ correlations are less than half the MZ correlations, then dominance genetic effects (D, nonadditive genetic effect in which one allelic version interacts with another at the same or different locus to affect behavior) could be considered for inclusion into the model. However, the classical twin approach is typically underpowered to assess D effects (Rietveld et al. 2003b).

The MZ-DZ correlation differences can also be indicative of rater biases or interaction effects (Boomsma 2005; Eaves 1976). When parents rate their children's behavior, they may take one twin as a 'standard' against whom they rate the other sibling's behavior, and thus they may either stress the similarities or the differences between the siblings, resulting in an apparent cooperation or competition effect (Rietveld et al. 2003b). The negative sibling interaction (or contrast, implying that a given behavior in one twin leads to an opposite behavior in the co-twin) lowers the DZ correlation relative to the MZ correlation, thus simulating a dominance genetic effect. It is possible to distinguish between contrast effects and genetic dominance effects by inspecting the observed variances for MZ and DZ twins (Eaves 1976). If there is a competitive effect, MZ and DZ variances are both deflated, with this effect being more marked in the MZ group, which leads to a smaller MZ variance (Eaves 1976).

Multivariate Genetic Model In multivariate analyses, comparing MZ and DZ differences in cross-twin cross-trait correlations allows decomposing the total phenotypic covariance of two or more traits into proportions due to A (additive genetic factors), C (shared environmental factors), D (dominance genetic effects) and E (non-shared environmental and error). The cross-twin cross-trait correlations are informative on the nature of covariation between phenotypes; similarly to single-trait (univariate) twin correlations, if MZ cross-twin cross-trait correlations are twice the DZ correlations, additive genetic effects are likely to be important, DZ cross-twin cross-trait correlations greater than half the MZ cross-twin cross-trait correlations suggest the importance of C, and so on. Significant within-individual cross-trait covariances but non-significant cross-twin cross-traits' covariances indicate that E factors play a role in the common etiological influences.

Multivariate genetic models were fitted (Neale and Cardon 1992), including sex and age as covariates in the model of the means. The Cholesky, or triangular, decomposition provides the fullest explanation of data without any specific hypothesis on the covariance matrices of A, C/D, and E. The re-parameterization of the Cholesky Model into a Correlated Factor Model, allows for the decomposition of the phenotypic correlations between the phenotypes into additive genetic (*ra*), shared environmental (*rc*) or dominance (*rd*) and individual-

specific environmental (*re*) correlations. These correlations provide an indication of the degree of overlap in etiology. The estimation of sibling interactions as additional sources of variance is done by means of a reciprocal path (*b*), set between the twins' observed phenotypes, which can be either positive or negative.

The product of the square root of two univariate heritabilities multiplied by the estimated genetic correlation is called a bivariate heritability. This provides the contribution of shared genetic factors to the phenotypic correlation between two traits; this is the percentage of the correlation between trait Y and trait Z that can be explained by shared genetic effects. The same reasoning and computing applies to environmental influences. By these measurements, a strong genetic overlap can be revealed between two heritable traits even in presence of modest phenotypic correlation, or, conversely, even weakly heritable traits can reveal a large proportion of genetic correlation.

By dividing the bivariate heritability by the phenotypic correlation, one obtains the proportion of genetic covariance between two traits, and the same procedure applies to environmental covariance.

The full Cholesky model was successively further refined by stepwise deletion of variance components in progressively more parsimonious models. These nested models were compared with the full model.

All model comparisons in multivariate models were made by hierarchical $\chi 2$ tests, since the difference between twice the negative log-likelihood (−2LL) for the reduced and the full model has a $\chi 2$ distribution, with degrees of freedom (df) given by the difference between the df for the two models (Heath et al. 1989). According to the principle of parsimony, models with fewer parameters are preferable if they do not result in a significant deterioration of fit. An index of parsimony is the Akaike's information criterion (AIC), (Aiken and West 1991) which is calculated as −2LL-2(Δdf). The AIC was employed for model selection: the lower the AIC value, the better the balance between explanatory power and parsimony.

In sum: to analyze the common etiology of SCT, INP and HIP we first estimated the phenotypic correlations and variances. Based on biometrical genetics theory, these guided the choice of which components (shared environment vs. non additive genetic factors, and possible sibling interaction) to include in the twin models. We used a Correlated Factors solution to determine the genetic and environmental contributions to both the variances of and covariances between the traits. In these models we added a sibling interaction (or contrast effect) parameter to account for significant differences between observed variances in the MZ and DZ groups. By following the principle of parsimony, we tried to reduce models by subtracting one component at a time from preceding models, until we reached a best fitting model.

Results

Table 1 shows the descriptive statistics for SCT, INP and HIP in the sample, divided by sex and zygosity. The only significant difference was a higher HIP mean score in boys compared to girls.

Cronbach's alpha was 0.65 for HIP, 0.76 for INP and 0.54 for SCT.

For SCT, the skewness value before transformation was 1.77, after transformation was 0.70; for INP skewness before transformation was 0.91, after transformation was 0.18; for HIP skewness before transformation was 1.18, after transformation was 0.22.

Table 2 shows the phenotypic (within-subject, left hand side) and the twin correlations (right hand side) for SCT, INP and HIP in the sample, as derived from the constrained correlation model. The within-subject correlation between SCT and INP is almost twice the correlation between SCT and HIP, a significant ($p<0.001$) difference according to Williams' formula to test the difference between two dependent correlations (Steiger 1980). The DZ cross-twin/within-trait (on the diagonal) correlations in the right hand side part of the table are much lower than half the MZ correlations for all 3 phenotypes, suggesting that non-additive genetic, or contrast effects may influence the traits in addition to the additive genetic and environmental effects.

The negative DZ correlation in INP supports the presence of a contrast effect for this specific phenotype. The greater MZ compared to DZ cross-twin/cross-trait correlations suggest that genetic influences explain part of the phenotypic covariance. In order to compare MZ and DZ within trait correlations, we calculated the confidence intervals (CI) for the difference between two independent correlations following Zou's approach (Zou 2007). For SCT, the difference of 0.2 between the MZ and DZ correlation had a 95 % CI between 0.06 and 0.33; for INP the MZ-DZ correlation difference of 0.33 had a 95 % CI between 0.21 and 0.45; for HIP the MZ-DZ correlation difference of 0.54 had a 95 % CI between 0.41 and 0.66. In all cases, the 95 % confidence interval did not encompass zero, implying significance at $p<0.05$.

The MZ variances were consistently lower than the DZ variances for all 3 phenotypes (respectively: 1.1 vs 1.3 for SCT, 2.11 vs. 2.50 for INP and 2.44 vs. 2.60 for HIP), indicating the possible role of contrast effect. By testing the equality of variances, we found that MZ-DZ variances differed significant for INP ($F=4.46$, $p=0.04$), but not for HIP and SCT (respectively: $F=1.99$, $p=0.16$ and $F=0.65$, $p=0.42$). In the light of these data, in the successive multivariate models we implemented an ADE model between INP, HIP and SCT, and added a *b* path for INP.

Table 3 shows the multivariate Cholesky ADE-b model fitting results for SCT, INP, and HIP. Figure 1 shows a

Table 1 Mean values of SCT, INP and HIP (with standard deviations in parentheses)

	Entire sample n=796	Boys n=374 (47 %)	Girls n=422 (53 %)	MZ n=288 (36.2 %)	DZ n=508 (63.8 %)
SCT	0.81 (1.1)	0.79 (1.09)	0.83 (1.12)	0.79 (1.04)	0.82 (1.14)
		t=0.46, p=0.64		t=−0.44, p=0.66	
INP	1.44 (1.54)	1.51(1.58)	1.38 (1.50)	1.35 (1.45)	1.49 (1.58)
		t=1.21, p=0.23		t= −1.29, p=0.21	
HIP	1.46 (1.60)	1.60(1.61)	1.34 (1.57)	1.34 (1.56)	1.53 (1.61)
		t=2.22, p=0.02		t= −1.58, p=0.11	

SCT sluggish cognitive tempo problems; *INP* inattention problems; *HIP* hyperactivity-impulsive problems; *MZ* monozygotic; *DZ* dizygotic

graphical representation of the full Cholesky model. The four nested models (i.e., Models 2–5) are reported in Table 3. In the first nested model (model 2) we observed a significant deterioration of the fit by dropping the sibling interaction effects on INP from model 1. In model 3 we tested the significance of dominance effects on variance and covariance; we found an improvement of the fit by dropping the D component, as shown by the relative AIC value. Then we tested an AE model without sibling interaction (model 4), which resulted in a fit deterioration. In the following attempts to further simplify the model by removal of the unique environmental paths on covariances, we tried to drop the E paths, one at the time, on covariance. We found that only the E path from SCT and HIP could be dropped without significant worsening of the model's fit (model 5). The resulting best fitting model was thus an AE model with sibling interaction in which all dominance paths were dropped, as well as and the environmental covariance path between SCT and HIP.

In sum, the variation and covariation between the three ADHD dimensions was influenced by additive genetic factors and non shared environmental factors. Specifically, individual differences for SCT were mostly explained by non-shared environmental factors, while genetic factors mostly influenced the variability for HIP and INP. Contrast effects had a significant role on INP.

Table 4 provides the estimated proportions of variance and covariance accounted for by etiological agents under the full model and the best fitting model (model 1 and 5) for each of the three phenotypes. All parameter estimates with a 95 % CI from the different multivariate models (model 2, 3 and 4) are available from the authors upon request. These estimates include additive and non additive genetic, unique environmental influences, and the b (sibling interaction) path value. The b path value for Inattention was significant and negative, which indicates a sibling contrast effect, as expected from the observed within-pair correlations and variances. When we repeated the model fitting analyses with non-transformed data, both the saturated and ACE models yielded results that did not differ substantially from those shown in the Tables 3 and 4. These data are available from authors on request.

Figure 2 is a graphic representation of the findings in Tables 3 and 4, according to a Correlated Factor model, which is a re-parameterized and standardized version of the Cholesky model. By applying the reasoning exposed in the method section, it is possible from the Correlated Factor model to obtain the proportion of phenotypic correlation explained by genetic and environmental influences, and then the proportion of covariance in the off diagonal in Table 4. For example, for the correlation between SCT and INP the proportion of phenotypic correlation due to A is: √.28*0.61*√.67=0.26, and that due to E is: √.72*0.44*√.33=0.21 (0.61 and 0.44 are the genetic and environmental correlations between SCT and INP yielded by the Correlated Factor model); then, by dividing these values by their sum (that, is the phenotypic correlation: 0.26+0.21=0.47), one easily gets the values off diagonal of Table 4 (0.26/0.47=55 % for A and 0.21/0.47=45 % for E). Thus, the phenotypic correlation of 0.47 between SCT and INP could be split into 0.26 due to genetic factors, and 0.21 due to non shared environmental factors. The same calculations could be applied to the other phenotypic correlations: the phenotypic correlation (0.29) between SCT and HIP can then totally be attributed to genetic influences (√.28*0.83*√.45=0.29) as expected from the covariance path, while the phenotypic correlation (0.47) between INP and HIP can be split into 0.35 due to genetic influence (√.67*0.65*√.45) and 0.12 (√.33*0.29*√.55), due to unique environmental factors.

Discussion

This study adds to previous work on ADHD dimensions by analyzing for the first time the genetic vs. environmental nature of covariation among ADHD inattentive, hyperactivity/impulsivity and SCT problems.

All three phenotypes were moderately and significantly correlated in this general population sample, with SCT and inattention problems showing higher phenotypic correlation than SCT and hyperactivity-impulsivity problems (left-hand part of Table 2) as expected (Garner et al. 2010; Hartman et al. 2004).

Table 2 Phenotypic (within-subject) and twin correlations (with 95 % CI) for SCT, INP and HIP in MZ and DZ twin pairs

	Within Subject			Within Scale (Diagonal) And Cross Scale (Off Diagonals) Correlations Twin 2								
				Twin 2								
				MZ					DZ			
Twin 1	SCT	INP	HIP	SCT	INP	HIP			SCT	INP	HIP	
SCT	1			**0.32 (0.15 to 0.45)**					**0.12 (0.00 to 0.24)**			
INP	0.47 (0.42 to 0.53)	1		0.23 (0.11 to 0.34)	**0.51 (0.38 to 0.62)**				0.03 (−0.05 to 0.13)	**−0.03 (−0.14 to 0.10)**		
HIP	0.29 (0.22 to 0.34)	0.47 (0.41 to 0.52)	1	0.26 (0.15 to 0.35)	0.32 (0.22 to 0.41)	**0.50 (0.37 to 0.60)**			0.20 (0.10 to 0.28)	0.07 (−0.03 to 0.16)	**0.17 (0.05 to 0.29)**	

Within-subject correlations were calculated in twins considered as individuals, regardless of zygosity

Within-trait twin correlations are shown in bold

Numbers in parentheses are 95 % confidence interval

SCT sluggish cognitive tempo problems; *INP* inattention problems; *HIP* hyperactivity-impulsive problems; *MZ* monozygotic; *DZ* dizygotic

Twin univariate models showed that SCT was the least heritable dimension, with non shared environmental influences significantly larger than those of INP and HIP, as shown in Table 4. This indicates that the contribution of environmental factors that shape sibling differences is more important for SCT than for INP and HIP, and that there are differences in the genetic and environmental etiology of the three ADHD symptom domains.

The cross twin correlations and variances (see Table 2) values were also consistent with other studies that reported for behavioral problems like inattention, hyperactivity, and impulsivity: small, -and sometimes even negative- DZ correlations (Eaves et al. 1997; Nadder et al. 2001; Price et al. 2001; Rietveld et al. 2003a; van Beijsterveldt et al. 2004). Overall, the MZ correlations were large, and more than twice the DZ correlations, suggesting the presence of genetic dominance, contrast effects, or both. As for previous twin studies of ADHD, our data and their interpretation favor the presence of a contrast effect, rather than non-additive genetic effects, to explain the discrepancy in MZ-DZ correlations (Eaves et al. 1997; Levy et al. 2006; Nadder et al. 2001; Price et al. 2001; Rietveld et al. 2003a; van Beijsterveldt et al. 2004). Contrast can be distinguished from non-additive genetic effects: indeed contrast, in addition to MZ correlations higher than twice the DZ correlations, lead to differences in variances in MZ and DZ twins, differently from non-additive genetic effects. This is what we found for INP, implying that intraclass correlations for inattention could indicate a contrast effect in which parents overestimate the difference between members of pairs. Other, larger twin studies of ADHD reported the presence of contrast effects on both ADHD inattentive and hyperactivity/impulsive problems (Eaves et al. 1997; Nadder et al. 2001; Price et al. 2001; Rietveld et al. 2003a; van Beijsterveldt et al. 2004), with estimates of the contrast effect that ranged from -0.02 (Rietveld et al. 2003b) to −0.24 (Eaves et al. 1997). Our figure relative to a contrast effect for inattention (b=−0. 16, as reported in Table 4, right-hand part) thus falls within the values reported in previous works with ADHD inattentive symptoms (Nadder et al. 2001; van Beijsterveldt et al. 2004). Mothers, however, were the only raters of ADHD problems here. Had teacher ratings been available, our findings and conclusions on contrast effect might have been different. Nikolas and Burt (2010) argued that teachers have a wider comparison base and thus they are less likely to rate DZ twins as dissimilar, which would diminish the estimates of genetic effect and of contrast effect. On the contrary, mothers may focus more on differences between their twins, which would inflate rater contrast effects (Nikolas and Burt 2010).

Assessments of multiple subjects within the same sibship may thus consider the influence of this additional source of variance, which has implications both at the clinical and

Table 3 Multivariate ADE model fitting results for SCT, INP and HIP

	−2LL	DF	AIC	X^2	ΔDF	**P**
1) Full Cholesky ADE-b	3681.30	2339	−996.70			
2) ADE	3688.45	2340	−991.55	7.15	1	0.01
3) AE- b	3685.27	2345	−1004.73	3.97	6	0.68
4)AE	3700.74	2346	−991.26	19.44	7	0.01
5) AE-b plus E path from SCT to HIP=0	**3685.46**	**2346**	**−1006.54**	**4.15**	**7**	**0.76**

Best-fitting model is printed in boldface type

−2LL minus twice the log-likelihood; *DF* degrees of freedom; *AIC* $\Delta\chi^2$ −2(Δdf); χ^2 (−2LLsubmodel) - (−2LLsaturated model); Δ*DF*(df saturated model)-(dfsubmodel); *P* p-value

research levels. Our multivariate correlated factor model shows that SCT, hyperactivity/impulsivity and inattention are correlated both at the environmental and genetic etiological levels (Fig. 2). Previous studies showed that genetic factors explain the phenotypic association between the ADHD hyperactive/impulsive and inattentive dimensions: genetic correlations, which indicate the degree of overlap in the genetic influences across the phenotypes, typically range from 0.52 to 0.83 in genetically informative studies (Haberstick 2008; McLoughlin 2007; Wood 2009). Our multivariate results, encompassing the SCT problems dimension, revealed a remarkable coherence with previous works: genetic correlations were substantial-to-high between phenotypes (ranging from 0.61 to 0.83 in Fig. 2), which means that more than half of the genes that influence phenotypic variation for each dimension are indeed shared among the 3 ADHD domains. Coherently with the result of bivariate heritability, the genetic component explained a large part of the three phenotypic correlations: 0.26 of the 0.47 phenotypic correlation between SCT and INP (i.e., 55 %), 100 % of the phenotypic correlation between SCT and HIP and 0.35 of the 0.47 (i.e., 75 %) phenotypic correlation between INP and HIP.

While the integration of SCT symptoms in DSM-V has been criticized (Harrington and Waldman 2010), it is clear from previous psychometric work and from the present twin data that a SCT construct has both psychometric and etiological validity within the ADHD realm. How can these findings be harmonized and possibly utilized in a clinical context? Possibly, the presence of prominent SCT symptoms could be used as a specifier of an ADHD diagnosis. Several studies found an association between SCT and internalizing problems over and above the contribution of ADHD symptoms (Becker and Langberg 2012), while hyperactive symptoms are more related to externalizing problems (Hofvander et al. 2011). Moreover, prior studies have found SCT to be associated with poor/abnormal neurocognitive performance, even when controlling for other ADHD symptoms (Bauermeister et al. 2011; Hinshaw et al. 2002). Our finding that SCT is one of 3 distinct -albeit correlated-problem

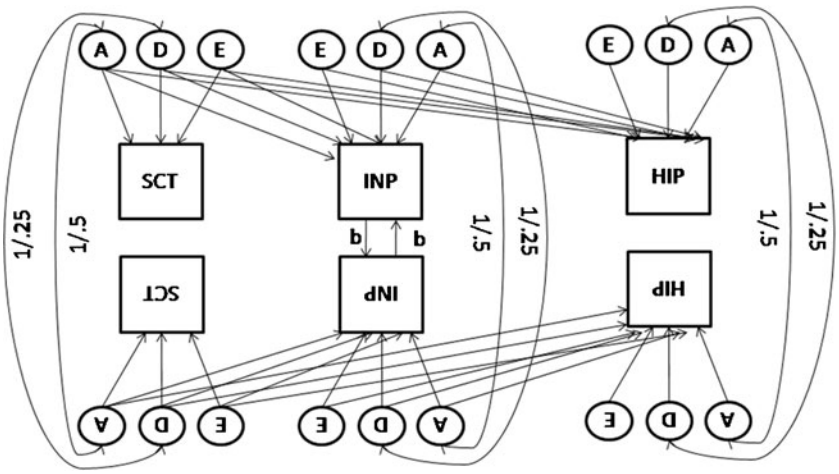

Fig. 1 Full Cholesky model. *SCT* sluggish cognitive tempo problems; *INP* inattention problems; *HIP* hyperactivity-impulsive problems. *A* additive genetic influence; *D* dominance genetic effect; *E* unique environmental influence; *b path* contrast effects; 1/0.25=The model assumed a correlation between twins' non additive genetic influences of 1.0 for MZ pairs (all genes are shared) and of 0.25 for DZ pairs (DZ twins stand only a 25 % chance of sharing both alleles, in the average case), 1/0.5=The model assumed a correlation between twins'additive genetic influences of 1.0 for MZ pairs (all genes are shared) and of 0.5 for DZ pairs (DZ twins share half of their segregating genes on average)

Table 4 Proportion of variances and covariances due to genetic and environmental factors estimated by the full and the best-fitting model

	A			D			E			B
	SCT	INP	HIP	SCT	INP	HIP	SCT	INP	HIP	
Full model										
STC	**0.22 (0.01 to 0.38)**			**0.09 (0.00 to 0.34)**			**0.69 (0.56 to 0.83)**			
INP	0.13 (−0.22 to 0.73)	**0.02 (0.00 to 0.74)**		0.40 (−0.15 to 0.83)	**0.58 (0.00 to 0.71)**		0.47 (0.29 to 0.69)	**0.40 (0.26 to 0.54)**		−0.08 (−0.21 to −0.02)
HIP	0.84 (0.05 to 1.33)	0.14 (−0.23 to 0.90)	**0.26 (0.01 to 0.51)**	0.16 (−0.33 to 1.02)	0.59 (−0.15 to 1.02)	**0.22 (0.00 to 0.52)**	0.00 (−0.35 to 0.31)	0.26 (0.12 to 0.45)	**0.52 (0.41 to 0.64)**	
Best fitting model										
	A			D			E			B
	SCT	INP	HIP	SCT	INP	HIP	SCT	INP	HIP	
SCT	**0.28 (0.15 to 0.40)**			–			**0.72 (0.60 to 0.85)**			
INP	0.55 (0.35 to 0.70)	**0.67 (0.52 to 0.76)**		–	–		0.45 (0.29 to 0.65)	**0.33 (0.24 to 0.48)**		−0.16 (−0.23 to −0.09)
HIP	1.00 (1.00 to 1.00)	0.74 (0.58 to 0.85)	**0.45 (0.33 to 0.56)**	–	–	–	–	0.26 (0.14 to 0.41)	**0.55 (0.44 to 0.67)**	

Numbers in parentheses are 95 % confidence interval; -=fixed to zero

In bold on the diagonal proportion of variance components, lower diagonal covariances component

SCT sluggish cognitive tempo problems; *INP* inattention problems; *HIP* hyperactivity-impulsive problems; *A* additive genetic influence; *D* non additive genetic influence; *E* unique environmental influence; *B path* contrast effects

dimensions in ADHD further vindicates its relevance in the clinical context.

More broadly, different pattern of neurocognitive performance -and perhaps comorbidities- may thus point to different etiological pathways for SCT and inattention and hyperactivity/impulsivity. Family studies have suggested that the presence or absence of comorbid psychopathology may in fact mark different etiological subtypes of ADHD (e.g., Faraone et al. 1991; Sprich-Buckminster et al. 1993).

On the other hand, it is certainly true that future research on SCT should rely on better, standardized scales that will allow rigorous tests of prognosis, treatment response, comorbidity, and patterns of familial history. For example, Penny et al. (2009) searched for an empirically supported measure of SCT through a pool of items from a literature review of past research on SCT, on the basis of the expert ratings and internal and external validity.

Here, we found that those individual differences in SCT, hyperactive-impulsive and inattentive problems are highly heritable and have a sizable genetic overlap. The genetic correlations indicate that more than half of the genes are shared between all three phenotypes; however, both genetic and environmental correlations are less than 1.0, which indicates a degree of etiologic independence, in coherence with psychometric studies of INP SCT and HIP in ADHD.

Limitations

Our results should also be looked at in the light of at least 5 potential limitations. The first is the relatively small size of our sample: the limited power and the consequent reduced ability to detect models' fit deteriorations in hierarchical comparisons may have affected some of the decisions about which model should be chosen as the best. Sample size could also have limited the power to detect genetic dominance, if any such sources of variance were truly present here. Indeed, some studies reported the presence of both dominant and additive genetic factors influencing the variance for ADHD (Hudziak et al. 2005). The statistical power to detect genetic dominance is, in general, very low in the classical twin study. It has been shown that even in presence of a sizable, true 25 % dominance effect on variance, the power remains as low as 0.18 even for sample size of 6,000 twin pairs (Rietveld et al. 2003b). However, as already discussed, there is growing evidence that contrast effects, rather than dominance, are more likely in ADHD. Interestingly, it has been shown that even a relatively small study of 300 pairs has sufficient power (0.89) to detect a contrast effect of 0.10 when genetic dominance is rejected from the model (Rietveld et al. 2003b).

The limited sample size also restrained the resolution of additional important issues, such as age- and sex- differences. Even though it is clear that ADHD is more common

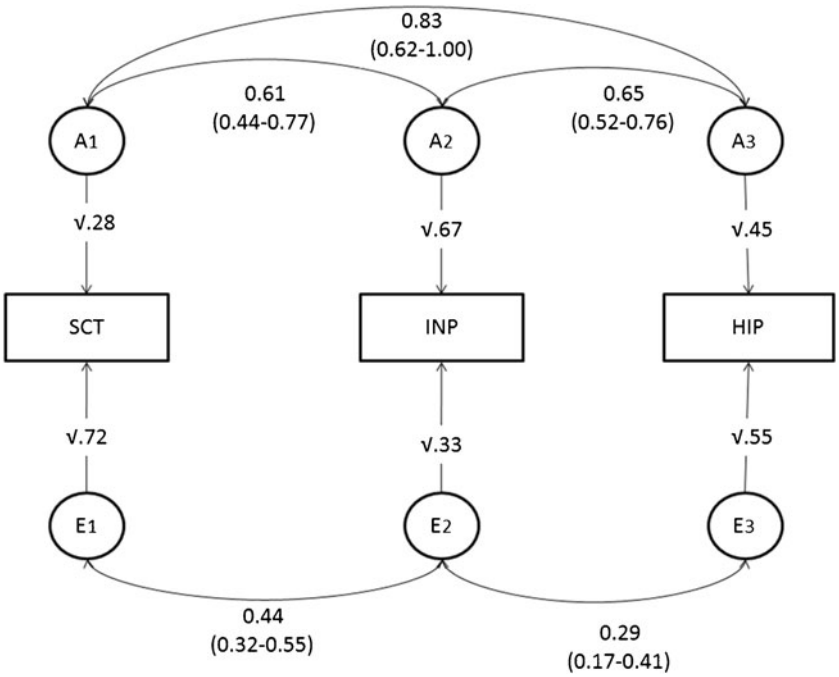

Fig. 2 Best fitting model, Correlated Factor model. *SCT* sluggish cognitive tempo problems; *INP* inattention problems; *HIP* hyperactivity-impulsive problems; *A* additive genetic influence; *E* unique environmental influence

in boys than girls, the question of whether genetic and environmental contributions to ADHD differ owing to sex has probably not yet been answered satisfactorily, with some evidence in favor, and some against (Freitag et al. 2010) qualitative/quantitative etiological overlapping: in general, when statistically significant sex differences were found, the effect sizes were small (Derks et al. 2009), and the pattern of sex differences inconsistent over studies. In some studies heritability was higher in boys, while in other studies heritability was higher in girls. The small effect sizes and the inconsistent pattern of results support the conclusion that the magnitudes of the etiological factors influencing variation in ADHD do not vary much as a function of the child's sex. Concerning age, it should be reminded that some researchers argue that the DSM criteria, and perhaps the CBCL DSM oriented scales, are not sufficiently sensitive to developmental variations in symptom expression (Barkley 1997; Faraone et al. 2000), and other authors recommend the use of age-specific diagnostic criteria for DSM-V and ICD-11 (Ramtekkar et al. 2010).

In terms of age, the heritability for ADHD is known to change in that the effects of 'D' decrease as a function of age. In that respect, our wide age range could have resulted in the best-fitting model to be AE (Rietveld et al. 2003a). Second, without ratings from different informants it is impossible to disentangle a sibling interaction from a rater bias effect in our data. It can significantly affect the estimates of twin resemblance and, as consequence, the relative importance of genetic and environmental factors.

Third, the endorsement rates for ADHD items in this sample could appear low when compared to North American samples. However, the mean score of Attention Problems (as estimated by the CBCL empirical scale) is perfectly in line with the findings of large, independent probability sample of Italian children (Frigerio et al. 2004), confirming that this sample is representative of ADHD inattention problem in Italian population.

Fourth, these 3 CBCL subscales encompass few items and we assumed them as representative of the 3 ADHD dimensions of INP, SCT and HIP, while a psychometric validation of these CBCL scales was beyond the scope of this paper. However the validity of SCT CBCL scale has recently been explored in a large sample of psychiatrically hospitalized children: SCT was found to be distinct from other dimensions of child psychopathology (Becker et al. 2013). The SCT scale showed quite a low Cronbach Alpha, compared to alphas from other studies that ranged from 0.86 (Wåhlstedt and Bohlin 2010) to 0.66 (Becker and Langberg 2012). Fifth, although an epidemiological sample has the advantage of avoiding referral bias, we had a less-than-optimal response rate, partially reflecting cultural attitudes towards issues of mental health in children. Some authors have suggested that a low response rate may imply the exclusion of the most severe cases (Cox et al. 1977); should this be true also for our study, the findings would be only partially extendable to subjects with clinical disorders.

However, most CBCL scores did not differ from those found in the general population (Frigerio et al. 2004), suggesting no major bias related to trait severity. Moreover, since this is a general population sample, the information yielded by this design does not necessarily apply to the more severe cases of ADHD symptoms.

Conclusion

In our sample, multivariate genetic twin analyses of the SCT, INP and HIP indicate moderate genetic overlap between the three components, providing some support to an ADHD syndrome that encompasses SCT symptoms, in keeping with previous psychometric studies of SCT in ADHD. Heritability was substantial for HIP and INT, and smaller for SCT, reflecting partially distinct patterns of etiological influence on variability. These findings could have some clinical relevance and influence the development and refinement of appropriate therapeutic and educational services specific to ADHD subtypes. Researchers could benefit by taking into account the nature of these phenotypes. This study should be considered preliminary and in need of replication, especially in a clinical setting, and future studies of larger samples are needed to test, for example, the difference between parent and teacher ratings. More research is needed to support a possible inclusion of SCT in future nosography.

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