Attention-Deficit/Hyperactivity Disorder and prenatal smoke and alcohol exposure

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Introduction

Symptoms and subtypes

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder with an early life onset, which is clinically heterogeneous, and consists of several behavioural components. Over the years the description of the disorder has been changed multiple times. The earliest descriptions include incapacity of attending by Crichton in 1798 (as cited in: Palmer & Finger, 2001) and an abnormal defect of moral control (Still, 1902). Lateron in the 1960s the terms minimal brain damage and minimal brain dysfunction were used, but these terms are now discarded. After that the terms hyperkinetic reaction of childhood, attention-deficit disorder and attention deficit disorder with hyperactivity were used, which more closely resemble the currently used term ADHD.

Today, in the DSM-IV, ADHD is described as a disorder which is characterized by age-inappropriate levels of inattention, hyperactivity, and impulsivity. Within this diagnosis three subtypes are defined: an inattentive, hyperactive/impulsive and a combined type. However, the combined type is the most commonly diagnosed subtype. Daydreaming, distractibility, and difficulty focusing on a task for a prolonged period are all manifestations of the inattention component of ADHD, and the hyperactivity component is manifested as fidgeting, excessive talking, and restlessness (Biederman, 2005). Furthermore, individuals with ADHD often have a compromised ability to suppress inappropriate behaviours in favour of appropriate ones, and seem to be less sensitive to punishment and reward (Masunami *et al.*, 2009). These symptoms make it difficult to form and maintain personal relationships, and often lead to accidents of all types. In addition, academic and social skill deficits are associated with childhood ADHD (Biederman, 2005).

There are several theories about the causation of these symptoms. In research the most prominent one is based upon executive function deficits (Barkley, 1997). This theory rose

from the observation that individuals with ADHD show deficits which are similar to deficits of patients with frontal lobe lesions (Pontius, 1973). Executive function is a term to describe a collection of higher order cognitive control processes that guide goal directed behaviour (Barkley, 1997). These processes include the ability to temporarily maintain and manipulate information needed for generating upcoming action (working memory) and the ability to inhibit inappropriate action (response inhibition). Individuals with ADHD have been shown to have deficits in both domains (Willcutt *et al.*, 2005). These properties are nowadays often investigated in research on ADHD.

Prevalence/persistence

Worldwide, ADHD is a highly prevalent disorder. However, prevalence estimates differ between geographic regions, most likely caused by methodological differences in epidemiological studies (Polanczyk *et al.*, 2007). One metaregression analysis study by Polanczyk and colleagues (2007) estimated the worldwide prevalence at about 5%. Another study performed by Faraone and colleagues (2003) found prevalence estimates between approximately 5 and 15% (Faraone *et al.*, 2003). In addition to regional differences, there are differences in prevalence between the genders and different age groups. Males are much more likely to be affected by ADHD with prevalence estimates of around 10% for males, with approximately 4% of females affected by the disorder (Polanczyk *et al.*, 2007). Current estimates of the prevalence of ADHD in children lies around 7%, while this estimate in adolescents lies around 3% (Polanczyk *et al.*, 2007). Although ADHD was previously considered a childhood disorder, now it is commonly recognized that ADHD can persists into adulthood, however this is not always the case. It is estimated that this occurs in about 30% of children diagnosed (Klein & Mannuzza, 1991; Lara *et al.*, 2009). There are some predictors for the persistence of ADHD into adulthood, including family history of ADHD, psychiatric comorbidity, and psychosocial adversity (Biederman *et al.*, 1995).

Treatment

The most common treatment methods for ADHD are behavioural therapies and medication or a combination of both. A study of Jensen and colleagues (2005), showed that a combination of medical and behavioural treatment gives the best results on short term. However, another study investigating the effectiveness of ADHD treatment did not find an additional effect of behavioural therapy in addition to pharmacological treatment (MTA Cooperative Group, 1999). Nonetheless, they report that the behavioural therapy may have provided advantages for non-ADHD symptoms and positive functioning outcomes (MTA Cooperative Group, 1999). A follow up of this study showed that in the long run, the outcome is not affected by which treatment is used (Molina *et al.*, 2009; MTA Cooperative Group, 1999). Thus, while these treatments can be very useful in the management of the disorder, they can not cure a patient from ADHD.

The most commonly prescribed medicines for ADHD are stimulants, which increase the extracellular concentrations of dopamine and/or noradrenaline (MTA Cooperative Group, 1999). One such drug is methylphenidate, a noradrenaline and dopamine reuptake inhibitor. Currently, this drug is seen as the most effective one (Heal *et al.*, 2009). However, there are also non-stimulant drugs prescribed for the management of ADHD symptoms, for instance Atomoxetine which is a specific noradrenaline re-uptake inhibitor (Heal *et al.*, 2009).

Comorbidity

ADHD has a very high comorbidity rate with other psychiatric disorders. One study reported that 70% of preschool children with ADHD had a comorbid (behavioural) disorder (Posner *et al.*, 2007). ADHD in children is often comorbid with oppositional-defiant disorder (ODD), conduct disorder (CD), anxiety, mood disorders, and learning disorders (Biederman, 2005). However, girls are less likely to have comorbidity with disruptive behaviour (Biederman *et al.*, 2002). Therefore, the behaviour of girls with ADHD is often not considered to be problematic. This could explain why less girls than boys are diagnosed with ADHD, because they are less likely to be referred to a psychiatrist (Biederman, 2005). In adults with ADHD comorbidity

mostly consists of anxiety disorders, but also antisocial and mood disorders are common (Shekim *et al.*, 1990). In addition, alcohol and drug dependency are more common among ADHD patients than the general population (Shekim *et al.*, 1990). Where anxiety and mood disorders are more common in females with ADHD, and antisocial disorders and alcohol and drug dependency are more common in males with ADHD (Biederman *et al.*, 2004).

Neurobiology

Structural brain imaging studies have shown that people diagnosed with ADHD have a smaller overall brain volume, and a wide variety of specific brain regions have been shown to be different from controls (Castellanos *et al.*, 2002; Durston *et al.*, 2004; Brieber *et al.*, 2007). These specific brain regions include the fronto-striatal areas, which could be predicted from the often found deficits in cognitive control in individuals with ADHD (Biederman, 2005). In addition to these regions also areas in the cingulate cortex, occipital, parietal, and temporal cortex, and the medial temporal lobe have been shown to be different from controls (Brieber *et al.*, 2007). Thus it seems that a large proportion of the brain is affected in ADHD. However, there are brain regions which are more affected than others. A very interesting structural MRI study of Shaw and colleagues (2007a) has now shown that these differences are reflected in a delay in brain development in ADHD patients. In this study it was also shown that this delay in development was most prominent in the middle prefrontal cortex. Apart from the cerebrum the cerebellum also seems to be reduced in size in individuals with ADHD (Castellanos *et al.*, 2002). Furthermore, the difference in the cerebellum is the only region that shows differences between ADHD patients and their non affected siblings (Durston et al., 2004).

Brain functioning studies in ADHD often use a "Go/NoGo" task or a stop signal task. Both are a measures for response inhibition, which, as mentioned earlier, is often disturbed in ADHD patients. In these studies, a decreased activation of the prefrontal cortex is often observed (Rubia *et al.*, 2005; Rubia *et al.*, 2001), however this effect is also seen in unaffected siblings of ADHD patients (Durston & Casey, 2006). This suggests that in true ADHD both the prefrontal cortex and cerebellum should be different from normal.

Genetics

Twin studies have found a relatively high heritability factor with an average of about 75-80% (Albayrak *et al.*, 2008; Faraone *et al.*, 2005). The currently most promising candidate genes that are involved in ADHD are all related to monoamine systems, such as dopamine and noradrenaline. This is in accordance with the beneficial effects of catecholamine reuptake inhibitors such as methylphenidate (Durston *et al.*, 2009). Several genes have been associated with the changes in brain volume and function mentioned above, such as the DAT1 and DRD4 gene which are both related to dopamine (Durston *et al.*, 2005). The DAT1 gene has been associated with smaller volumes of the caudate nucleus (Durston *et al.*, 2005) and the DRD4 gene with smaller volumes of the prefrontal cortex and orbitofrontal cortex (Shaw *et al.*, 2007b; Durston *et al.*, 2005). However, none of the genes found until now have a very great impact by themselves. It is has been suggested that instead of one gene, only a combination of risk genes can play a causative role in the disorder (Durston *et al.*, 2009).

Environmental factors

As mentioned earlier ADHD has a heritable factor of 77%, thus 33% of the development of ADHD is accounted for by other factors, for instance in the environment. During early life the environment can have a great impact on the development of an individual, and adverse environmental circumstances can therefore induce serious changes, affecting the individual the rest of his life. Thus it is reasonable to think environmental factors that have the greatest impact on the development of ADHD occur in early life. It is indeed the case that most environmental factors associated with ADHD are adverse circumstances early in life, prenatally and shortly after birth. Prenatal influences associated with ADHD include prenatal maternal stress (Talge *et al.*, 2007; Grizenko *et al.*, 2008), maternal alcohol use (Mick *et al.*, 2002; Pineda *et al.*, 2007), maternal smoking (Mick *et al.*, 2002; Pineda *et al.*, 2007; Gatzke-Kopp & Beauchaine, 2007), second hand smoke exposure (Gatzke-Kopp & Beauchaine, 2007), and even pre-pregnancy obesity (Rodriguez, 2009). Other ADHD associated

influences include health complications in early life, such as problems during delivery, low birth weight, traumatic brain injury, childhood seizures, and substance exposure after birth (Pineda *et al.*, 2007). In addition, there are psychosocial adversities that seem to be risk factors for ADHD development, such as low social class, parental psychopathology, and chronic family conflict (Biederman *et al.*, 2002). Although there are so many environmental risk factors, it is very likely that an individual should already be genetically predisposed to be affected by the disorder, since ADHD has such a high heritability factor.

Two of the most interesting environmental risk factors are maternal smoking and maternal alcohol use, because these risk factors could be easily prevented, and thereby ultimately decrease the prevalence of ADHD. Furthermore, both nicotine and alcohol have an effect on monoamine neurotransmitter systems.

Prenatal smoke exposure

A large number of pregnant woman smoke, with some studies reporting up to 25% (Arria *et al.*, 2006; Beck *et al.*, 2002). Nicotine is a substance that crosses the placenta and gets concentrated in the foetal tissue. Once nicotine reaches the foetus it directly affects serotonin and dopaminergic systems, brain cell growth, and DNA and RNA synthesis in the brain (Wakschlag *et al.*, 1997). In addition, in a rat study it was found that there were more apoptotic cells in the hind-, fore-, and midbrain of embryos exposed to nicotine (Roy *et al.* 1998) This study also found that prenatal exposure to nicotine at levels that were insufficient to cause general dysmorphogenensis caused damage to the developing neuroepithelium (Roy *et al.*, 1998). Apart from these direct effects, prenatal nicotine exposure is associated with lower birth weight, because of placenta pathology caused by smoking, and ADHD is also associated with lower birth weight (Jauniaux & Burton, 2007).

Thus, levels of exposure to nicotine that do not affect the viability of the foetus may result in disruption of normal brain development that could lead to behavioural and attentional problems in childhood and adolescence (Biederman *et al.*, 2009).

There are several studies indicating that the behaviour of newborns is directly affected by the smoking habits of their mother during pregnancy, including higher irritability, decreased attention, decreased response to inanimate auditory stimuli, greater need for handling, and a lower score on self regulation (Stroud *et al.*, 2009; Mansi *et al.*, 2007) . Some of these behavioural symptoms such as higher irritability and decreased attention can be viewed as very early symptoms of ADHD. However, it is not determined if these symptoms are indeed the early signs of ADHD, as a clear diagnosis can not be established before the child gets older. Nevertheless, it has been found that children with ADHD are more likely to have been exposed to prenatal nicotine (Gatzke-Kopp & Beauchaine, 2007; Mick *et al.*, 2002; Pineda *et al.*, 2007), as mentioned earlier. Although these findings seem to be straightforward and show clear evidence that prenatal nicotine exposure is a risk factor for the development of ADHD, it should be taken into account that ADHD patients are more likely to smoke, and thus more likely to smoke during pregnancy. Together with the fact that ADHD has a very high heritability factor, this would confound the findings in studies that investigate the relation between smoking during pregnancy and the development of ADHD because then genetic factors should ideally be corrected for. One elegant study by Thapar and colleagues (2009) investigated this by using a design in which two groups of offspring were compared, one in which the offspring was related and one in which the offspring was not related to the woman who underwent the pregnancy. This was done by using offspring conceived with assisted reproductive technologies, in which the offspring was unrelated to the pregnant woman because of oocyte donations, embryo donations, or because of gestational surrogates. The offspring of related mothers were also conceived by using assisted reproductive technologies. This study did not show a relationship between prenatal nicotine exposure and ADHD, thus findings in other studies of a relationship between prenatal nicotine exposure and ADHD may have been confounded by genetic factors (Thapar *et al.*, 2009). Therefore, more research is needed to disentangle the environmental and genetic effects of prenatal nicotine exposure on ADHD development.

Prenatal alcohol exposure

Alcohol can also pass the placenta, and can have a direct effect on the foetus, just as nicotine. But it can also have an indirect effect by disturbing the interactions between mother and foetus (Weinberg *et al.*, 2008). Prenatal alcohol exposure is associated with neurobehavioral deficits (Streissguth *et al.*, 1989). The core symptoms of ADHD, inattention and hyperactivity, are commonly seen in all forms of foetal alcohol spectrum disorders (Kodituwakku, 2007). In addition, there is some evidence that an interaction is present between the ADHD risk gene DAT1 and foetal alcohol exposure (Brookes *et al.*, 2006). Because of this relationship between an ADHD risk gene and prenatal alcohol exposure, it is worthwhile to further investigate this subject. However, there are some issues that need to be taken into account when investigating the neurobehavioural symptoms in relation to foetal alcohol exposure. For instance, prenatal alcohol exposure has different effects on males and females (Weinberg *et al.*, 2008). In addition, it could be that just as for nicotine, genetic factors that both increase the likelihood of alcohol consumption as well as ADHD, confound findings. Thus for both prenatal nicotine and alcohol exposure more research is needed to disentangle the various factors that could lead to ADHD.

Question

The question that I want to answer in this thesis is; what are the pre and perinatal influences that play a role in the development of ADHD. Within this subject I would like to concentrate on prenatal nicotine and alcohol exposure, and the consequences on brain development. In addition, I would like to discuss the different pathways on which these substances can exert their influence on the development of ADHD. In order to do this, both a literature study and a pilot study on MRI and self reported data are performed.

Methods MRI study

Participants

A total of 25 girls and 88 boys aged 6 to 12 years participated in this study, of which 38 were diagnosed with ADHD, and 75 controls. Subjects were recruited as described in a previous paper by Durston and colleagues (2004). Within the ADHD group 6 participants had the inattentive subtype, 8 participants had the hyperactive/impulsive subtype, and 24 had the combined subtype. Within the control group 22 participants were prenatally exposed to alcohol, and 7 prenatally exposed to maternal smoking. Within the ADHD group 6 participants were prenatally exposed to alcohol, and 5 were prenatally exposed to maternal smoking. Of the controls prenatally exposed to alcohol 2 were also exposed to prenatal smoke exposure, none of the ADHD participants were prenatally exposed to both substances. See Table 1 for measures on age, IQ, father's educational level, and mother's educational level per group.

	Controls Mean, (SD), range	ADHD Mean, (SD), range
Age (years)	9.3, (1.46), 6.28-11.91	9.7, (1.66), 6.55-12.00
IQ	114.09, (16.24), 75-145	103.92, (18.24), 71-156
Fathers educational level (in years of education)	13.50, (2.43), 6-16	12.9, (2.76), 6-16
Mothers educational level (in years of education)	13.52, (2.26), 10-16	11.50, (3.44), 0-15 *

Table 1 difference between controls and ADHD * $p < .05$

Magnetic Resonance Imaging data acquisition and processing

Standard T1 weighted fast field echo (FFE) scans with 130 to 150 1.5-mm (older scans, before 2005) or 160-180 1.2mm (newer scans) contiguous coronal slices of the whole head

(echo time [TE] = 4.6 ms, repetition time [TR] = 30 ms, flip angle 30°, field of view [FOV] 256 mm, in-plane voxel size 1 mm × 1 mm) were acquired on 1.5T Philips scanners in University Medical Centre Utrecht. T1-weighted 3D-FFE scans were used for brain analyses. An additional T2-weighted dual echo turbo spin-echo scan with 65 to 75 3.0-mm contiguous coronal slices (TE1 = 14 ms, TE2 = 80 ms, TR 6,350 ms, flip angle 90°, FOV 256 mm, in-plane voxel size 1 mm × 1 mm) or a single shot EPI scan (sensitivity-encoding [SENSE] factor 2.5; flip angle 90°; 60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; FOV 240 mm; TE 78 msec) and MTR scan (60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; FOV 240 mm; flip angle 8°; TE 4.5 msec; TR 37.5 msec) were used to define intracranial volume (Durston *et al.*, 2004; Langen *et al.*, 2009). Total brain, lateral ventricles, third ventricle, and cerebellum were measured automatically using histogram analysis and a series of mathematical morphological operators (Schnack *et al.*, 2001b; Durston *et al.*, 2004). Segmentations were checked visually and edited if necessary. Maps of cerebral gray and white matter were obtained using histogram analysis (Schnack *et al.*, 2001a). Some scans were not useful to measure gray and white matter volume, because of motion, but still useful to determine the other volumes. From these scans the useful data were still used.

Questionnaire

As a part of an extensive self-report demographic questionnaire, questions about pregnancy and delivery were answered by parents of subjects included in the study. In addition, there were questions about smoking and alcohol consumption of the mother during pregnancy. These latter questions were both separated in two parts; did you smoke/drink during pregnancy, and if so how many per day, per week, or per month. The main data used in this study were the answers on smoking and alcohol consumption of the mother recalculated to amount exposure per day.

Statistical Analysis

Statistical analyses were performed using SPPS 15.0. Volume measures of the intracranial volume, total brain, cerebrum, cerebral grey matter, cerebral white matter, cerebellum, lateral ventricles, and third ventricle were included in the statistical analyses. For the lateral and third ventricle a log transformation was performed to normalise data. Because age and gender have a great influence on brain volume, and because of suboptimal matching between groups, effects of age and gender were filtered out by regressing these factors out of the data first, and saving unstandardised residuals. These unstandardised residuals were saved after regression analysis over all data (ADHD and control together) of all brain volumes separately on age and gender. Both the unstandardised residuals and raw data were then correlated with the relative amount of smoking and drinking separately. These analyses were performed for the entire group and for ADHD patients and controls separately. When significant correlations were revealed further explorative analyses were performed using Mann-Whitney U tests. In these analyses the ADHD and control groups were split up in an exposed and non-exposed group to analyse differences within the ADHD and control group. In addition, social-economic status was compared using a Mann-Whitney U test for smokers versus non-smokers, and drinkers versus non-drinkers.

Methods literature review

Original research papers were retrieved through PubMed. Search terms were 'Attention deficit and hyperactivity disorder'; 'ADHD' and 'prenatal influences'; 'prenatal alcohol exposure'; 'prenatal nicotine exposure' and variations of these terms. From the search results most relevant studies were extracted and results from these studies described in this thesis.

Results MRI Study

Educational level

The Mann-Whitney U test for comparison of educational level between the mothers who smoked and did not smoke during pregnancy, revealed a trend of lower educational level for mothers who did smoke (U=388.5, z=-1.903, p=0.57), no difference in educational level of the fathers was found. The Mann-Whitney U test for comparison of educational levels of the parents between drinkers and non-drinkers revealed a higher educational level for the fathers (U=676.5, z=-3.085, p<.01). Thus it should be taken into account that the groups do not match on social economic status and that our results could be confounded by these differences.
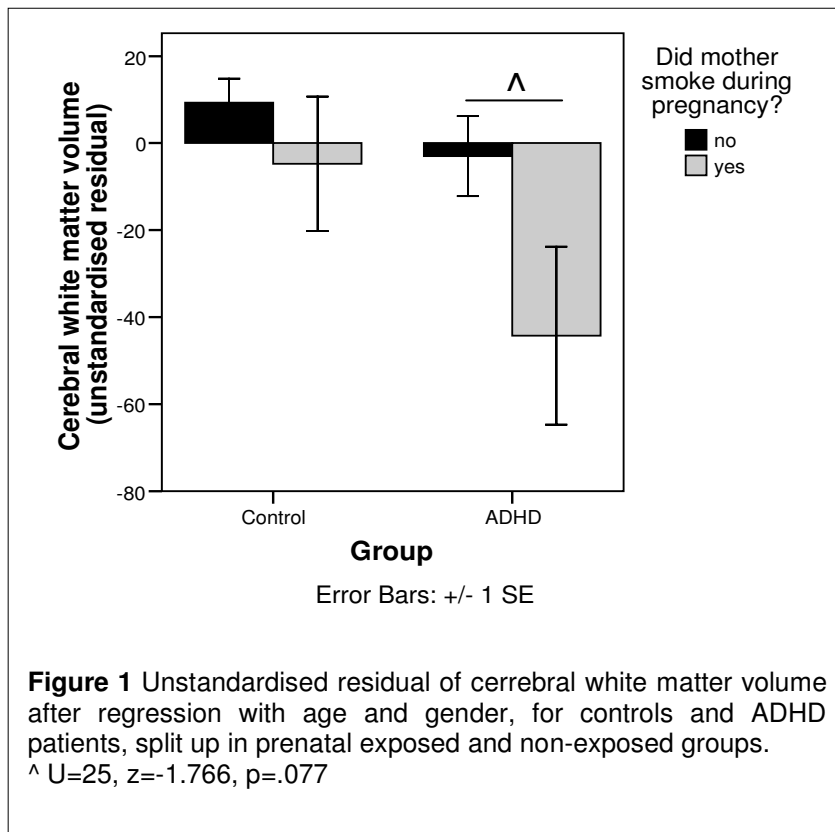
prenatal smoke exposure

Correlations

A significant correlation between prenatal smoke exposure and cerebral white matter (r=-.21, n=107, p<.05) was found and a trend for total brain volume (r=-.18, n=113, p=.063) and total cerebral volume (r=-.18, n=113, p=.059) when analysing the whole group at once, using the unstandardised residuals. A trend for a correlation between prenatal smoke exposure and cerebral white matter (r=.327, n=34, p=.059) was also found when only data of ADHD patients were included in the analysis on the unstandardised residuals, but not in controls. None of the other measures showed a significant correlation, and no significant differences were found within controls. When analysing the raw data of the whole group only a very slight trend was found for a correlation between cerebral white matter and prenatal smoke exposure (r=-.164, n=107, p=.092). However, as mentioned earlier, the raw data is confounded by age and gender differences.

Mann-Whitney U tests

With explorative Mann-Whitney U tests it was investigated whether there were differences between controls and ADHD patients when groups were split into smokers and non-smokers. Significant differences between non-smoking controls and non-smoking ADHD patients were found for total brain volume (U=374.00, z=-.951, p<.05), and cerebral volume (U=372, z=-2.033, p<.05), none of the other measures were significant in this analyses. No significant differences within the control or ADHD group were found for prenatal smoke exposure versus no prenatal smoke exposure. However, a trend was found for a lower cerebral white matter volume in the ADHD group with prenatal smoke exposure compared to ADHD patients without prenatal smoke exposure (U=25, z=-1.766, p=.077, Figure 1).

Figure 1 Unstandardised residual of cerrebral white matter volume after regression with age and gender, for controls and ADHD patients, split up in prenatal exposed and non-exposed groups.
^ U=25, z=-1.766, p=.077

prenatal alcohol exposure

Correlations

Analysis of the unstandardised residuals of the whole group revealed a trend for correlation between prenatal alcohol exposure and cerebral white matter (r=-.189, n=107, p=.051).
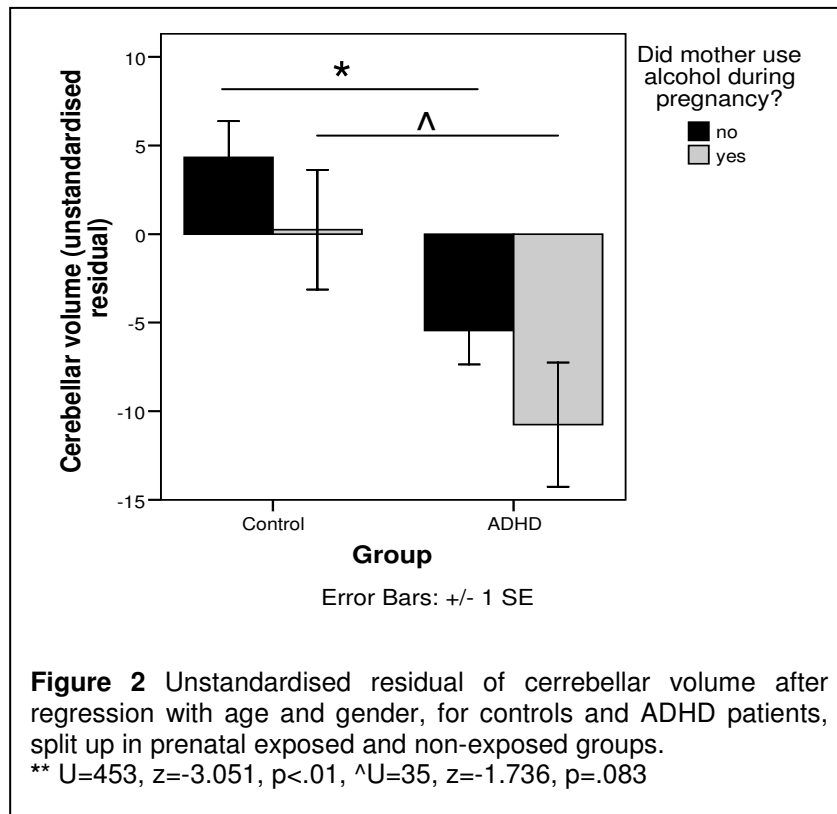
When groups were analysed separately, a significant correlation between prenatal alcohol exposure and total cerebral volume (r=-.230, n=75, p<.05) and cerebral white matter (r=-.293, n=73, p<.05) were found in the control group. Furthermore, trends were found for a negative correlation between prenatal alcohol exposure and intracranial volume (r=-.205, n=74, p=.080), and total brain volume (r=-.222, n=75, p=.056) for controls and log of 3rd ventricle (r=-.296, n=38, p=.072) and a very slight trend for cerebellar volume (r=-.273, n=38, p=.098) in the ADHD group.
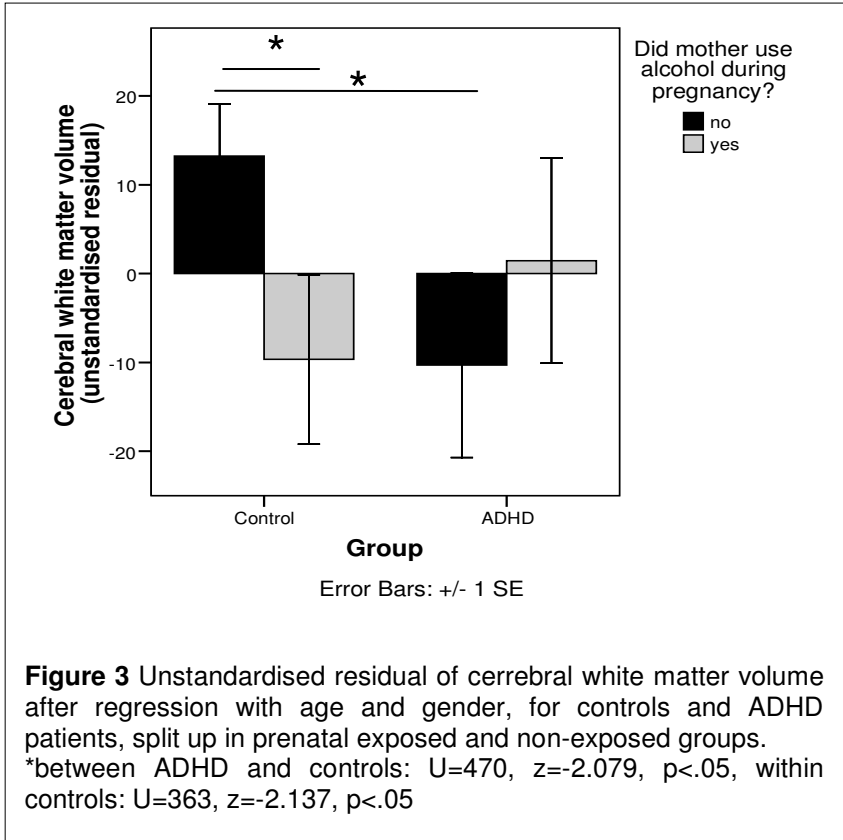
When analysing raw data of all subjects together, significant negative correlations between prenatal alcohol exposure and intracranial volume (r=-.197, n=103 p<.05), total brain volume (r=.-185, n=113, p<.05) and cerebral white matter (r=-.242, n=107, p<.05) were revealed. Furthermore, these analyses showed a trend for total cerebral volume (r=-.182, n=113, p=.053). When control and ADHD data was analysed separately a significant correlation was revealed between prenatal alcohol exposure and intracranial volume (r=-.263, n=74, p<.05), total brain volume (r=-.283, n=75, p<.05), cerebral volume (r=-.290, n=75, p<.05) and cerebral white matter volume (r=-.358, n=73, p<.01) in controls. Furthermore there was a similar trend for the log of the lateral ventricle volume (r=-.205, n=75, p=.077) in the controls, and in the ADHD group (r=-.289, n=38, p=.070)

Mann-Whitney U tests

With explorative Mann-Whitney U tests it was investigated whether there were differences between controls and ADHD patients if groups were split into prenatally exposed and non-exposed to alcohol. Significant differences between non-exposed controls and non-exposed ADHD patients were found for total brain volume (U=495, z=-2.744, p<.01) cerebral volume (U=505, z=-2.647, p<.01), cerebellar volume (U=453, z=-2.144, p<.01, Figure 2), cerebral grey matter (U=464, z=-2.079, p<.05), cerebral white matter volume (U=470, z=-2.079, p<.05, Figure 3), and the log of 3rd ventricle volume (U=565, z=-2.070, p<.05). Furthermore a trend was found for intracranial volume (U=431, z=-1.816, p=.069). Between exposed controls and ADHD patients a trend was found for cerebellar volume (U=35, z=-1.737,

p=.083, Figure 2), none of the other measures differed between exposed controls and exposed ADHD patients. Furthermore a significant difference was found within controls between prenatally exposed and non-exposed groups for cerebral white matter (U=363, z=-2.137, p<.05, Figure 3), no other measures were different within ADHD and control groups.

Figure 2 Unstandardised residual of cerrebellar volume after regression with age and gender, for controls and ADHD patients, split up in prenatal exposed and non-exposed groups.
** U=453, z=-3.051, p<.01, ^U=35, z=-1.736, p=.083

Figure 3 Unstandardised residual of cerrebral white matter volume after regression with age and gender, for controls and ADHD patients, split up in prenatal exposed and non-exposed groups.
*between ADHD and controls: U=470, z=-2.079, p<.05, within controls: U=363, z=-2.137, p<.05

Discussion

Literature review

As mentioned in the introduction there are several studies that suggest that prenatal alcohol and/or nicotine exposure can increase the likelihood of the development of ADHD. However, studies on this subject all are limited by from confounding factors, such as social economic status and heritability of ADHD. In addition, the results of studies concerning this subject are often based upon retrospective questionnaires, making it difficult to determine the exact amount of exposure. In this section findings of earlier studies on the relation between prenatal alcohol and nicotine exposure and ADHD are described and discussed.

Prenatal nicotine exposure

Relationship between ADHD and prenatal smoke exposure

Several studies report an increased risk for ADHD with prenatal smoke exposure, but the increase the incidence of ADHD when prenatally exposed to maternal smoking differs across studies. For instance, Biederman and colleagues (2009) found that maternal smoking during pregnancy increased the likelihood of ADHD by a factor of 2.5. Another study conducted by Obel and colleagues (Obel *et al.*, 2009) found a 2.0 times higher risk for ADHD in children which were prenatally exposed to maternal smoking, however, only in a subgroup of which they did not have complete data sets (missing either teachers or parents information). In the group of which they had a complete data set they only found a 1.3 fold increase which was not significant. Therefore this data should be interpreted with care. Another study investigating prenatal influences on ADHD even found a risk increase with an odds ratio as high as 8.9. In this study subjects were included with exposure of 4 cigarettes or more per day (Pineda *et al.*, 2007). All these studies adjusted for confounding factors, such as age, gender, social class, and maternal use of alcohol during pregnancy. However, in the studies performed by Biederman and colleagues (2009) and Pineda and colleagues (2007),

psychiatric assessment was done using DSM-III-R criteria, while in the study by Obel (2009) the assessment of symptoms was done by using questionnaires about hyperactivity and inattention symptoms, filled out by teachers and parents. Furthermore, in the study of Obel and colleagues, 3 population based pregnancy cohorts were used to recruit subjects, while the study of Biederman and colleagues recruited subjects with and without ADHD from a longitudinal case control family study. Thus these studies had fairly different methodologies, both for patient recruitment and symptom assessment, which can explain why these studies reported such different numbers. Nevertheless, both these studies clearly indicate a relation between prenatal smoke exposure and an increased risk for the development of ADHD.

Structural brain imaging

As mentioned in the introduction nicotine crosses the placenta and gets concentrated in foetal tissue, where it affects brain cell growth, and DNA and RNA synthesis in the brain (Wakschlag *et al.*, 1997). In addition, nicotine can increase the amount of apoptotic cells, and cause damage to the neuroepithelium in the developing brain (Roy et al., 1998). These damages in early life can affect the development of the brain for a life time. This is shown in an MRI study were it was found that children with prenatal smoke exposure had a smaller head circumference, less cerebral grey matter, and a decrease in the total brain volume (Rivkin *et al.*, 2008). Since ADHD patients have less cerebral grey matter on average (Brieber *et al.*, 2007; Durston *et al.*, 2009; Giedd *et al.*, 2001; Castellanos *et al.*, 2002), a possible link between prenatal nicotine exposure and ADHD is easily made.

Genotype interactions

Some very interesting findings about gene environment interaction related to ADHD are the interactions between the DAT1, DRD4 and DRD5 genes and prenatal smoke exposure (Neuman *et al.*, 2007; Kahn *et al.*, 2003; Becker *et al.*, 2008). The DAT1 gene is of particular interest in research concerning ADHD because it is a gene encoding for the dopamine transporter which is the site of action of psychostimulants (Lim *et al.*, 2006). Three studies

investigating this gene in relation to ADHD found that the risk allele (10 repeat allele of a 40-basepare variable number tandem repeat polymorphism) of this gene without prenatal smoke exposure did not increase the risk for ADHD (Neuman *et al.*, 2007; Kahn *et al.*, 2003; Becker *et al.*, 2008). However, when these risk alleles were present combined with prenatal smoke exposure the risk of ADHD increased significantly compared to prenatal smoke exposure or the risk allele on its own (Neuman *et al.*, 2007; Kahn *et al.*, 2003; Becker *et al.*, 2008). One of the studies investigating the DAT1 gene environment interaction, also investigated the DRD4 gene for an interaction with prenatal smoke exposure. The DRD4 gene is, like the DAT1 gene, involved in the dopamine system. It encodes for the dopaminergic receptor. Risk alleles of this gene were found to have similar interactions with prenatal smoke exposure as the DAT1 risk allele does (Neuman *et al.*, 2007). However, another study found the DRD4 risk allele not to have an interaction with smoking but with birth weight, and low birth weight is also known to be a risk factor for ADHD (Langley *et al.*, 2008). Therefore, it is important to include measures of birth weight when doing research on ADHD in relation with prenatal smoke exposure. The DRD5 gene is also encoding for the dopaminergic receptor, and a microsatellite marker in this gene was found to interact with prenatal smoke exposure increasing the risk for ADHD (Langley *et al.*, 2008). These gene environment interactions emphasise that ADHD is a multifactorial disorder, and is not caused by just one risk factor.

Contradictory findings

There are some studies that suggest that prenatal nicotine exposure does not have any influence on the development of ADHD. One of those studies is already described in the introduction (Thapar *et al.*, 2009). In this study the subjects were children of mothers who were unrelated to each other (due to conception through assisted reproductive technologies). In this study no relationship between prenatal maternal smoking and ADHD symptoms in later life were found (Thapar *et al.*, 2009). Because this study is based on data from children of unrelated mothers, this study filters out a large amount of genetic confounding factors, for the reason that smoking is often used as a kind of self medication and ADHD has a high

heritability factor. In this study therefore, it is less likely that prenatal smoke exposure and risk genes are co-occurring in the same individual. When considering the findings of this study combined with the findings that the DRD4 and DAT1 gene can only increase the risk for ADHD when there is also prenatal smoke exposure (Neuman *et al.*, 2007), one would argue for a definite gene environment interaction and not a causative role for either genes or environment separately. This would implicate that the highest risk factor for the development of ADHD in an individual is having a parent with ADHD, since this both increases the risk for a risk gene, and the risk for a smoking or alcohol using parent during pregnancy.

Prenatal alcohol exposure

Relationship between prenatal alcohol exposure and ADHD

Results from studies investigating the relationship between prenatal alcohol exposure and ADHD are less consistent than results on prenatal nicotine exposure. There are some studies confirming a relationship between prenatal alcohol exposure and ADHD. One study even reported a highly significant (p=.0008) odds ratio of 14.1, which was adjusted for gender, child's age, and school grades using an alcohol exposure criterion of "drunkenness during the first 2 months" (Pineda *et al.*, 2007). Another study confirming a relationship between prenatal alcohol exposure and ADHD, showed a frequency distribution of ADHD by different levels of prenatal alcohol exposure (Bhatara *et al.*, 2006). In this study, alcohol exposure was divided into four groups; no risk (no exposure), unknown, some risk (low exposure), and high risk (high exposure). In the high risk group over 49% were diagnosed with ADHD in contrast to 0.8% of the subjects in the no risk group, with the unknown and some risk group having a frequency of respectively 14.9 and 30.3% (Bhatara *et al.*, 2006), thus indicating a dose response effect. A third study reported that ADHD patients were 2.5 times more likely to be exposed to alcohol than controls, after adjustment for familial psychopathology, social adversity, comorbid conduct disorder (Mick *et al.*, 2002). However, not all studies confirm these findings. Rodriguez and colleagues (2009) did not find an effect of prenatal alcohol exposure, not with an unadjusted simple raw data model, nor with a

model adjusted for smoking, social adversity, birth weight and gestational age. In addition, another study found an increased risk for ADHD when prenatally exposed to alcohol but this was found to be due to familial risk factors (Hill *et al.*, 2000). Thus, the influence of prenatal alcohol exposure on ADHD remains unclear, and findings confirming a relationship may be confounded by genetic confounds. However, it is worth noting that some components of the behavioural phenotype of foetal alcohol syndrome disorders (FASD) are similar to ADHD symptoms (Bertrand *et al.*, 2005), therefore closer investigation of the overlap of FASD and ADHD could give more insight into the subject.

Structural brain imaging

Although many studies have been done on the neurobiological changes when foetuses were exposed to such a high amount of alcohol that it caused foetal alcohol spectrum disorders (FASD), not many studies have been done on the effect of lower doses of alcohol that could probably cause less apparent neurobiological changes. However, studies done on FASD could give an indication what kind of changes are induced by moderate prenatal alcohol exposure. Structural brain imaging studies on FASD consistently report global decreases in brain volume, and reductions of frontal, temporal, parietal, and (to a lesser degree) occipital lobes in children with FASD in comparison with controls (Norman *et al.*, 2009). More locally focused analyses of structural brain imaging studies, have shown volume reductions of the corpus callosum (Riley *et al.*, 1995), cerebellum (Mattson *et al.*, 1992; Autti-Ramo *et al.*, 2002), and basal ganglia (Mattson *et al.*, 1992; Archibald *et al.*, 2001). Volume reductions of the corpus callosum and cerebellum have also been shown in non-FASD but prenatally exposed children (Autti-Ramo *et al.*, 2002; Riley *et al.*, 1995). In another study not related to foetal alcohol spectrum disorders, it was found that, as with prenatal nicotine exposure, prenatal alcohol exposure is correlated with a smaller head circumference, less white matter, and smaller total brain volume (Rivkin *et al.*, 2008). A very interesting finding is that individuals with high prenatal alcohol exposure have relatively more gray matter and less white matter in comparison to controls (Sowell *et al.*, 2001), while ADHD is associated with a

lower than normal grey matter volume (Durston *et al.*, 2004). This could suggest that prenatal alcohol exposure is balancing out signs of ADHD with regard to the balance between white and grey matter. In contrast, the smaller cerebellum volume in prenatally alcohol exposed individuals would suggest an amplification of ADHD related neurobiological abnormalities since this is also an important affected region in ADHD (Durston *et al.*, 2004; Castellanos *et al.*, 2002). Overall not much is known about the structural brain changes relating to moderate prenatal alcohol exposure but much can be learned from studies relating to FASD, which could give more insight into the relationship between ADHD and prenatal alcohol exposure.

Genotype interactions

An interaction between genotype of specific risk genes and prenatal alcohol exposure has been found to increase the risk for ADHD. The gene with which this interaction with prenatal alcohol exposure is found is the DAT1 gene (Brookes *et al.*, 2006). Thus, the same gene that has been shown to increase the risk of ADHD in interaction with prenatal maternal smoke exposure interacts with prenatal alcohol exposure. Furthermore, it is the same risk allele that increases the risk of ADHD in combination with prenatal alcohol exposure as with prenatal smoke exposure (Brookes *et al.*, 2006). However, these findings have not been confirmed by other studies so far. In contrast, a study by Langley and colleagues (2008), who did find an interaction effect with smoking for the DRD5 (but not for the DAT1 or DRD4 gene), did not find any interaction effects of prenatal alcohol exposure with any of the genes they tested (DAT1, DRD4, DRD5, and 5HTT). No other studies on gene/prenatal alcohol exposure were found in the literature search, thus evidence for any interaction between genotype and prenatal alcohol exposure is still weak. A possible role for a genetic factor in the modulatory effects of prenatal alcohol exposure can not yet be rejected.

MRI study

Prenatal smoke exposure

In the exploratory data analyses of the current study, volumetric measures of several brain regions showed to be correlated with prenatal smoke exposure. To be specific, cerebral white matter volume was found to be smaller in prenatally exposed individuals when analysing the whole group. When analysing only data of ADHD patients a trend was found for the same measure. This trend was also apparent when non-exposed ADHD patients were compared to exposed ADHD patients using a Mann-Whitney U test. Although this statistical test only revealed trends this indicates that maternal smoking during pregnancy could have a great influence on brain development, since we had only a small data set, with suboptimal matching of the diagnostic groups. That this trend was only found in ADHD individuals and not in controls could indicate that there is some interaction with other factors which are only present in ADHD patients, such as a specific genotype. The finding that prenatal smoke exposure is related to cerebral white matter has not been reported previously. We did not find a decrease in cerebral grey matter in relation to prenatal smoke exposure which has been found previously (Rivkin *et al.*, 2008). However, we did find evidence of smaller total brain and cerebral volume in children prenatally exposed to maternal smoke, although probably due to smaller white matter volumes, this corresponds to previously found differences between ADHD patients and controls in earlier studies (Brieber *et al.*, 2007; Durston *et al.*, 2004; Shaw *et al.*, 2009; Durston *et al.*, 2009).

Prenatal alcohol exposure

Although previous studies showed a decrease in cerrebellar volume (Autti-Ramo *et al.*, 2002; Mattson *et al.*, 1992), we did not replicate these findings, although we found a very slight trend for cerebellar volume reduction in the ADHD group which was prenatally exposed. We did replicate the finding of Rivkin and colleagues (2008) who found a decrease in cerebral

white matter volume in prenatally exposed children both in analyses over the whole group as well as in the control group separately (Rivkin *et al.*, 2008). Also findings of overall brain volume reductions in children exposed to prenatally alcohol were replicated in our control group. In addition to previous findings we found trends for a correlation between volume increases of the lateral ventricles and prenatal alcohol exposure, in the control group.

When directly comparing prenatally non-exposed controls to ADHD patients earlier findings of differences between these groups were confirmed, such as a smaller total brain volume, cerebral volume, cerebral grey and white matter in the ADHD group (Brieber *et al.*, 2007; Durston *et al.*, 2004; Brieber *et al.*, 2007; Shaw *et al.*, 2009). Prenatally exposed controls revealed to have an overall smaller cerebral white matter volume. As previously mentioned this is in accordance with earlier findings (Rivkin *et al.*, 2008).

Limitations

Because of the exploratory nature of this study, it was not possible to match controls and ADHD patients properly and to get equal group sizes. This reduces statistical strength significantly. For instance, in our analyses, no correction for parental educational level is conducted, which could confound or findings. Earlier studies have shown relations between ADHD and social economic status (Biederman *et al.*, 1995), and this relation is also present in our data. Thus, although our study can give an indication about the relationship between prenatal alcohol and smoke exposure and brain volume differences in children with ADHD, findings should be interpreted with care.

Conclusion

Prenatal alcohol as well as prenatal smoke exposure can have a significant impact on brain development, both in typically developing individuals and ADHD patients. For prenatal smoke exposure there is strong evidence that specific genes related to the dopamine system amplify its effect on the risk of developing ADHD. This suggests that nicotine has its effects on development via modulation of the dopamine system, and thus increases the risk of ADHD when there is genetic predisposition. In contrast, only limited evidence is currently available for the possible role of prenatal alcohol exposure on the development of ADHD. This could be a reason why there is also very little knowledge about modulating effects of genes on the effect that prenatal alcohol exposure has on brain development in ADHD. However, there is some evidence which suggests that, as with prenatal nicotine exposure, the dopamine system is probably involved in the modelatory effect of prenatal alcohol exposure. Nevertheless, the current data on the effect of prenatal alcohol exposure is not sufficient to draw the conclusion that it does or does not increase the risk for ADHD.

For prenatal maternal smoke exposure, we found a volumetric difference of white matter between exposed and non-exposed within ADHD individuals but not within controls. Although this is not previously been reported, this finding strengthens previous findings that prenatal smoke exposure could have a higher (or only have an) impact when a person is already genetically predisposed to develop ADHD. The findings in our study on prenatal alcohol exposure show that cerebellar volume is more reduced in prenatally exposed ADHD individuals than in prenatally exposed controls. This suggests that prenatal alcohol exposure has a greater impact on, and/or an additional effect on brain development when an individual is already genetically predisposed to ADHD. However, while a difference between the exposed and non-exposed control group on cerebral white matter volume was found, this was not found between the exposed and non-exposed ADHD group. This is in contrast with the idea that prenatal alcohol exposure would have a greater impact on individuals

genetically predisposed to ADHD. Thus, on basis of data presented here no conclusion can be drawn on the question whether prenatal alcohol exposure has a greater impact on individuals who are predisposed to develop ADHD, or whether prenatal alcohol exposure increases the risk for ADHD development.

Recommendations for future research

To be able to draw clear conclusions on the effect of prenatal alcohol and smoke exposure more research has to be done both for prenatal smoke and alcohol exposure. One suggestion for research on the effect of prenatal smoke exposure on the development of ADHD would be to investigate whether prenatally smoke exposed ADHD individuals with a genetic predisposition have greater brain volume differences in comparison to controls than do non-exposed ADHD individuals. Because there is limited data on moderate prenatal alcohol exposure and its influence on brain development it would be interesting to use MRI studies to investigate the changes in brain structure and function after moderate prenatal alcohol exposure. This could subsequently be used to clarify our understanding of the relationship between prenatal alcohol exposure and ADHD. Furthermore, it would be interesting to investigate whether the greatest risk factor for ADHD is to have a parent with ADHD. This would be interesting because it is known that ADHD is highly associated with self medication, both through use of alcohol and nicotine, but also other substances that could have a great impact on foetal brain development. Furthermore, ADHD has a high heritability factor. Therefore the probability of having a combination of risk genes and environmental risk factors in one individual is highly increasing when one or both of the parents have ADHD. In sum, it is suggested that future research could give more insight about prenatal risk factors and their influence, and ultimately disentangle the genetic and environmental effects on development of ADHD.

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