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What is This?
Parent-of-Origin Effects in ADHD: Distinct Influences of Paternal and Maternal ADHD on Neuropsychological Functioning in Offspring

Andrieke J. A. M. Thissen1, Nanda N. J. Rommelse2, Marieke E. Altink2, Jaap Oosterlaan3, and Jan K. Buitelaar1,2,4

Abstract

Objective: The authors examined parent-of-origin effects in transmission of ADHD and neuropsychological functioning. Proof of these effects can identify more etiologically homogeneous ADHD subgroups and facilitate genetic studies. Method: The authors included 238 ADHD and 147 control families. ADHD in children was assessed using parent and teacher ratings, while parents completed self-reports. Children were assessed with neuropsychological paradigms measuring IQ, motor, timing, and executive functions. Results: Paternal and maternal ADHD were equally positively related to ADHD in offspring. Paternal ADHD was related to poorer time reproduction in offspring and to lower verbal and total IQ in daughters. Maternal ADHD was related to poorer inhibition and motor control in offspring. No mediating effects of neuropsychological functions were found between parent and offspring ADHD symptoms. Conclusion: Neuropsychological functions may be more sensitive to parent-of-origin effects than ADHD symptoms and possibly useful in detecting the transmission of different gene-brain network pathways depending on parental sex. (J. of Att. Dis. 2012; XX(X) 1-XX)

Keywords

parent-of-origin, ADHD, neuropsychological functioning, endophenotype, intergenerational transmission

ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity leading to impaired functioning in multiple settings (Diagnostic and Statistical Manual of Mental Disorders [4th ed., text rev.]; DSM-IV-TR; American Psychiatric Association [APA], 2000). It is a highly heritable disorder, with heritability estimates of 75% or more (Freitag, Rohde, Lempp, & Romanos, 2010; Nikolas & Burt, 2010). Hence, a sizable proportion of children with ADHD, up to 25% to 30%, will have at least one parent affected with ADHD (Faraone & Biederman, 1997) and an even larger percentage will have parents with ADHD traits not meeting full diagnostic criteria. How exactly the risk from parent to offspring is transmitted is largely unknown. However, there is evidence to suggest that genomic imprinting—an epigenetic parent-of-origin effect in which certain genes are only active when inherited from mother or father—may play an important role in ADHD. Hyperactivity in mice was the first documented behavioral effect of imprinted genes (Cattanach & Kirk, 1985), and a number of neurological disorders that frequently co-occur with ADHD (e.g., Tourette’s syndrome, bipolar affective disorder, and autism) vary in symptoms or severity based on the parent-of-origin (Cook et al., 1997; Goos & Ragsdale, 2008; Lichter, Jackson, & Schachter, 1995; McMahon, Stine, Meyers, Simpson, & DePaulo, 1995). As the disorder occurs mainly in males, it has been hypothesized that the transmission runs mainly through the paternal line (Rhee, Waldman, Hay, & Levy, 1999). Several studies indeed found support for a paternal overtransmission of risk alleles (Hawi et al., 2005, 2007).
2009; Quist et al., 2003; Smoller et al., 2006), but others found no evidence for parent-of-origin effects (Anney et al., 2008; Kim et al., 2007; Laurin et al., 2007) or even larger effects for maternal than paternal history of ADHD on offspring (Goos, Ezzatian, & Schachar, 2007). Further research on this issue is thus warranted because proof of parent-of-origin effects can lead to the identification of more etiologically homogeneous phenotypes by grouping according to parental history of ADHD. This is important because variations in familial risk may be obscured when parental risk is not taken into account. If parents differ in the relative quantity or quality of risk factors, phenotypic manifestation of ADHD in offspring may vary on the basis of parental origin (Goos & Silverman, 2001). Furthermore, including parent-of-origin effects can improve power for genetic analyses in detecting linkage if the locus of interest is in fact imprinted (Shete & Amos, 2002).

When studying parent-of-origin effects, the gender of the child is a key aspect to take into consideration. Boys are more frequently diagnosed with ADHD than girls, with reported sex ratios ranging from 3:1 to 8:1 (Rhee et al., 1999). It is proposed that the etiology of ADHD might differ between both sexes, with girls requiring a greater liability to develop ADHD than boys (Goos et al., 2007; Rhee et al., 1999), which is demonstrated by a genetic study showing a genetic loading twice as high in girls compared with boys (Hawi et al., 2005). In relation to parent-of-origin effects, various findings have been reported. On one hand, it has been found that ADHD transmission is strongest from fathers to daughters and weakest from mothers to sons (Hawi et al., 2005). On the other hand, it has been documented that ADHD transmission is strongest from fathers to sons compared with daughters (Goos et al., 2007). However, other studies did not find a differential parent-of-origin effect in male and female offspring (Goodman & Stevenson, 1989; Seidman et al., 2005; Thapar, Hervas, & McGuffin, 1995), making this an area in need of further research that could benefit from innovative approaches to this issue.

A relatively new approach is to include neuropsychological measures into these family designs. Neuropsychological traits have been put forward as useful indicators in detecting etiologically more homogeneous subgroups of patients. Moreover, such traits may be more closely linked to the underlying genetic susceptibility for ADHD than the behavioral phenotype (Kendler & Neale, 2010). It is proposed that ADHD-related neuropsychological dysfunctions can be divided into three main domains that appear fairly independent from each other considering their genetic and neurobiological basis: cognitive control (e.g., inhibition and switching), reward processing (e.g., sensitivity to reinforcement), and temporal processing (e.g., intertrial variability and time estimation; Durston, van Belle, & de Zeeuw, 2011; Sonuga-Barke, Bitsakou, & Thompson, 2010; Wåhlstedt, Thorell, & Bohlin, 2009). However, several neuropsychological functions that cannot be categorized in one of these domains, for instance, working memory, attention, IQ and perception, are also known to be impaired in patients with ADHD (Frazier, Demaree, & Youngstrom, 2004; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Nazari et al., 2010; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and therefore worthwhile to include in family-genetic analyses of parent-of-origin effects in ADHD as well.

A handful of studies have reported the usefulness of neuropsychological traits in the study of parent-of-origin effects in ADHD. Studies have shown parents of children with (a risk for) ADHD display weaker executive and motor functions (Alberts-Corush, Firestone, & Goodman, 1986; Curko Kera, Marks, Berwid, Santra, & Halperin, 2004; Nigg, Swanson, & Hinshaw, 1997) and demonstrated parent–offspring correlations for impaired executive and motor functioning on several tasks, varying between 0.13 and 0.51 for mothers and between 0.19 and 0.34 for fathers (Jester et al., 2009; Nigg, Blasky, Stawicki, & Sachek, 2004). For response variability, the relation was only apparent in mothers and clearer results were found for girls on response inhibition in both mothers and fathers (Nigg et al., 2004). Two studies examined maternal and paternal ADHD (based on self- or investigator report) in relation to offspring inhibition (and ADHD) but found no significant effects (Crosbie & Schachar, 2001; Goos, Schachar, Crosbie, & Payne, 2009). This contrasts with another study that reported a strong relationship between family history of ADHD and both attention and executive impairment in male offspring (Seidman, Biederman, Faraone, Wever, & Ouellette, 1997). To date, the most comprehensive study using neuropsychological traits to examine parent-of-origin effects in ADHD demonstrated that paternal, but not maternal, inhibition was of influence on children’s inhibition, regardless of child’s sex or symptom severity in child or parent (Goos et al., 2009). Together, these prior studies have provided initial support for the viability of neuropsychological traits to detect (gender specific) parent-of-origin effects in ADHD, but further research in this area is needed.

In the absence of a clear-cut lead in the current literature, the present study took an exploratory approach and addressed three questions. First, can we identify parent-of-origin effects using parental self-reported ADHD to predict offspring neuropsychological functioning? Second, do such parent-of-origin effects differ between male and female offspring? Third, does offspring neuropsychological functioning mediate parent–offspring ADHD symptom relationships? Because a substantial number of children with ADHD eventually no longer meet criteria for the diagnosis (Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2006), we also considered age-dependant changes in ADHD and related neuropsychological deficits. In addition, we investigated whether paternal and maternal ADHD influenced each other’s effect on offspring ADHD to explore whether ADHD symptoms in both parents might have an additive
effect. We collected parental ADHD data in a large sample of ADHD and control families and collected neuropsychological data of affected children, nonaffected siblings and controls, covering the domains of executive functioning (inhibition, verbal and visuospatial working memory), motor control (with and without adaptation), timing abilities (estimation and reproduction), and IQ. These domains are sensitive to the effects of ADHD, have been put forward as fruitful traits in ADHD genetic research (Castellanos & Tannock 2002; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008), and have established genetic loading (Rommelse, Arias-Vasquez, et al., 2008).

**Method**

**Participants**

Participants were recruited through child psychiatric clinics in the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study that aims to identify genes that increase the risk for ADHD (Brookes et al., 2006; Neale et al., 2010). All procedures were approved by the Medical Ethical Testing Committee (METC) of the University Medical Center Utrecht. Families with at least one child with ADHD combined subtype (this most severe subtype of ADHD will probably provide the best results for linkage and association) and at least one additional sibling, regardless of gender, participated. Additional control families were recruited from primary and high schools in the same geographical regions as the participating ADHD families. Controls and their first-degree relatives were required to have no formal or suspected ADHD diagnosis. A total of 238 ADHD families and 147 control families fulfilled inclusion and exclusion criteria and completed informed consent forms. Within the ADHD families, 238 probands (all with combined subtype ADHD), 112 affected siblings (64 with combined subtype, 28 with inattentive subtype and 20 with hyperactive-impulsive subtype) and 195 nonaffected siblings participated, resulting in two groups: affected siblings \( (n=350) \) and nonaffected siblings \( (n=195) \). Control families consisted of 271 children. All children were of European Caucasian descent and were between the ages of 5 and 19. Probands and siblings were not required to meet a maximum age difference because sibling relations were not investigated in this study. Children were excluded if they had an IQ \(<70\), a diagnosis of autism, epilepsy, brain disorders, or known genetic disorders, such as Down syndrome or Fragile-X-syndrome. Participating families included a group of 384 biological mothers and a group of 383 biological fathers of European Caucasian descent. Both groups consisted of 146 control parents. All parents were between the ages of 31 and 62. Tables 1 and 2 provide the children’s and parent’s characteristics, respectively. Note that the tables include information about affection status to illustrate the sample in exact detail, whereas affection status of participants was not used as a factor in the analyses as continuous symptom dimensions were used.

**Screening**

The exact screening procedures and measures for ADHD phenotyping for children have been described previously (Brookes et al., 2006). Briefly, screening questionnaires (parent and teacher Conners’ long version rating scales [Conners, 1998] and parent and teacher Strengths and Difficulties Questionnaires [SDQ; Goodman, 1997]) and a semistructured, standardized, investigator-based interview (Parental Account of Children’s symptoms [PACS]; Brookes et al., 2006; Taylor, 1986) were used to identify children with ADHD symptoms (see Rommelse, Oosterlaan, Buitelaar, Faraoe, & Sergeant, 2007, for the standardized algorithm that was applied to the data to derive each of the 18 Diagnostic and Statistical Manual of Mental Disorders [4th ed., DSM-IV; APA, 1994] symptoms, providing operational definitions for each behavioral symptom). Probands were already clinically diagnosed before inclusion, and interviews were conducted with probands as well as siblings that screened positive. Concerning control children, the Conners’ long version for parents and teachers was completed, and control children were required to obtain nonclinical scores on all scales measuring ADHD-related symptomatology.

**Measures**

**Parental ADHD.** Information concerning current parental ADHD symptoms was obtained using the Dutch version of the Conners’ Adult ADHD Rating Scale—Self-Report: Short Version (CAARS-S:S; Conners et al., 1999) in 80% of the sample and with the Dutch ADHD self-report questionnaire (Kooij et al., 2005) in 10% of the sample. The other 10% was missing due to nonresponse. Both questionnaires have excellent psychometric properties and are known to correlate strongly with each other (Erhardt, Epstein, Conners, Parker, & Sitarenios, 1999; Kooij et al., 2008), as was the case in our sample \( (N=380) \); parents completed both forms with a 3- to 4-year interval [follow-up study] between both measures, \( r = .69, p < .001 \). For each parent, all item scores on the CAARS-S:S or, when missing, all item scores on the Dutch ADHD self-report questionnaire concerning current behavior, were summarized into a total score which was used as a measure of current parental ADHD severity.

**Child ADHD.** The parent and teacher Conners’ N-subscale (ADHD Combined) scores were used separately to provide two measures of ADHD severity in children, allowing comparison of the effect of different rater sources. Parent and teacher Conners’ L-subscale (ADHD Inattentive) and
M-subscale (Hyperactive-Impulsive) scores were used to verify possible differential effects on inattention and hyperactivity-impulsivity.

**Neuropsychological Paradigms.** Table 3 provides a brief description of the eight neuropsychological paradigms used. Details on each paradigm are provided elsewhere (Rommelse, Altink, et al., 2007; Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008; Rommelse, Oosterlaan, et al., 2007). All have been shown sensitive to the effects of ADHD (Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008) and have established genetic loading in the present sample (Rommelse, Arias-Vasquez, et al., 2008).

**Data Analyses**

Missing data were randomly distributed and the percentage of missing data for all measures was less than 5% for child neuropsychological and ADHD measures and 10% for parental ADHD measures. All missing values were replaced using multiple imputations. Based on the pooled results of five imputations, p values were calculated, using the adjusted standard error, using Rubin’s rules (Rubin, 1987). Neuropsychological measures and ADHD measures were successfully normalized and standardized into z scores by applying a Van der Waerden transformation. For IQ measures, digit span, and visuospatial sequencing, z scores were mirrored, so that higher z scores of all measures

### Table 1. Sample Characteristics Children

<table>
<thead>
<tr>
<th></th>
<th>Affected siblings, n = 350</th>
<th>Nonaffected siblings, n = 195</th>
<th>Normal controls, n = 271</th>
<th>Group main effecta</th>
<th>Pairwise group comparisons (p &lt; .05)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD) years of age</td>
<td>11.5 (2.8)</td>
<td>11.5 (3.6)</td>
<td>11.6 (3.2)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>% male</td>
<td>75.4</td>
<td>45.1</td>
<td>40.6</td>
<td>88.7***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>M (SD) estimated full-scale IQ</td>
<td>99.5 (11.6)</td>
<td>103.8 (10.9)</td>
<td>106.0 (10.2)</td>
<td>29.0*</td>
<td>1 &lt; 2 &lt; 3</td>
</tr>
<tr>
<td>Conners’ parent DSM-IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention M (SD)</td>
<td>69.5 (9.8)</td>
<td>47.9 (7.0)</td>
<td>46.5 (4.8)</td>
<td>836.6***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>Hyperactive-impulsive M (SD)</td>
<td>75.5 (12.0)</td>
<td>49.0 (6.9)</td>
<td>47.3 (5.1)</td>
<td>932.1***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>Conners’ teacher DSM-IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention M (SD)</td>
<td>64.6 (9.7)</td>
<td>48.3 (6.0)</td>
<td>46.4 (4.6)</td>
<td>550.8***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>Hyperactive-impulsive M (SD)</td>
<td>68.0 (12.0)</td>
<td>48.3 (6.5)</td>
<td>47.2 (5.0)</td>
<td>526.8***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>ADHD diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention n (%)</td>
<td>28 (8)</td>
<td>40.6</td>
<td>40.6</td>
<td>88.7***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>Hyperactive-impulsive n (%)</td>
<td>20 (6)</td>
<td>40.6</td>
<td>40.6</td>
<td>88.7***</td>
<td>1 &gt; 2 = 3</td>
</tr>
<tr>
<td>Combined n (%)</td>
<td>302 (86)</td>
<td>40.6</td>
<td>40.6</td>
<td>88.7***</td>
<td>1 &gt; 2 = 3</td>
</tr>
</tbody>
</table>

Note: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.).

For all tests: F(2, 812); group differences for % right handed and male were tested with χ² tests.

1 = affected siblings; 2 = nonaffected siblings; 3 = normal controls.

T-scores.

*p < .05. ***p < .001.

### Table 2. Sample Characteristics Parents

<table>
<thead>
<tr>
<th></th>
<th>ADHD (MA) n = 238</th>
<th>Control (MC) n = 146</th>
<th>Pairwise group comparisons (p &lt; .05)</th>
<th>ADHD (FA) n = 237</th>
<th>Control (FC) n = 146</th>
<th>Pairwise group comparisons (p &lt; .05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD) years of age</td>
<td>40.9 (4.4)</td>
<td>42.7 (5.1)</td>
<td>MA &lt; MC***</td>
<td>43.4 (5.4)</td>
<td>45.2 (5.1)</td>
<td>FA &lt; FC***</td>
</tr>
<tr>
<td>M (SD) ADHD scorea</td>
<td>−0.33 (1.2)</td>
<td>−0.93 (0.66)</td>
<td>MA &gt; MC***</td>
<td>−0.08 (1.14)</td>
<td>−0.73 (0.67)</td>
<td>FA &gt; FC****</td>
</tr>
<tr>
<td>≥Clinical cutoff—n (%)b</td>
<td>22 (9.4)</td>
<td>1 (0.8)</td>
<td>MA &gt; MC***</td>
<td>23 (10.7)</td>
<td>0 (0)</td>
<td>FA &gt; FC****</td>
</tr>
</tbody>
</table>

z scores were obtained from the Conners’ Adult ADHD Rating Scale—Self-Report: Short Version (CAARS-S:S) or the Dutch Self-Report Questionnaire.

a/z score ≥ 1.5 on CAARS-S:S or the Dutch Self-Report Questionnaire.

b*p < .01. ***p < .001.
would have the same meaning: weaker neuropsychological performance or more ADHD symptoms.

To test whether parental ADHD was related to children’s ADHD and neuropsychological performance, effect sizes were calculated using generalized estimated equations (GEE) with a linear regression model, robust estimators, and exchangeable structure for working correlation matrices. To correct for the familial dependency within the data set (e.g., at least two mother–child effects were calculated in most families), family number was used as repeated measure. Independent variables were maternal and paternal ADHD symptoms, age and sex of the child, and the two interaction terms: paternal ADHD by child sex and maternal ADHD by child sex. Separate analyses were run for each of the dependent variables: parent and teacher reported child ADHD symptoms and the 10 dependent variables derived from the neuropsychological paradigms. To determine whether neuropsychological functioning mediated the relationship between parent and child ADHD, the effect of parental ADHD on child ADHD was analyzed with and without the effects of the neuropsychological measures taken into account. Mediation effect sizes were computed using a multiple mediation bootstrap analysis (Preacher & Hayes, 2004). If maternal or paternal ADHD or both were significantly related to a dependent measure, we verified parent-of-origin effects by defining and testing contrasts for the regression weights associated with maternal and paternal ADHD. If parental ADHD by child sex interactions were significant, we verified child sex effects by defining and testing contrasts for the regression weights associated with ADHD in sons and daughters. In case of maternal and paternal ADHD both being significantly related to the dependent measure, paternal by maternal ADHD interaction was included. A false discovery rate correction (Benjamini & Hochberg, 1995) was employed to correct for multiple comparisons maintaining alpha at p < .05. Only the effects that remained significant after correction for multiple testing were reported. Effect sizes were defined in terms of B, indicating the z score increase of the dependent measure at increase of 1 z score on the independent measure.

**Results**

**Relation Between Parental and Offspring ADHD and Both Offspring ADHD and Neuropsychological Performance**

Paternal and maternal ADHD were positively related to ADHD symptoms in offspring as reported by parents ($B = 0.13$, 95% CI [confidence interval] = [0.07, 0.18], and 0.17, 95% CI = [0.12, 0.22], $p < .001$, respectively) and teachers

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Measurement potential</th>
<th>Dependent variable(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ-paradigms</td>
<td>Estimated full-scale IQ</td>
<td>Performance, verbal and total IQ</td>
</tr>
<tr>
<td>Time paradigms</td>
<td>Timing estimation</td>
<td>Variability in reaction times (SD in ms)</td>
</tr>
<tr>
<td>Executive paradigms</td>
<td>Inhibition</td>
<td>Stop signal reaction time (SSRT)</td>
</tr>
<tr>
<td>Motor paradigms</td>
<td>Motor control</td>
<td>Precision (left hand)</td>
</tr>
</tbody>
</table>

Note: WISC/WAIS-III = Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale–III.

*Details on each of the paradigms are provided elsewhere (Rommelse, Altink, et al., 2007, Rommelse, Oosterlaan, et al., 2007, Rommelse, Altink, Oosterlaan, Beem, et al., 2008; Rommelse, Altink, Oosterlaan, Buschgens, et al., 2008).

*Moving a mouse cursor on top of a randomly moving target (asterisk).

*Tracing an invisible midline between an inner and outer circle with a mouse cursor.
versus

**Figure 1.** Child ADHD and neuropsychological functioning as a function of parental ADHD

Note: Effects are defined as sons’ and/or daughters’ z score increase on the Conners’ Parent or Teacher Rating Scale or neuropsychological task performance as a result of 1 z score increase of their parents’ on a parental self-report scale. Higher z scores indicate more ADHD symptoms/poorer neuropsychological performance. Underscored effects indicate maternal parent-of-origin effects (i.e., predictive value of mother significantly higher than father’s).

(B = 0.12, 95% CI = [0.05, 0.18], p < .001, and B = 0.09, 95% CI = [0.03, 0.15], p = .005, respectively; see Figure 1, for an illustration of the effects). Maternal and paternal effects sizes did not differ significantly from each other (p > .30), indicating that there was no evidence for parent-of-origin effects. No Paternal × Maternal ADHD interaction effect was found on child ADHD (p > .15), indicating that paternal and maternal ADHD did not influence each other’s effect on offspring ADHD, which is in line with former findings (Takeda et al., 2010). Including child’s gender and age did not change the results, suggesting neither a child’s gender nor a child’s age effects in parent–offspring ADHD relations. Analyses conducted with child’s inattentive (i) or hyperactive-impulsive (hi) symptoms only, yielded comparable results for paternal, B (i) = 0.14, B (hi) = 0.11, p < .001 versus B = 0.13, p < .001, and maternal, B (i) = 0.16, B (hi) = 0.16, p < .001, versus B = 0.17, p < .001, ADHD in relation to offspring ADHD as reported by parents as well as reported by teachers, paternal B (i) = 0.12, B (hi) = 0.11, p < .001 versus B = 0.12, p < .001, and maternal B (i) = 0.07, B (hi) = 0.11, p < .03 versus B = 0.09, p = .005.

Because performance on all paradigms was significantly predicted by the child’s age (p < .001), parental ADHD by child’s age interactions were added to all subsequent analyses in which we examined whether parental ADHD symptomatology was related to offspring neuropsychological performance (see Figure 1, for an illustration of the effects). Paternal ADHD was related to offspring time reproduction (B = 0.09, 95% CI = [0.03, 0.16], p < .001) and verbal and total IQ in daughters (B = 0.13, 95% CI = [0.03, 0.20], p < .01), but not in sons. Paternal and maternal effects sizes on the three aforementioned measures did not differ significantly from each other (p > .07, > .50, > .19, respectively), illustrating that these paternal effects of ADHD were not parent-of-origin effects, whereas the difference between the paternal effect sizes on daughters and sons was significant for both IQ measures (p < .01), indicating a child sex effect.

A main effect of maternal ADHD was found on children’s inhibition abilities (B = 0.30, 95% CI = [0.09, 0.50], p < .05). On child motor control, both with and without continuous adaptation, maternal ADHD effects interacted with child’s age (B = −0.03, 95% CI = [−0.05, −0.008], p < .05). This interaction was similar for both paradigms and post hoc GEE analyses revealed a (marginally) significant effect of maternal ADHD on motor control for children <12 only (B = 0.07, 95% CI = [−0.01, 0.14], p = .07, and B = 0.10, 95% CI = [0.01, 0.18], p < .05, respectively). Maternal and paternal effect sizes on children’s performance on inhibition and motor control with and without adaptation differed significantly from each other, indicating a maternal parent-of-origin effect of ADHD on all three measures (p < .03, < .01, respectively).

No significant relations were found between parental ADHD and offspring’s timing of motor output, performance IQ, verbal, or visuospatial working memory.

**Does the Child’s Neuropsychological Functioning Mediate the Relation Between Parental and Offspring ADHD Symptoms?**

When the relationship between parental ADHD and child neuropsychological functioning was taken into account, the effects of paternal and maternal ADHD on child ADHD as reported by parents remained essentially unchanged (B = 0.13 vs. 0.12, p < .0001 vs. < .0002 for fathers; B = 0.17 vs. 0.16, p < .0001 vs. < .0001 for mothers). This indicates that neuropsychological functioning did not mediate the relationship between parental ADHD and parent-reported offspring ADHD. Similar effects were obtained for the relation between parental ADHD and offspring ADHD as reported by teachers (z = 0.12 vs. 0.12, p < .0002 vs. < .0003 for fathers; z = 0.09 vs. 0.09, p = .004 vs. .012 for mothers). The insignificant mediation of all neuropsychological measures was confirmed by a multiple mediation bootstrapping analysis, revealing minimal indirect effects of paternal ADHD on child ADHD trough time reproduction, Effect (z) = 0.02, 95% CI = [0.003, 0.03], and verbal IQ. Effect (z) = 0.0001, 95% CI = [−0.005, 0.02], and of maternal ADHD on child ADHD trough inhibition, Effect (z) = 0.01, 95% CI = [−0.003, 0.03], motor control with adaptation, Effect (z) = 0.002, 95% CI = [−0.003, 0.007], and without adaptation, Effect (z) = 0.001, 95% CI = [−0.003, 0.005].
Discussion

Using parental self-reported ADHD symptoms and data on offspring ADHD symptoms as well as offspring neuropsychological functioning, we examined parent-of-origin effects in ADHD and whether such parent-of-origin effects may be gender specific. In line with previous observations (Faraone & Doyle, 2000; Minde et al., 2003; Sprich, Biederman, Crawford, Mundy, & Faraone, 2000), but in contrast to others (Crosbie & Schachar, 2001; Hawi et al., 2005, 2009; Quist et al., 2003; Smoller et al., 2006), we found that paternal and maternal ADHD increased the risk for ADHD symptomatology in offspring to a similar extent, with similar effects for boys and girls. However, clear parent-of-origin effects were found in relation to neuropsychological functioning in offspring with a selective maternal effect on executive functioning (inhibition) and motor functioning (two motor control paradigms). Evidence for a selective paternal effect was found on timing (time reproduction) and IQ (verbal and total IQ). The majority of these findings did not vary as a function of child sex, except for the effect of paternal ADHD on child’s IQ, which was only present in girls. All effects were small, except for maternal ADHD on offspring inhibition, which was medium sized. The relationship between parental ADHD and child ADHD was not mediated by child neuropsychological functioning.

The finding that parent-of-origin effects were detected using neuropsychological data and not using ADHD symptom data is in line with previous studies (Crosbie & Schachar, 2001; Goos et al., 2009; Nigg et al., 2004) and supports the utility of these measures in ADHD family-genetic research, as parent-of-origin stratified analyses can provide more power to linkage analyses. These results suggest that it may be opportune to investigate the potential of neuropsychological deficits apart from the clinical manifestation of ADHD, to construct parent-specific causal pathways underlying cognitive deficits (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005). For instance, whereas maternal ADHD was mainly associated with offspring’s motor control and inhibition, paternal ADHD was only associated with offspring’s time reproduction and IQ. The brain networks underlying these functions are different, with inhibition and timing of long intervals being mainly related to fronto-striatal circuits (Duncan, Emslie, Williams, Johnson, & Freer, 1996; Lewis & Miall, 2003), motor functioning mainly involving cerebellar and basal ganglia functioning (Berquin et al., 1998) and IQ having more diffuse brain correlates like thalamic, hippocampal, and gray matter volume (Ramsden et al., 2011; Schumann et al., 2007; Xie, Chen, & De Bellis, 2011). Therefore, different gene-brain network pathways might be involved in the transmission of neuropsychological traits depending on the sex of the parent. As the majority of these parental influences did not vary as a function of child sex, transmissions could be due to genomic imprinting and also environmental factors (such as the distinguishable transmission of traits from one parent vs. the other as a result of different personality or parenting styles) or a combination of both. As focus on the investigation of gene-environment interactions in complex disorders like ADHD is increasing, our data indicate how neuropsychological traits can be used to unravel parental effects. For example, molecular studies have found links between deficient inhibition and the dopaminergic system (Cornish et al., 2005; Cummins et al., 2011). Because the dopamine system is affected by gender (Becker, 1999; Lavlaye, Booij, Reneman, Habraken, & van Royen, 2000), the exclusive effect of maternal ADHD on offspring’s inhibition could result from environmental factors acting differently on mothers’ than fathers’ dopamine system to affect offspring.

Some critical comments concerning the use of neuropsychological functions in ADHD family-genetic research must also be made. No mediating effect was found of neuropsychological functions between parent and offspring ADHD symptoms. Taken this into consideration, together with the absence of parent-of-origin effects in ADHD symptom transmission, yet the presence of such effects in ADHD—neuropsychological function transmission—this may suggest neuropsychological functions are best seen as epiphenomena (i.e., related to the same genes as the ADHD phenotype but not on a causal pathway in between genes and ADHD symptoms; Walters & Owen, 2007). In addition, in line with previous studies (Nigg et al., 2004; Thapar, Harrington, Ross, & McGuffin, 2000), effect sizes for parent–offspring relationships were generally smaller for neuropsychological functions compared with ADHD symptoms (except for inhibition). However, we believe both issues do not necessarily counterargue the use of neuropsychological functions in ADHD family-genetic research. First, even though neuropsychological functions may not mediate between genes and phenotype, they can still be useful in gene-finding experiments if they are used to create etiologically more homogeneous subgroups of patients (Goos et al., 2007). Second, the smaller effect sizes found here for neuropsychological functions compared with ADHD symptoms may well be attributable to discrepancy between measurement instruments. That is, it is to be expected that correlations between ADHD symptom questionnaires (parent and child) are higher than those between a questionnaire and neuropsychological tasks because of measurement homogeneity. Effect sizes are probably higher when neuropsychological functions are also measured in parents, which have indeed been reported previously (Goos et al., 2009; Nigg et al., 2004). In any case, compared with ADHD symptom measures—in the present study suffering from the limitations inherent in self-report measures and in general suffering from the heterogeneous phenotypic presentation of ADHD in adulthood—neuropsychological functions seem to be more sensitive to parent-of-origin effects, paving the way for future studies on this topic.
In summary, we illustrated that transmission patterns of ADHD-related neuropsychological deficits can differ considerably from those of the defining symptoms of the disorder. This was supported by the essentially unchanged relation between parent−offspring ADHD after the possible mediating effects of neuropsychological deficits were taken into account. Further unraveling the nature of these patterns can lead to identification of more homogeneous etiological subgroups in ADHD, as specific neuropsychological deficits might reflect differential underlying neural substrates. In addition, parent-of-origin effects may help identify children for specific treatment interventions based on unique maternal and paternal contributions to neuropsychological deficits. For future research, we suggest the inclusion of parental neuropsychological measures and other neuropsychological domains as well, to map out possible causal pathways underlying ADHD-related deficits and to perform a more detailed exploration of the nature of intergenerational transmission of ADHD.

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