The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 61:12 (2020), pp 1309–1316 doi:10.1111/jcpp.13210

Volitional eye movement control and ADHD traits: a twin study

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Background: Top-down volitional command of eye movements may serve as a candidate endophenotype of ADHD, an important function underlying goal-directed action in everyday life. In this twin study, we examined the relation between performance on a response inhibition eye-tracking paradigm and parent-rated ADHD traits in a population-based twin sample. We hypothesized that altered eye movement control is associated with the severity of ADHD traits and that this association is attributable to genetic factors. **Methods:** A total of 640 twins (320 pairs, 50% monozygotic) aged 9–14 years) from the Child and Adolescent Twin Study in Sweden (CATSS) participated. Twins performed the antisaccade task indexing inhibitory alterations as either direction errors (following exogenous cues rather than instructions) or premature anticipatory eye movements (failure to wait for cues). We calculated the associations of eye movement control and ADHD traits using linear regression mixed-effects models and genetic and environmental influences with multivariate twin models. **Results:** Premature anticipatory eye movements were positively associated with inattentive traits (β = .17; 95% CI: 0.04, 0.31), while controlling for hyperactive behaviors and other covariates. Both premature anticipatory eye movements and inattention were heritable (h^2 = 0.40, 95% CI: 0.22, 0.56; h^2 = 0.55; 95% CI: 0.42, 0.65; respectively), and their genetic correlation was small but statistically significant (r = .19, 95% CI: 0.02, 0.36). However, the genetic correlation did not remain significant after adjusting for covariates (age, sex, hyperactivity traits, IQ). No link was found between direction errors and ADHD traits. **Conclusions:** This study indicates that there is a specific, genetically influenced, relation between top-down eye movement control and the inattentive traits typical of ADHD. **Keywords:** Attention-deficit/hyperactivity disorder; inhibition; attention; eye movements; oculomotor function; behavioral genetics; executive function.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition of complex etiology with a pleiotropic genotype and symptomatology likely caused by diverse etiological pathways (Sonuga-Barke, Bitsakou, & Thompson, 2010). Deep phenotyping and endophenotypes can aid the understanding of ADHD pathophysiology by clarifying the mechanisms between phenotype and genotype. An endophenotype is a heritable trait located along the causal pathway between the genotype and the phenotype. Endophenotypes are useful for reducing complexity and achieving a mechanistic understanding of the building blocks of a condition (Gottesman & Gould, 2003). Impairments in response inhibition have been suggested to represent an ADHD endophenotype (Doyle et al., 2005) and have been reported across different inhibition-probing tasks, such as the stop-signal paradigm and more recently, with the accessibility of eye tracking, the antisaccade task. The antisaccade task is a response inhibition task sensitive to the top-down inhibitory mechanisms needed to perform a volitional saccade instead of a reflexive one (Hutton & Ettinger, 2006). In the antisaccade task, a stimulus appears in the center of a screen and is followed by a peripheral stimulus. The participant is instructed to look toward the mirror location of the peripheral stimulus, rather than reflexively looking at the new peripheral stimulus. Such direction errors reflect top-down inhibitory control in goal-attaining behavior. Higher levels of direction errors are common in individuals with ADHD, although there are some exceptions (Rommelse, Van der Stigchel, & Sergeant, 2008). In addition to direction errors, a higher number of anticipatory eye movements (i.e., gaze shifts occurring before the peripheral stimulus is shown) have been reported in individuals with ADHD (Rommelse et al., 2008). These anticipations also reflect a failure in goal-oriented top-down behavior dependent on the prefrontal and frontostriatal regions, but differ from direction errors as they do not implicate a vector inversion operation and lack the phasic visual response (since they precede the target) (Munoz & Everling, 2004). It is also likely that, due to the different processes, they are characterized by

Conflicts of interest statement: See Acknowledgements for full disclosures.

differential neural activity in areas known to play a role in saccade suppression and execution (e.g., dorsolateral prefrontal cortex (DLPFC), the frontal eye fields [FEF] and the superior colliculus) and vector inversion (lateral ipsilateral area and FEF) despite some similarities (e.g., DLPFC) due the complex involvement of these structures and the task itself (Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Munoz & Everling, 2004).

Twin studies have shown that the ability to inhibit reactive responses in the antisaccade task is a heritable trait (Friedman et al., 2008; Vaidyanathan et al., 2014), but, to our knowledge, direct support for an etiological link between the performance on the antisaccade task and ADHD is lacking. Further, while previous studies have shown that other types of response inhibition are genetically associated with ADHD (Crosbie et al., 2013; Kuntsi et al., 2014), it is not clear how these findings relate to response inhibition at the level of eye movements. Moreover, while previous work has shown that performance on the antisaccade task is heritable and linked to ADHD, no study has assessed the putative genetic association between the two directly. In this study, we assessed performance on the antisaccade task and ADHD traits in a large community sample of twins with the overall aim to further contribute to the understanding of the etiological associations between the two. Molecular genetic (Demontis et al., 2019), polygenic risk score (Martin, Taylor, & Lichtenstein, 2017), and twin studies (Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012) all support a dimensional approach of ADHD. Thus, studies across the continuum of ADHD traits in population-based samples are valuable for the understanding of clinical expression of ADHD found in the extreme end of the trait distribution.

Therefore, in the current study we tested the hypotheses that: (1) higher levels of inhibition errors should be associated with higher levels of ADHD traits, (2) there are shared etiological genetic influences between inhibition and individual dimensions of ADHD traits. Because of the partial independence of the symptom domains of ADHD (McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007), we investigated the association of ADHD traits but also of ADHD dimensions (inattentive and hyperactive/impulsive traits) with task performance. Similarly, we analyzed direction errors and anticipation errors (anticipatory eye movements) separately to understand potential specificity at the level of task performance.

Methods

Participants

The sample consisted of children aged 9–14 years recruited from the longitudinal Child and Adolescent Twin Study in Sweden (CATSS) (Anckarsater et al., 2011). The CATSS study is a nation-wide population longitudinal twin study of health in childhood and adolescence targeting all twins in Sweden (overall response rate: 80%). In CATSS, information on mental and physical health is collected through a telephone interview with the twins' parents. In this study, twins already participating in CATSS were invited to take part in additional behavioral assessments (a cognitive assessment plus parental-reported measures of ADHD and a background questionnaire) and an eye-tracking task. Individuals were excluded if they had severe uncorrected hearing or vision impairment, a known genetic syndrome or medical condition likely to significantly affect brain development or the child's ability to participate in the study (e.g., cerebral palsy, Down's syndrome, cystic fibrosis). Also, families not fluent in Swedish were excluded, as this would render their responses on the questionnaires invalid. Opposite sex twins and twins with missing values on their co-twin were also excluded. Zygosity was determined by molecular genetic analysis of saliva samples, and only in those few cases where DNA samples were not available, we determined zygosity using a highly accurate twin similarity questionnaire (Anckarsäter et al., 2011).

We collected eye-tracking data from $N = 723$ children, of whom 640 could be included in the final analyses, reflecting also that inclusion required valid data and all additional assessments for the whole pair. The final sample consisted of 158 monozygotic (MZ; 55.7% females) pairs and 162 dizygotic (DZ; 53.1% females) pairs, with a mean age of 11.1 (SD = 1.3) years. It is representative of the larger CATSS sample in terms of sex, but with slightly higher levels of parental education (40% of fathers and 56.9% of mothers with ≥3 years of university/college studies or higher) when compared to CATSS (Siqueiros Sanchez et al., 2019). A total of 14 participants (2.18%) had received a diagnosis of ADHD (from a healthcare professional/service as reported by the parents) at the time of this study's assessments. Table 1 shows means, standard deviations, minimum and maximum values for age, ADHD traits, performance on response inhibition measures, and unstandardized IQ scores (for distribution plots, see Figures S1 and S2). Informed consent was obtained from the parents of all the twins who participated. The study was approved by the regional ethics board in Stockholm and was conducted in accordance with the Declaration of Helsinki.

Procedure

The testing session consisted of one eye-tracking battery which included the antisaccade task and several other paradigms not related to the current research questions [see also Kennedy et al. (2017) and Siqueiros Sanchez et al. (2019)], a cognitive assessment, and parental-report questionnaires. We used remote infrared eye tracking (Tobii T120; 120 Hz sampling rate) to record eye movements. The stimuli were displayed as full-screen on a 23″ monitor with a 1,024 × 1,280 pixel resolution using Tobii Studio. The participant sat in front of the eye tracker and the display screen at a distance of approximately 60 cm; the experimenter administering the task remained out of sight after verbal task instructions were given. A 9-point calibration image was used to determine the positions of the eyes before the task began. The task begun only after a successful calibration was achieved according to the experimenter (repeated if necessary). While twin 1 performed the eye-tracking task, twin 2 performed the cognitive task (administered by a psychologist), and the parent(s) completed electronic questionnaires about the twins. After a short break, the twins (and parents) switched; the total duration of the visit was about 120 min. Twins on ADHD medication were asked to refrain from taking it on the testing day.

The antisaccade task

In this task, a central stimulus appears on a screen and is followed by a new stimulus that appears in the periphery. The

Table 1 Study sample characteristics

	Mean (*SD*)	Min-Max	Skewness	Kurtosis
Demographics				
Sex (female = 54,4%)	–	–	–	–
Age	11.12 (1.28)	9–14	0.70	−0.48
ADHD traits				
Inattention	4.22 (4.74)	0–26	1.77	3.67
Hyperactivity/impulsivity	4.21 (5.86)	0–39	2.40	7.40
Inhibition measures				
% of commission errors	0.36 (0.24)	0–1	0.79	0.10
% of anticipatory eye movements	0.15 (0.21)	0–1	2.00	3.64
WISC subscales				
Number repetition	8.52 (2.36)	2–17	−0.002	−0.08
Coding	9.22 (2.47)	1–17	0.18	−0.31
Vocabulary	10.53 (2.86)	2–19	−0.02	0.13
Matrices	10.38 (2.68)	3–19	0.21	0.16

participants are instructed to look as fast as they can to the mirror location of the peripheral stimulus once it appears. The stimuli used for this task is the same employed in the gap–overlap task (Siqueiros Sanchez et al., 2019) (with two conditions: Gap, Overlap). In the gap condition, the central stimulus (CS) disappears 200 ms before the peripheral stimulus (PS) appears. In the overlap condition, the central stimulus remains displayed when the peripheral stimulus appears. The CS consisted of a black cross and the PS of a yellow circle, both were 1.5° visual degrees wide; the background was gray. A total of 48 trials were administered, preceded by three practice trials and a repetition of instructions when deemed necessary. The probability of condition presentation (gap vs. overlap) was 50-50. Fifty percent of the time, the target appeared on the left side and the other 50% on the right side; side presentation was also randomized. The fixation cross was displayed for either 1,600 ms (long trials) or 1,200 ms (short trials), while the PS was displayed for 1,000 ms, thus trials lasted either 2,600 ms or 2,200 ms in total and were presented consecutively after each other. Condition (gap/overlap) and duration (long/short trials) presentation were randomized.

The dependent measures were *direction errors* (the proportion of direction errors in respect to total number of valid trials) and *anticipatory eye movements* (the proportion of anticipatory eye movements relative to total number of valid trials). Please refer to the Analysis of eye tracking data section for a detailed description of these variables.

ADHD traits

We measured ADHD traits using the Swedish version of the parent-response long version of the Conners 3 (Conners, 2008; Thorell et al., 2018). It has sound psychometric properties with a high test–retest reliability (r = .71–.98), satisfactory to excellent internal consistency (α = .52–.94), and good diagnostic validity regarding discrimination of ADHD from other disorders. We used the inattention and hyperactivity/impulsivity subscales raw total scores, plus a summation of the two to reflect total ADHD traits. These subscales with a combined total of 24 items (max score inattention: 30, hyperactivity/impulsivity: 42) address inattentive behaviors as well as hyperactive and impulsive behavior during the last month.

Intellectual ability

In this study, we assessed cognitive ability using scores from the vocabulary, digit span, coding, and matrix reasoning subscales of The Wechsler Intelligence Scale for Children 4th Edition (WISC-IV) (Wechsler, 2003). The WISC-IV is the most widely used test for general intelligence ability in international research and practice, providing both an overall score of intelligence and functioning scores for subscales.

Analysis of eye tracking data

Data were analyzed using custom scripts written in MATLAB (MathWorks) (available upon request). Trials were collapsed across duration (1,200/1,600) and side (left/right) but were analyzed independently for each condition (gap/overlap). To identify saccades, the script compared the median of two sliding windows of 67 ms length applied to the sampled gaze position (which was an average of left and right eye positions). If the rate of change in position exceeded a velocity threshold of 39°/s, it was labeled as a saccade. This slightly conservative threshold was selected after visual data inspection and also taking into account the sparse stimulus, and before conducting the main analyses of the study. To be counted as a directional saccade, the saccade was required to start within a Central Area of Interest (AOI), defined as 7°3′ wide and 10°4′ high, and end outside this AOI following the appearance of the PS. Saccades shorter than 60 ms or longer than 800 ms were excluded. These thresholds are in line with previous research (Munoz, Broughton, Goldring, & Armstrong, 1998) and were carefully chosen based on the sample's data distributions.

In order to be considered valid, a trial needed to fulfill the following inclusion criteria: (a) Valid gaze data were found inside the central AOI for at least 50% of the samples during the last 200 ms before the gaze first exited it (following the PS appearance). This ensured that the leaving latencies were not based on spurious data and ruled out anticipatory eye movements. (b) Gaze was within the central AOI for at least 50% of the time the fixation cross was displayed prior to peripheral target onset. This ensured that participants had looked at the fixation cross prior to the gaze shift and that trials with substantial data loss were excluded. Finally, (c) we required that the gaze data sample following the identified saccade was part of a fixation, defined as at least 50% of the gaze data during the subsequent 200 ms being on either side of the central AOI.

If a saccade was made toward the PS (target) instead of toward its mirror location, it was flagged as a direction error, which was expressed as a proportion of the total number of valid trials. Anticipatory eye movements (anticipations) were also expressed as a proportion of anticipatory eye movements in respect to number of valid trials plus trials with anticipatory eye movements (as these do not qualify as valid trials – see above). An anticipatory eye movement was deemed as such when at least 50% of the gaze data samples during the last 200 ms before the PS appeared, where already outside the

central AOI. It was considered an anticipation regardless of which side the gaze went to (mirror/target). The detection of an anticipatory eye movement during a trial automatically invalidated it, since the lack of anticipatory eye movements is one of the criteria for trial validity.

Statistical analyses

Phenotypic associations. We examined the associations between response inhibition measures (proportion of direction errors and of anticipations) and individual ADHD traits (inattention and hyperactivity/impulsivity). As covariates, we included different aspects of IQ using the WISC-IV subscales scores (digit span, coding, vocabulary, and matrix reasoning), age, and sex. To analyze this association, we used multiple linear regression mixed-effects models, which accounted for the nonindependence within twin pairs. Furthermore, to account for the skewness of the dependent variables (i.e., the response inhibition measures), we bootstrapped asymmetric standard errors (Figures S1 and S2). To simplify effect size comparisons, all reported coefficients are standardized coefficients.

Twin analyses. To examine the sources of covariation between our variables, we used a bivariate twin model. Monozygotic twins are genetically identical; therefore, when contrasted against same-sex dizygotic twins (who only share 50% of their genes) on a trait, one can make inferences about the sources of variation in said trait. For example, if MZ twins are more similar than DZ twins, this can be attributed to genetic effects. The sources of variation in a trait can be partitioned into genetic [heritability; additive (A) and/or nonadditive (D)] and environmental influences, which can be further partitioned into shared (C; including everything that makes twins similar to one another aside from genetics, e.g., the family environment, socioeconomic status) and nonshared (E; including everything that makes twins different from one another, e.g., illness at the day of testing). Using multivariate twin analysis, one can estimate the genetic and environmental sources of covariation between two (or more) variables. The extent of genetic overlap (same set of genes) between the traits is called the *genetic correlation.* Similarly, it is also possible to estimate the extent of overlap among shared and nonshared environmental influences (Rijsdijk & Sham, 2002). We used the Bayesian Information Criteria (BIC) to examine goodness of fit. BIC identify the most parsimonious model by weighing both how well the models fits the data, and how few parameters it uses, with lower BIC values indicating a better fitting model (Raftery, 1995). All statistical and twin modeling analyses were conducted using MPlus (Muthén & Muthén, 1998–2010).

Results

Group comparisons

Despite our few participants with an ADHD diagnosis, this group of individuals scored higher on the response inhibition task and on the ADHD trait scales (Table 2). We found moderate effect sizes for direction errors $g_{\text{Hedges}} = 0.61$ (95% CI: 0.06, 1.16) and for anticipatory eye movements, $g_{\text{Hedges}} = 0.80$ (95% CI: 0.27, 1.33). These effect sizes are fully in line with previous work showing problems with both types of saccadic inhibition in ADHD, although it is important to note that the precision of these estimates was poor due to the small number of diagnosed individuals.

Table 2 Means and standard deviations of response inhibition and ADHD traits for participants with and without an ADHD diagnosis

	N	Mean (*SD*)	Range
Direction errors (n = 628)			
No diagnosis	615	0.36 (0.24)	0–1
ADHD diagnosis	13	0.51 (0.32)	0.06–1
Anticipatory eye movements (n = 636)			
No diagnosis	622	0.14 (0.21)	0–1
ADHD diagnosis	14	0.31 (0.29)	0–1
Inattentive traits (n = 616)			
No diagnosis	604	4.02 (4.45)	0–26
ADHD diagnosis	12	14.58 (6.98)	7–25
Hyperactive/Impulsive traits (n = 616)			
No diagnosis	604	3.96 (5.39)	0–35
ADHD diagnosis	12	17.17 (11.67)	1–35

Phenotypic associations in the full sample

Direction errors. Total ADHD traits did not predict direction errors ($\beta = -.01$; 95% CI: $-0.07, 0.04$) in our sample. Neither did inattention ($\beta = .03$; 95% CI: −0.09, 0.16), nor hyperactivity/impulsivity ($\beta = -.08$; 95% CI: −0.23, 0.07). Therefore, we did not pursue any more analyses including this variable.

Anticipatory eye movements. Total ADHD traits was a significant predictor of anticipatory eye movements ($\beta = .11$, 95% CI: 0.04, 0.19). Inattention ($\beta = .19$, 95% CI: 0.09, 0.29), but not hyperactivity/impulsivity ($\beta = -.01$, 95% CI: −0.09, 0.07), was significant predictor of anticipatory eye movements, even after including covariates (age, sex, hyperactivity, and IQ; $\beta = .15$, 95% CI: 0.02, 0.28), suggesting that higher more anticipatory eye movements is specifically associated with higher inattention traits.

Twin analysis

Monozygotic twin correlations were more than twice as large as those of dizygotic twins for both inattention (*r*MZ = 0.27, 95% CI: 0.13, 0.41; *r*DZ = 0.06, 95% CI: 0.001, 0.12) and anticipatory eye movements (*r*MZ = 0.39 95% CI: 0.17, 0.61; *r*DZ = 0.02, 95% CI: −0.11, 0.15), suggesting the influence of genetic effects. However, past research has usually found that rMZ is not more than twice as large as rDZ (Faraone & Larsson, 2018). We attribute the somewhat unusual sample correlations with the skewed distribution of both variables and (small) sample variation.

Based on the twin correlations, we fitted a correlated factors ADE model (see Figure S3). Both an AE model and a DE model (which models dominant, instead of additive, genetic effects) were also fitted for comparison. Upon comparison, an AE model was identified as reasonable compromise between model fit and both previous theoretical conceptions (ACE model as starting point) and past research findings (Pettersson et al., 2019) (Table 3).

The unadjusted AE model's (Figure 1) estimates suggest a high heritability for inattention (h^2 = 0.70; 95% CI: 0.60, 0.79) and moderate heritability anticipatory eye movements (h^2 = 0.49; 95% CI: 0.35, 0.62). The bivariate modeling identified a moderately sized genetic correlation between inattention and proportion of anticipatory eye movements, but the precision was relatively low (r = 0.19; 95% CI: 0.02, 0.36).

After adjusting for the covariates in our bivariate model (Figure S4), the heritability estimates for both inattention (h^2 = 0.57; 95% CI: 0.44, 0.67) and anticipatory eye movements (h^2 = 0.40, 95% CI: 0.21, 0.56) remained significant. However, while the genetic correlation between inattention and anticipatory eye movements did not reach statistical significance after adjusting for covariates (r_a = .09; 95% CI: −0.16, 0.36), the confidence intervals between the unadjusted and adjusted models were relatively similar. Results were similar in a model that included all covariates except for hyperactivity/impulsivity (Figure S5).

Discussion

In this study, we showed that inattentive traits, as reported by parents, are phenotypically linked to subtle alterations in eye movements. We also showed that this phenotypic link is partially underpinned by shared genetic effects, suggesting that poor performance on the antisaccade task could be an endophenotype for inattentive ADHD subtype.

The phenotypic association between anticipatory eye movements in the antisaccade task and parent-reported inattentive behaviors is consistent with the case–control literature. Previous studies reported an increased number of premature saccades in the antisaccade task in participants with ADHD when compared to controls (Karatekin, 2006; Klein, Raschke, & Brandenbusch, 2003). In line with the literature, twin correlations and univariate twin modeling estimates suggested a genetic influence on both our measures. Heritability estimates for inattention (h^2 = 0.57) and anticipatory eye movements (h^2 = 0.40), when adjusting for covariates, were moderate, similar to those reported in previous ADHD traits studies (Larsson et al., 2012) and those assessing response inhibition measures (Crosbie et al., 2013; Kuntsi et al., 2014). There was evidence for a significant genetic correlation between inattention traits and anticipatory eye movements (r_a = .193), a finding that parallels studies using the stop-signal paradigm which also found genetic associations between a subset of their response inhibition measures and ADHD traits (Crosbie et al., 2013; Kuntsi et al., 2014). However, after adjusting for covariates the correlation was non-significant. Such results might be explained by the generalist genes hypothesis (Kovas & Plomin, 2006; Pettersson, Anckarsäter, Gillberg, & Lichtenstein, 2013; Plomin & Deary, 2014), which postulates that pleiotropic or 'generalist' genes act on many phenotypes leading to a lack of specificity at the genetic level. Alternatively, we might have lacked the

Table 3 Model fitting results for inattention and anticipatory eye movements' bivariate model

	Model fit	
Model	AIC	BIC
ADE	3,395.93	3,444.92
AE	3,399.72	3,437.41
DE	3,389.96	3,427.65

AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria.

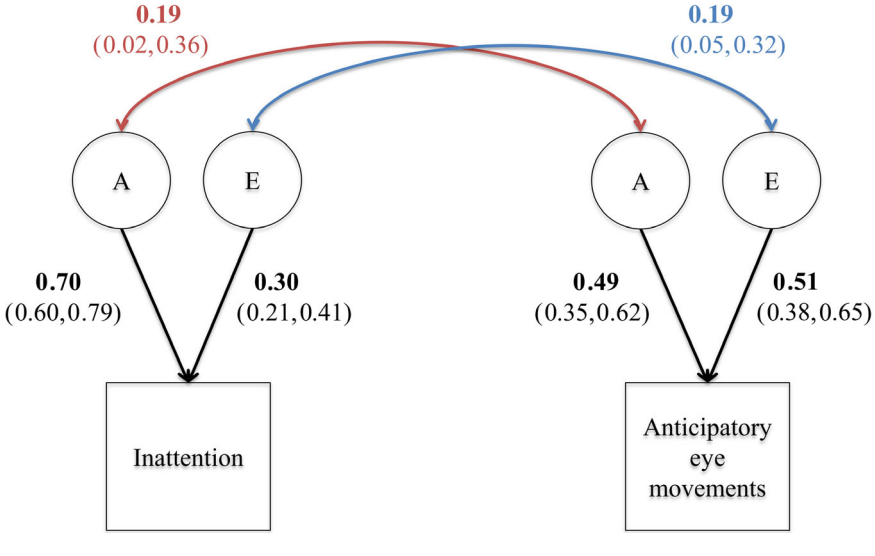

Figure 1 Path diagram of the AE bivariate model correlated factors solution for inattention and anticipatory eye movements. Path coefficients and 95% confidence intervals for additive genetic influences (A) and nonshared environmental (E) effects are standardized (black arrows). Genetic correlations (red arrows) and nonshared environmental correlations (blue arrows) are displayed in the upper part of the figure [Colour figure can be viewed at wileyonlinelibrary.com]

statistical power to detect unique genetic contributions after controlling for all covariates (Kuntsi et al., 2014).

Physiologically, this finding may be attributable to the dopaminergic system. An EEG event-related potential (ERP) study (Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001) attributed the elevated number of anticipatory eye movements in individuals with ADHD to a dampened and nearly absent mean contingent negative variation (CNV), a motor readiness/preparation electrophysiological component linked to dopaminergic activity in the basal ganglia (Barry, Johnstone, & Clarke, 2003; Linssen et al., 2011). This deficit in anticipatory control is also in line with the cognitive-energetic model (Sergeant, 2005), which suggests that low CNV activation could be a consequence of energetic state. Anticipatory eye movements have also been linked to fixation and saccade cells located in the superior colliculus, the FEF and DLPFC (Feifel et al., 2004; Munoz & Everling, 2004), structures belonging to the fronto-parietal, dorsal attentional, and visual networks which imaging studies have shown to be altered in ADHD (Castellanos & Proal, 2011).

In contrast to our findings with anticipatory eye movements, we did not observe an association between direction errors and ADHD traits. These results are in line with other dimensional studies that did not observe this association (Polner, Aichert, Macare, Costa, & Ettinger, 2015) or that failed to do so consistently across different experimental conditions (Kuntsi, Wood, Van Der Meere, & Asherson, 2009). Nonetheless, Aichert et al. (2012) reported a weak but significant association between direction errors and impulsivity. It is notable, however, that despite the lack of association in our study, we observed mean differences between our diagnosed sample and our subthreshold (typical) sample, which is in line with most case–control studies [for a review see Rommelse et al. (2008)]. Potential explanations for these discrepancies are that ADHD trait ratings fail to capture the impairments responsible for performance differences (Fuermaier et al., 2015), for example, motivation and arousal (Sergeant, 2005), or inhibition deficits are not consistently (Kuntsi et al., 2009) nor universally present in ADHD individuals (Munoz, Armstrong, Hampton, & Moore, 2003). Therefore, although we cannot entirely rule out the possibility of direction errors being a state-marker for ADHD, this intriguing pattern presses a more in-depth study of direction errors in individuals with ADHD versus those with high ADHD traits, subthreshold, and undiagnosed.

Limitations and future directions

This study is not without limitations. As mentioned, our study may lack power to detect small, but meaningful, associations as a result of sample size, but also to explore potential sex-effects. Also, while our sample included a subgroup with a clinical diagnosis from a healthcare practitioner (parent-report), this group was small, did not reach an expected population prevalence, and was not independently validated by us.

Twin studies like the present provide information on the ratio of genetic variation to phenotypic variation and can identify common genetic (and environmental) casual pathways of co-occurring phenotypes. However, they cannot directly inform on the identity of the genetic variants implicated. Thus, one potential avenue for follow-up studies is molecular genetic studies. Approaches that require genotyping and the use of genetic instruments (e.g., phenome-wide and genome-wide association studies, polygenic scores) can aid in identifying genetic pathways (Pingault et al., 2018). By identifying specific genes, we can attempt to explore causation direction and disentangle genetic pleiotropic effects in cross-phenotype associations (like the one observed in this study) either experimentally, through animal models, or using observational methods (like Mendelian randomization). Another prospective direction is the incorporation of longitudinal twin designs in order to explore the stability of the observed shared etiology across the life span (Greven, Rijsdijk, Asherson, & Plomin, 2012). By increasing the mechanistic knowledge, that is by better understanding the interplay between neurocognitive traits and pathophysiology (e.g., whether volitional eye movement control contributes to inattention), is a key step toward improving treatment options, for instances by identify within-disorder subgroups for a more personalized treatment approach, potentially implementing diagnostic markers (Johnson, Gliga, Jones, & Charman, 2015), and/or early targeting intervention linked to eye movement control (Wass, Porayska-Pomsta, & Johnson, 2011).

Conclusion

Premature (or anticipatory) eye movements are heritable and positively associated with ADHD traits, and more specifically with inattentive traits. This phenotypic association appears to reflect a shared genetic etiology. Thus, this study deepens our understanding of the ADHD phenotype by identifying a unique, and partly genetic, relation between inattentive behaviors and response inhibition; however, whether eye movements play a causal role in ADHD pathophysiology or function as a potential endophenotype of inattention remains to be determined. Understanding in more detail, the link between top-down eye movement control and behavioral problems in everyday life is an important task for further research.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1. Distribution of inattention and hyperactivity/impulsivity traits in the sample.
Figure S2. Distribution of eye tracking variables, proportion of direction errors and anticipatory eye movements.
Figure S3. Path diagram of the ADE model correlated factors solution.
Figure S4. Path diagram of the AE model correlated factors solution (including covariates).
Figure S5. Path diagram of the AE model correlated factors solution not including Hyperactivity/Impulsivity dimension as a covariate.

Acknowledgements

The authors would like to thank Viktor Persson, Fanny Engman, Clara Holmberg, Anna Sahlström, Sigrid Elfström, Ida Hensler, Anton Gezelius, Helena Nizic, Ronja Runnström Brandt, Mathilda Eriksson, Lotta Sjöberg, and Linnea Adolfsson for invaluable help with the data collection. S.B. discloses that he has in the last 5 years acted as an author, consultant/lecturer for Shire, Medice, Roche, Eli Lilly, Prima Psychiatry, GLGroup, System Analytic, Ability Partner, Kompetento, Expo Medica, Clarion Healthcare, Abilia, and Prophase. S. B. receives royalties for textbooks and diagnostic tools from Huber/Hogrefe, Kohlhammer and UTB. The remaining authors have declared that they have no competing or potential conflicts of interest.

Funding information

H2020 Marie Skłodowska-Curie Actions (642996); Vetenskapsrådet (2015-03670); Riksbankens Jubileumsfond (NHS14-1802:1).

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Key points

- Response inhibition deficits have been genetically linked to ADHD; however, it is not clear if this is extended to response inhibition at the level of eye movements.
- Premature eye movements are associated with severity of ADHD traits.
- This association is specific to inattentive traits and partly genetic in origin.
- Eye movements can be informative of the underlying mechanisms of complex disorders like ADHD, and aid our understanding of developmental psychopathology.

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Accepted for publication: 3 January 2020