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ORIGINAL ARTICLE

Cortical thickness and inattention/hyperactivity symptoms in young children: a population-based study

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Background. While many neuroimaging studies have investigated the neurobiological basis of attention deficit hyperactivity disorder (ADHD), few have studied the neurobiology of attention problems in the general population. The ability to pay attention falls along a continuum within the population, with children with ADHD at one extreme of the spectrum and, therefore, a dimensional perspective of evaluating attention problems has an added value to the existing literature. Our goal was to investigate the relationship between cortical thickness and inattention and hyperactivity symptoms in a large population of young children.

Method. This study is embedded within the Generation R Study and includes 6- to 8-year-old children (n=444) with parent-reported attention and hyperactivity measures and high-resolution structural imaging data. We investigated the relationship between cortical thickness across the entire brain and the Child Behavior Checklist Attention Deficit Hyperactivity Problems score.

Results. We found that greater attention problems and hyperactivity were associated with a thinner right and left postcentral gyrus. When correcting for potential confounding factors and multiple testing, these associations remained significant.

Conclusions. In a large, population-based sample we showed that young (6- to 8-year-old) children who show more attention problems and hyperactivity have a thinner cortex in the region of the right and left postcentral gyrus. The postcentral gyrus, being the primary somatosensory cortex, reaches its peak growth early in development. Therefore, the thinner cortex in this region may reflect either a deviation in cortical maturation or a failure to reach the same peak cortical thickness compared with children without attention or hyperactivity problems.

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Introduction

While attention problems are one of the core characteristics of attention deficit hyperactivity disorder (ADHD), the ability to pay attention falls along a continuum within the population and children with ADHD are at one extreme of the spectrum (Polderman *et al.* 2007; Lubke *et al.* 2009). In addition, attention problems are commonly found in other childhood psychiatric disorders, such as early-onset psychoses and pervasive developmental disorders (Swaab-Barneveld *et al.* 2000; Muratori *et al.* 2005; Karatekin *et al.* 2010; van Rijn *et al.* 2012). There has been considerable debate recently over whether child psychopathology falls within diagnostic categories with clearly defined boundaries, or whether symptoms could be better described within a dimensional (continuous) framework. Numerous studies provide evidence in favour of a dimensional approach, as it provides greater statistical power and contributes

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an additional perspective to the existing literature (Hudziak *et al.* 2007; Polderman *et al.* 2007; Lubke *et al.* 2009; Shaw *et al.* 2011). Furthermore, dimensional approaches are being evaluated as a part of the National Institute of Mental Health's research domain criteria (Insel *et al.* 2010).

While many neuroimaging studies have investigated the neurobiological basis of ADHD (for a review, see Durston, 2003), few studies have evaluated the underlying neurobiology of attention problems from a dimensional perspective. Shaw *et al.* (2011) studied cortical thickness in a non-clinical sample of 193 typically developing youth, as well as in a clinical sample of 197 children with ADHD (both aged 8–18 years). They found that the rate of cortical thinning changed gradually with the degree of symptom severity; youth with higher levels of hyperactivity and impulsivity in the non-clinical sample had a slower rate of cortical thinning and children with a clinical ADHD diagnosis showed the slowest rate of cortical thinning (Shaw *et al.* 2011). Additionally, a recent study by Ducharme *et al.* (2012) evaluated the association between cortical thickness and attention problem scores in a sample of healthy children between 6 and 18 years of age. Their findings demonstrated an association between increased attention problem scores and specific regions with a thinner cortex, as well as slower cortical thinning with ageing in different areas involved in attention processes (Ducharme *et al.* 2012).

Studies using clinical samples to examine cortical thickness in children with ADHD have shown a highly significant thinner cortex over wide areas of the brain, implicating a thinner cortex to be an important marker for ADHD (Narr *et al.* 2009). In a large longitudinal study of children and adolescents with ADHD, Shaw *et al.* (2006) also showed that children with ADHD have significantly thinner cortices across the entire brain. In a subsequent study, Shaw *et al.* (2007) found that, although the overall pattern of cortical development was similar in children with ADHD and controls, the trajectories of cortical thinning were different. They reported that children with ADHD were delayed in attaining peak cortical thickness throughout most of the cerebrum. The only region in which they found the ADHD group to show slightly earlier maturation was the sensorimotor region (Shaw *et al.* 2007). The increase in cortical thickness during normal development may be driven by mechanisms like dendritic spine growth and the expansion of supporting glia (Chklovskii *et al.* 2004; Sur & Rubenstein, 2005). The cortical thinning that follows may reflect intracortical myelination and the creation of efficient neural networks (by the elimination of unused synapses), including those networks that support cognition (Huttenlocher & Dabholkar, 1997; Hensch, 2004). The delayed maturation and later cortical thinning in ADHD may therefore point to less efficient brain networks, possibly causing the cognitive and behavioural difficulties that children with ADHD experience.

Because of the lack of studies focusing on attention problems in general population samples of children and the recent tendency towards favouring a dimensional perspective of child psychopathology, the goal of our study was to investigate the relationship between cortical thickness and inattention/hyperactivity symptoms along a continuum in a very large, population-based sample of young children. By including a large sample of children within a narrow age range, our goal was to obtain a clear snapshot of this relationship during a very specific period of child neurodevelopment. Furthermore, the recruitment of children from a large longitudinal prenatal population-based cohort study of child development provides the ability to assess multiple potential confounding factors and is more representative of the population at large.

Method

Participants

This study is embedded within the Generation R Study, a multi-ethnic population-based cohort study, investigating children's health, growth and development from fetal life until young adulthood in Rotterdam, the Netherlands. An overview of the Generation R Study design and population is described elsewhere (Jaddoe *et al.* 2012; Tiemeier *et al.* 2012).

A total number of 8305 children participated in the study phase from 5 to 16 years (Jaddoe *et al.* 2012). At age 6 years, a pilot brain magnetic resonance imaging (MRI) study began within the Generation R Study. An overview of this neuroimaging component of the Generation R Study and participant selection is provided elsewhere (White *et al.* 2013). A total of 608 children aged 6 to 8 years were scanned between September 2009 and February 2012. Of the 608 children with imaging data, a total of 104 children were excluded based upon poor image quality. For the children with good-quality imaging data, data on attention problems were missing in 45 children. Furthermore, data were collected on six twin pairs and three sibling pairs. Twin pairs were excluded from the analyses, as well as a randomly selected child from each sibling pair. This resulted in a final study sample of 444 children.

Covariates

Participant characteristics are presented in Table 1. To define child ethnicity, the ethnicity categorization of

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Table 1. *Participant characteristics* (*n*=444)

Characteristics	
Child characteristics	
Gender, % boys	51.8
Ethnicity, %	
Dutch	65.8
Other Western	8.1
Turkish or Moroccan	9.2
Surinamese or Antillean	9.0
Other non-Western	7.9
Gestational age at birth, weeks	40.0 (1.7)
Birth weight, g	3455 (542)
CBCL Attention Problems score	2.02 (2.12)
Range	0–9
CBCL Attention Deficit Hyperactivity Problems score	3.75 (3.12)
Range	0–12
IQ	102.01 (14.15)
Handedness, % right	89.4
Age at CBCL completion, years	6.13 (0.41)
Range	5.25–7.92
Age at MRI scanning, years	7.70 (0.92)
Range	6.13–9.61
Time interval between CBCL and MRI, years	1.6 (0.84)
Psychostimulant use, %[a]	
Yes	3.6
No	89.6
Maternal characteristics	
Education level, %	
High	47.1
Medium	38.7
Low	14.2
Monthly household income, %	
>€2000	72.5
€1200–2000	20.3
<€1200	7.2
Alcohol use during pregnancy, %	
Never	38.1
Until pregnancy was known	12.8
Continued during pregnancy	49.1
Smoking during pregnancy, %	
Never	78.4
Until pregnancy was known	3.8
Continued during pregnancy	17.8

Values are given as mean (standard deviation), unless otherwise indicated.

CBCL, Child Behavior Checklist 1.5–5; IQ, intelligence quotient; MRI, magnetic resonance imaging.

[a] Data regarding psychostimulant use missing in *n*=30.

Statistics Netherlands (Statistics Netherlands, 2004*a*) was used. Children with both parents born in the Netherlands were considered Dutch and children were classified as non-Dutch (further categorized as 'other Western', 'Turkish/Moroccan', 'Surinamese/Antillean' or 'other non-Western') if one parent was born outside the Netherlands. Maternal education was defined as highest education completed, according to the definition of Statistics Netherlands (Statistics Netherlands, 2004*b*) and household income was defined by the total net monthly income of the household. Information on maternal alcohol use and smoking during pregnancy was obtained using questionnaires in each trimester of pregnancy. Information on the date of birth, gender and birth weight was obtained from midwives and hospital registries. Gestational age was established using ultrasound measures during pregnancy. The intelligence quotient (IQ) of the child was assessed during the assessment wave at 6 years of age, using a shortened version of the Snijders-Oomen Niet-verbale intelligentie Test – Revisie (SON-R 2.5–7), which is a non-verbal intelligence test suited for children of 2.5–7 years of age (Tellegen *et al.* 2005). Handedness of the child was obtained using the Edinburgh Handedness Inventory (Oldfield, 1971) on the day of the scan, as well as information regarding the use of psychostimulant medication.

Child Behavior Checklist (CBCL)

During the assessment wave at 6 years of age, all parents were asked to fill out the CBCL 1.5–5 (Achenbach & Rescorla, 2000). The preschool CBCL was chosen because many children were younger than 6 years at the time of the assessment and older-age versions are inappropriate for such young children (as they contain questions on, for example, tobacco smoking and the use of other substances). The use of one version of the CBCL was desired, in order to enhance comparability between all children. In the CBCL 1.5–5, the primary caregiver is asked to answer 99 items as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true, on the behaviour of their child in the preceding 2 months. Good reliability and validity have been reported for the preschool version of the CBCL (Achenbach & Rescorla, 2000). To measure inattention and hyperactivity, we used the raw sumscore of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented Attention Deficit Hyperactivity Problems (ADHP) scale. The ADHP scale measures attention problems and symptoms of hyperactivity. Cronbach's α's were similar in the 5-year-old children and in children of 6 years and older for the ADHP scale (α=0.83 and α=0.86, respectively), indicating that the attention and hyperactivity problems were reliably measured in the children older than 5 years of age. The primary caregiver

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completed the CBCL; this was the mother in 93.5% of the cases.

Imaging

MR images were acquired using a GE Discovery MR750 3.0 T scanner (GE Healthcare Worldwide, USA) with an eight-channel head coil. The high-resolution T_1-weighted image was collected using an inversion recovery prepared fast spoiled gradient recalled sequence with the following parameters: TR (repetition time)=10.3 ms, TE (echo time)=4.2 ms, TI (inversion time)=350 ms, NEX (number of excitations)=1, flip angle=16°, readout bandwidth=20.8 kHz, matrix 256×256, imaging acceleration factor of 2, and an isotropic resolution of $0.9\times0.9\times0.9$ mm^3. Before scanning took place, children were familiarized with the scanning environment during a mock scanning session. All procedures have been described in detail elsewhere (White *et al.* 2013).

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center and the Central Committee of Research involving Human Subjects. Written informed consent was obtained from the parents of all participants.

Image quality

In the 608 children with imaging data, we performed image quality assurance in two steps. The first step was a visual inspection of the image quality of the T_1 sequence prior to preprocessing the data. All images were rated on a six-point scale (unusable, poor, fairly good, good, very good, excellent). The next step of quality assurance took place after the images were processed through the FreeSurfer pipeline, and consisted of a visual inspection of the segmentation quality of the data. All images were rated on a seven-point scale (not constructed, poor, fair, fairly good, good, very good, excellent). T_1 data that were rated as unusable or poor were not used (n=34), as well as the children whose FreeSurfer output was not constructed or rated as poor (n=70), leading to a total of 104 children that were excluded based upon poor image quality (i.e. excessive movement or other artifacts). In the total sample of 608 children with structural imaging data, we utilized a χ^2 analysis to evaluate if there was a relationship between image quality and attention problems. We found no differences in image quality between children with more or fewer attention problems and/or more or less hyperactivity.

Image processing

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) version 5.1. The technical details of these procedures are described in prior publications (Dale *et al.* 1999; Jovicich *et al.* 2006; Reuter *et al.* 2012). Cortical thickness was calculated as the closest distance from the grey/white boundary to the grey/cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The surface-based map was smoothed using a 10 mm full-width half-maximum Gaussian kernel prior to the surface-based analyses. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas *et al.* 2002) and manual measurements (Kuperberg *et al.* 2003; Salat *et al.* 2004). FreeSurfer morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths (Han *et al.* 2006). Numerous studies using FreeSurfer in typically and atypically developing school-age children are available (O'Donnell *et al.* 2005; Derauf *et al.* 2009; Ghosh *et al.* 2010; Ducharme *et al.* 2012; Juuhl-Langseth *et al.* 2012; Webb *et al.* 2012; Yang *et al.* 2012).

Statistical analyses

As the boundaries of *a priori*-defined regions of interest may not exactly overlap the boundaries of the actual areas in which abnormalities are located, we chose to perform vertex-wise exploratory analyses of cortical thickness across the entire brain. To investigate the relationship between cortical thickness and inattention and hyperactivity symptoms, we performed surface-based General Linear Model vertex-wise cortical analyses using the FreeSurfer in-built module QDEC (www.surfer.nmr.mgh.harvard.edu). QDEC allows users to perform inter-subject/group averaging and inference on the morphometry data produced by the FreeSurfer processing stream. We ran QDEC to investigate the correlation between cortical thickness on vertices covering the entire cortex and the CBCL ADHP score. Age during scanning and gender were included as covariates in the analysis. To correct for multiple testing (for all brain vertices), a Monte Carlo null-Z simulation was performed, using a threshold of 1.3 (p<0.05). Monte Carlo null-Z simulation is a cluster-wise correction and controls the rate of false-positive clusters (method based on Hagler *et al.* 2006). Monte Carlo-corrected p values are reported.

Cortical thickness data of significant cluster(s) identified in the vertex-wise QDEC analyses were extracted for each individual and imported into SPSS (version 20.0; IBM, USA) for further detailed analyses. Using these extracted cortical thickness measures, we performed linear regression analyses with cortical thickness of the cluster(s) (residualized for age during

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Table 2. *QDEC correlation of cortical thickness and CBCL ADHP score*[a]

Location	Cluster size, mm^2	Talairach coordinates			Vertices within cluster, *n*	Cluster-wise p[b]	Peak p within cluster
		x	y	z			
Postcentral, RH	3013.0	29.3	−40.7	57.9	7223	0.00010	0.00006
Postcentral, LH	1009.2	−30.0	−28.9	63.4	2283	0.01160	0.00030

CBCL, Child Behavior Checklist 1.5–5; ADHP, Attention Deficit Hyperactivity Problems; RH, right hemisphere; LH, left hemisphere.

[a] Analyses accounting for gender. Age during scanning used as a nuisance factor.

[b] Monte Carlo simulation ($p<0.05$) applied to correct for multiple testing.

scanning) as the independent variable and the ADHP score as the dependent variable. These analyses were performed correcting for other, possibly confounding, factors that could not be corrected for using QDEC, given constraints on the model setup. In this way we evaluated whether the association(s) would remain present after correcting for other, possibly important, factors. Regression analyses were corrected for gender and age when the CBCL was completed; other possibly important variables were considered confounders and were added to the regression analyses only when they changed the effect estimate (*B*) by 5% or more. These included ethnicity, IQ and maternal smoking during pregnancy.

In all analyses, missing values of potential confounding environmental or risk factors (0.2% for handedness, 7.4% for IQ, 2.0% for maternal education, 4.8% for household income, 4.6% for alcohol use during pregnancy and 1.5% for smoking during pregnancy) were imputed using the multiple imputation (Markov chain Monte Carlo) method in SPSS 20.0 with five imputations and 10 iterations. In all analyses, CBCL scores were square root transformed to approach a normal distribution.

Results

Vertex-wise analyses

The results of the initial vertex-wise QDEC analyses are presented in Table 2 and Fig. 1. After correcting for multiple testing, we observed a significant cluster in the right and left postcentral gyrus. We found thickness of the right ($p=0.0001$) and left ($p=0.01$) postcentral gyrus to be negatively correlated with the CBCL ADHP score, indicating a thinner cortex in relation to higher ADHP scores.

Detailed analyses of clusters

Using the extracted cortical thickness data from both clusters for each individual, we first calculated bivariate correlations between cortical thickness of the identified clusters and the CBCL ADHP score. We observed significant (all $p<0.01$) negative correlations between, on the one hand, the thickness of the right postcentral ADHP cluster and the left postcentral ADHP cluster and, on the other hand, the CBCL score ($r_{442}=-0.26$ and $r_{442}=-0.22$, respectively), such that a thinner cortex was associated with more attention problems and hyperactivity.

We then performed linear regression analyses in SPSS, while correcting for potential confounders (age when CBCL was completed, gender, ethnicity, IQ and maternal smoking during pregnancy) and with cortical thickness residualized for age during scanning (Table 3). For the adjusted model with the additional covariates, the ADHP score showed a significant association with the thickness of the right postcentral cluster ($B=-1.24$, $p<0.001$) and the thickness of the left postcentral gyrus ($B=-0.95$, $p<0.001$). When excluding children that used psychostimulant medication (or that had missing data regarding medication use) all results remained the same.

To rule out a potential confounding effect of other co-morbid behavioural or emotional problems, we additionally adjusted the analyses for the other CBCL DSM-oriented scale scores (affective problems, anxiety problems, pervasive developmental problems and oppositional defiant problems). The results remained similar. We also additionally adjusted the analyses for scan quality, to rule out a potential confounding effect of scan quality on the association between cortical thickness and CBCL attention and hyperactivity problems. These analyses again yielded similar results.

Discussion

In a large population-based group of 6- to 8-year-old children, we found that cortical thickness in the region surrounding the postcentral gyrus was significantly negatively associated with symptoms of inattention

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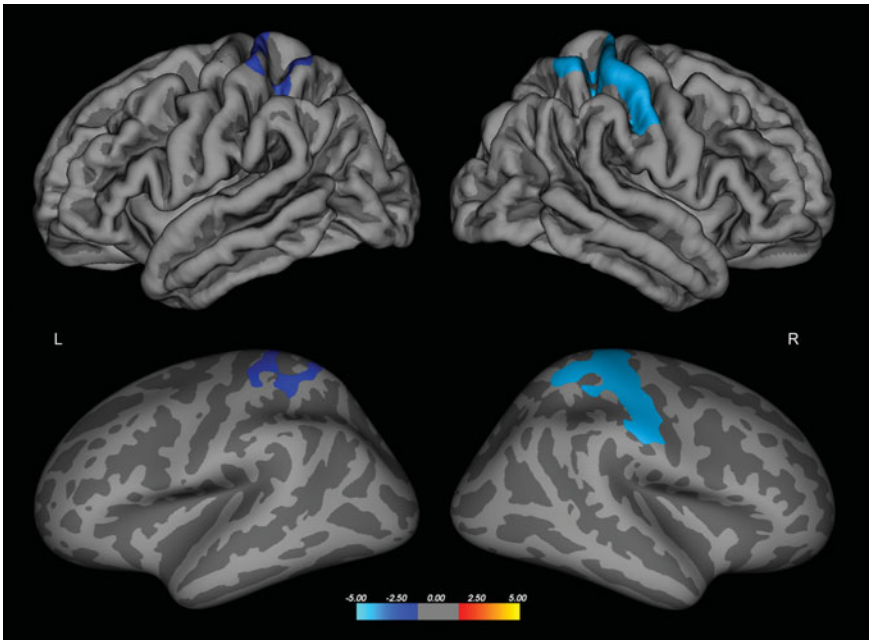

Fig. 1. Statistical maps of the significant clusters in the left (L) and right (R) hemispheres for the Child Behavior Checklist (CBCL) Attention Deficit Hyperactivity Problems Scale, represented on both the pial (top) and inflated (bottom) surfaces. Monte Carlo simulation was applied to correct for multiple testing. Colours represent the $-\log_{10}(p)$; the blue (negative) cluster equals a negative relationship between cortical thickness and CBCL score.

and hyperactivity. A thinner cortex in this region was related to a higher CBCL inattention and hyperactivity score. The relationship remained present after adjusting for several confounding factors, including gender, age, ethnicity, IQ and maternal smoking.

The postcentral gyrus is a structure of the parietal lobe where the primary somatosensory cortex is located (Brodmann areas 1 to 3). The cluster also extends into the somatosensory association cortex (Brodmann area 5). Earlier studies of cortical mapping of motor and sensory areas of the human cortex showed that there is a considerable overlap between the motor and sensory areas of the brain. There appears to be considerable functional heterogeneity of the precentral and postcentral areas, with approximately 25% of all motor activations located postcentrally. This indicates that the human motor and sensory areas have no exact boundaries and are not simply divided by the central sulcus (Penfield & Boldrey, 1937; Nii *et al.* 1996), implicating that the clusters found in our study are potentially involved in both sensory and motor functioning.

Somatosensory processing plays an important role in typical development and has been found to be disturbed in various neurodevelopmental disorders. It is known that the development of motor skills depends heavily on the somatosensory system and touch also plays an important role in social and communication skills in early childhood and beyond. Neurodevelopmental disorders are characterized by behavioural, emotional, motor or cognitive problems, and touch plays a role in all of these areas (Cascio, 2010). Interestingly, it has been shown that brain responses to somatosensory stimuli are aberrant in children with ADHD (Parush *et al.* 2007), possibly suggesting a deficit in the perception-to-action system of the brain (Dockstader *et al.* 2009).

Shaw *et al.* (2007) showed that children with clinical ADHD were delayed in attaining peak cortical thickness throughout most of the cerebrum, except for the sensorimotor area, which seemed to be maturing earlier. After reaching peak cortical thickness, cortical thickness declines in both typically developing children and those with ADHD. For the sensorimotor region peak cortical thickness is reached at approximately 7.0 years of age in children with ADHD and 7.4 years of age in healthy controls (Shaw *et al.* 2007). The mean age of the children in our group was 7.7 years, which is approximately the expected period of peak cortical thickness in this region. Therefore, the thinner cortex in the somatosensory region in our study either suggests that the peak cortical thickness is less in children with attention problems and hyperactivity or, alternatively, may point to a deviation in the developmental trajectory of cortical thickness. This deviation could either represent earlier thinning, as was shown by Shaw *et al.* (2007), or a delay in reaching peak cortical thickness. Additional measurement points will be necessary to model trajectories of cortical thickness.

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Table 3. *SPSS regression analyses of thickness clusters and CBCL ADHP score*[a]

	Model 1		Model 2 (adjusted)	
	B (95% CI)	*p*	*B* (95% CI)	*p*
Postcentral cluster thickness, RH	−1.36 (−1.85 to –0.87)	<0.001	−1.24 (−1.72 to –0.75)	<0.001
Postcentral cluster thickness, LH	−1.06 (−1.51 to –0.61)	<0.001	−0.95 (−1.40 to –0.50)	<0.001

CBCL, Child Behavior Checklist 1.5–5; ADHP, Attention Deficit Hyperactivity Problems; CI, confidence interval; RH, right hemisphere; LH, left hemisphere.

[a] Cortical thickness was residualized for age during scanning. Model 1 only adjusted for gender and age when the CBCL was completed. Model 2 additionally adjusted for ethnicity, child intelligence quotient and maternal smoking during pregnancy. The *B*'s are not interpretable since mathematically transformed scores were used in the analyses.

In contrast to our findings, two previous studies on cortical thickness and attention problems in a broader sense (Ducharme *et al.* 2012; Walhovd *et al.* 2012) did not find a direct association between attention problem scores and cortical thickness. However, Ducharme *et al.* (2012) found (in a sample of 257 children) an 'attention problems × age' interaction with cortical thickness. According to the authors, they did not find a direct relationship because of a disappearance of the negative association between attention problems and cortical thickness with age. Since we, in contrast to Ducharme *et al.* (2012), studied a very small age range, this may explain why we did find a direct association between greater attention problems and cortical thickness. In addition, the study of Ducharme *et al.* (2012) included only healthy children. In their study all children had a CBCL Attention Problems *t* score below 70, which is the clinical cut-off, whereas we used a population-based sample that included children with clinically elevated CBCL scores (3.2% of our sample had a *t* score at or above 70). This may also explain the discrepancy between the findings, as it might be more difficult to find an association in a population that is free of clinically affected persons. In addition, our large study sample and narrow age range provides greater power to detect a direct association between cortical thickness and attention problems in a population-based sample. Another study that did not find an association between cortical thickness and attention problems is a study by Wolosin *et al.* (2009). The discrepancy between our findings and theirs might be explained by a lack of power in the study of Wolosin *et al.* (2009), since their study sample consisted of only 56 children (Wolosin *et al.* 2009). Another difference between the two studies is that Wolosin *et al.* (2009) compared children with a clinical diagnosis of ADHD (21 children) and healthy controls (35 children), whereas we studied attention problems along a continuum. Furthermore, the age range of their sample was different, as they studied children between the ages of 8 and 12 years. The combination of these differences and a lack of power might possibly explain the discrepancy in findings between the studies.

Shaw *et al.* (2011) also examined the relationship between hyperactivity/impulsivity and cortical thickness in a sample of 193 typically developing children (and 197 children with ADHD). Interestingly, they found the rate of cortical thinning to be slower in children with higher levels of hyperactivity/impulsivity in the region surrounding the supplementary motor area, extending into the region located in our study (Shaw *et al.* 2011). While they also found other regions implicated, their sample included a longitudinal design with a much broader age range, which allowed them to assess trajectories as well as differences. Since the children in our study fall within a very narrow age range, our results represent a very specific neurodevelopmental period.

Studies of typically developing children have shown a characteristic temporal progression within regions of brain development. In a longitudinal study of healthy children, Gogtay *et al.* (2004) showed that the primary sensorimotor cortices mature first, together with the frontal and occipital poles of the cortex. Maturation then progresses in a parietal to frontal wave of development (Gogtay *et al.* 2004). Since the children of our study are young, it is not surprising that we found differences in brain regions that have been shown to be the first to mature. As other brain regions, such as prefrontal areas, are still developing in these young children, it is possible that cortical thickness deviations in these regions will emerge later as the neurodevelopmental differences become unmasked. This hypothesis is in line with previous work of Shaw *et al.* (2007) in a sample of both children and adolescents with ADHD. In this older sample the authors showed a deviation in attaining peak cortical thickness in other parts of the brain as well, such as prefrontal regions (Shaw *et al.* 2007). In addition, in a study on cortical thickness

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in adults with ADHD, exploratory analyses showed a thinner cortex in adult ADHD in multiple brain regions, including a cluster in the left sensorimotor region, although these findings did not survive the stringent correction for multiple testing (Makris *et al.* 2007). However, to actually test our hypothesis on the potential later emergence of deviations in cortical thickness in regions that mature later in development, longitudinal studies that also include older children and adolescents will be needed.

An important strength of our study is the very large sample size and narrow age range, which provided us with greater power to detect differences than previous studies (Ducharme *et al.* 2012; Walhovd *et al.* 2012). In addition, the small age range allowed us to evaluate cortical morphology during a very specific window of development. Since neurodevelopment in young children is still ongoing, a larger age range may result in age-dependent differences that dilute or mask the findings, as pointed out in the study of Ducharme *et al.* (2012). Another strength is the young age and narrow age range of the children, since ADHD is often diagnosed in school-age children and our study provides a snapshot of brain development at a period closer to this age. Furthermore, few studies on cortical morphology have been performed in a large group of children this young. Additional strengths of the study include the population-based design, which provides greater generalizability with the population. Finally, tapping a prenatal longitudinal cohort study provides a wealth of information covering numerous environmental and other risk factors that can be used to control for potential confounding factors in the relationship between cortical thickness and attention problems and hyperactivity.

A limitation of our study is that the neuroimaging was performed at only one time point. Therefore, no inferences can be made on causality (direction of effect) or trajectories of neurodevelopment. Also, the neuroimaging and the collection of the CBCL data were done at different time points. The mean time interval between the collection of the CBCL and the neuroimaging was 1.6 years. Although CBCL ADHP scores have been shown to have high stability over time in both clinical (Stanger *et al.* 1996; Biederman *et al.* 2001) and population-based samples (McConaughy *et al.* 1992; Verhulst & van der Ende, 1992), this may influence the results. To try to account for this, we controlled for both age when CBCL was completed and the age during scanning. Finally, due to the lack of a suitable child atlas, we used an adult atlas within FreeSurfer for segmentation of the images. However, as noted before, numerous studies in both typically and atypically developing children have used FreeSurfer successfully (O'Donnell *et al.* 2005; Derauf *et al.* 2009; Ghosh *et al.* 2010; Ducharme *et al.* 2012; Juuhl-Langseth *et al.* 2012; Webb *et al.* 2012; Yang *et al.* 2012).

To conclude, we demonstrated in a large, population-based sample that young (6- to 8-year-old) children who show more attention problems and hyperactivity have a thinner cortex in the region of the right and left somatosensory cortex. Since there is evidence that cortical grey matter in this region peaks during this age range, the thinner cortex in this region may reflect either a decrease in peak cortical thickness in children with more attention problems and hyperactivity, or, alternatively, a deviation in cortical maturation. Longitudinal studies starting in young children will be important to better understand the growth trajectories of cortical thickness in children with attention and hyperactivity problems. Our finding of a thinner cortex in a population-based sample of children showing attention problems and hyperactivity also provides support for the dimensional aspect of attention and hyperactivity problems in children.

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Declaration of Interest

F.C.V. is head of the Department of Child and Adolescent Psychiatry/Psychology at the Erasmus

Medical Center, which publishes the Achenbach System of Empirically Based Assessment (ASEBA) and from which he receives remuneration. All other authors report no conflicts of interest.

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