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Journal of Attention Disorders 2010 13: 649 originally published online 18 September 2009
DOI: 10.1177/1087054709347200

Journal of Attention Disorders
Volume 13 Number 6
May 2010 649-657
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10.1177/1087054709347200
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Is the Inattentive Subtype of ADHD Different From the Combined/Hyperactive Subtype?

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Objective: To compare the ADHD combined/hyperactive subtype (ADHD/CH) to the ADHD inattentive subtype (ADHD/I) on the level of comorbidity, treatment response, and possible etiological factors. **Method**: A total of 371 clinically referred children diagnosed with ADHD aged between 6 and 12 years are recruited for a double-blind, placebo-controlled trial of methylphenidate. Comorbidity, treatment response, and stress during pregnancy are assessed for each participant. Genotyping is done for the DAT, DRD4, and 5-HTT genes. Mothers report smoking or alcohol consumption during their pregnancy and their child's birth weight. **Results**: The ADHD/CH children show both a higher frequency of conduct disorder and good response to treatment, are exposed to more moderate stress during their mothers' pregnancy, and show a higher frequency of L/L genotype for the 5-HTT-linked polymorphic region. **Conclusion**: The significant differences found between the ADHD/CH and the ADHD/I subtypes raise the possibility that the two may be separate disorders. *(J. of Att. Dis. 2010; 13(6) 649-657)*

Keywords: *ADHD subtypes; treatment response; etiology*

Attention-deficit hyperactivity disorder (ADHD) affects up to 8% to 12 % of school-aged children (Biederman & Faraone, 2005). It presents with symptoms of inattention, hyperactivity/impulsivity or both. The consequences of this disorder are well recognized and include the inability to thrive in both school and social settings. It is estimated that 70% to 80% of the risk of developing ADHD can be attributed to genetic factors (Faraone et al., 2005). The rest may be of environmental origin, such as perinatal risk factors (Ben Amor et al., 2005).

Of the different subtypes of ADHD (predominantly inattentive [ADHD/I], hyperactive/impulsive [ADHD/H], or combined [ADHD/C]), it is estimated that ADHD/I is the most prevalent in population-based studies, followed by ADHD/C and ADHD/H, respectively (Gaub & Carlson, 1997; Wolraich, Hannah, Pinnock, Baumgaertel, & Brown, 1996). Studies have, however, found that in clinical samples, ADHD/C is the most prevalent, followed by ADHD/I and ADHD/H, respectively (Faraone, Biederman, Weber, & Russell, 1998).

In the last decade, a heated debate has emerged that questions whether ADHD/I is a separate disorder instead of a subtype of ADHD (Milich, Balentine, & Lynam, 2001). Although ADHD/C and ADHD/I patients have problems with inattention, the type of inattention suffered by both may be different.

Many comorbidities are associated with ADHD, including conduct disorder (CD; Rhee, Willcutt, Hartman, Pennington, & DeFries, 2008), oppositional defiant disorder (ODD; Gadow et al., 2007), anxiety disorder (Bowen, Shavira, Bailey, Stein, & Stein, 2008), and depression (Blackman, Ostrander, & Herman, 2005). Faraone et al. (1998) found that children with ADHD/C had more ODD and CD than children with ADHD/I or ADHD/H. He also found that although all three subtypes presented the same level of anxiety disorders, both ADHD/C and ADHD/I

Authors' Note: We acknowledge the precious support of Dr. William Harvey, Marie-Ève Fortier, and Johanne Bellingham. Financial support for the clinical trial was provided to Dr. Joober and Dr. Grizenko by the Canadian Institute for Health Research and by the Fonds de la recherche en santé du Québec. Financial support for the writing of the manuscript was provided to Michael Paci by the Mach Gaensslen Foundation of Canada. Please address correspondence to Dr. Natalie Grizenko, Bond Pavilion, Douglas Mental Health University Institute 6875, LaSalle Boulevard,Verdun, QC; e-mail: grinat@douglas.mcgill.ca

had significantly more depressive disorders than ADHD/H. Gaub and Carlson (1997) found that children with combined and hyperactive subtypes had more externalizing behaviors than the inattentive subtype and controls. They, however, also found that ADHD/C and ADHD/I had higher levels of internalizing disorders than ADHD/H and controls.

Three articles reviewing work comparing ADHD/C and ADHD/I have all underscored the paucity of studies comparing the two subtypes on the level of treatment response and etiology such as genetics and environmental factors (Bayens, Royers, & Vande Walle, 2006; Milich et al., 2001; Woo & Rey, 2005). This study aims to try to fill this gap by comparing both subtypes on all three levels.

This study will mainly focus on the response of subtypes to methylphenidate (MPH). MPH is a stimulant that acts on the dopaminergic systems in the brain. The effectiveness of MPH as a treatment of ADHD symptomatology and comorbidity has been widely observed. However, it has also been observed that only about 70% of patients with ADHD respond to it (Spencer et al., 1996). In 1991, before *DSM-IV* (American Psychiatric Association, 1994), Barkley, DuPaul, and McMurray compared the response of attention-deficient children who were hyperactive to those who were not. They found that hyperactive children responded more. They also reported that the nonhyperactive ADHD children who responded needed smaller doses of MPH. A study by Stein et al. (2003) also found that ADHD/I children needed lower doses of MPH than did ADHD/C children for significant improvement.

The association between ADHD pathophysiology and specific genes is very controversial (Mick & Faraone, 2008). The dopamine system includes two genes that have been strongly associated with ADHD: DAT, which codes for the dopamine transporter (Waldman et al., 1998), and DRD4, which codes for a dopamine receptor (Swanson et al., 1998). Genes from the serotonin system have also been associated with ADHD. They include the 5HTT, which codes for a serotonin transporter and possesses the 5-HTT-linked polymorphic region (5HTTLPR, Curran, Purcell, Craig, Asherson, & Sham, 2005). Some studies linking genetic variants to ADHD provide clues to ADHD subtype differences at a molecular genetic level. In fact, Waldman et al. (1998) reported that the number of DAT high-risk alleles (10 repeats in the variable number of tandem repeats) was directly associated with the number of hyperactive-impulsive symptoms but not with the number of inattention symptoms in a group of 117 probands. They also found a linkage disequilibrium for the 10-repeat allele in the ADHD/C group but not in the ADHD/I group when examining 122 families. Moreover, Curran et al. (2005) reported an association between the L allele of the 5-HTTLPR and hyperkinetic disorders, which corresponds better to ADHD/C than ADHD/I.

Environmental factors may also play a role in ADHD. Studies have associated the risk for ADHD with low birth weight (Linnet et al., 2006), as well as with maternal smoking (Linnet et al. 2003), maternal alcohol consumption (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), and maternal stress during pregnancy (Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008). Although the effect of environmental risk factors on specific ADHD subtypes is not clear, some results offer interesting clues. For example, a study by Cornelius, Ryan, Day, Goldschmidt, and Willford (2001) underlined that ADHD children whose mothers smoked during pregnancy have impulsive symptoms. These results point toward ADHD/C rather than ADHD/I. Also, in a recent study by Grizenko et al. (2008), it was reported that ADHD patients whose mothers had experienced moderate to severe stress during pregnancy had more severe internalizing and externalizing symptoms, which once again seems to point to ADHD/C.

The aim of this study is to explore whether the inattentive subtype of ADHD and the combined/hyperactive subtype represent separate disorders. To our knowledge, this is the first study to compare ADHD subtypes on the level of comorbidity, treatment response, and etiology, all at once. Our hypothesis is that significant differences will be found between subtypes on all these levels.

Method

Sample

Children were recruited over the last 9 years from both the disruptive behavior disorders program and the general outpatient clinic of the Douglas Institute, a psychiatric university teaching hospital affiliated with McGill University in Montreal. In all, out of a sample 371 children, 298 boys (80.3%) and 73 girls (19.7%) participated in our study. Participants' mean age across the sample was 8.98 years ($SD = 1.79$). The study sample comprised of 86.1% White (85.2% non-Hispanic, 0.6% Hispanic, and 0.3% half-Hispanic), 5.7% Black, 4.3% half-Black, 1.9% Native Canadian, 1.6% Asian, and 0.6% half-Asian participants. Out of the total number of participants, 35% were from families with a total income of less than 20,000 Canadian dollar/year (low income), 25% of the participants were from families with an income between 20,000 and 40,000 Canadian dollars (lower middle income), and 40% of the participants were from families with an income of more than 40,000

Canadian dollars (middle income and above). The fathers of the participating children had a mean education duration of of 12.1 years (range 3 to 25 years, *SD* = 3.3) and the mothers had a mean duration of 12.8 years of education (range 5 to 27 years, *SD* = 3.2).

Diagnosis

Every participant was diagnosed with ADHD based on clinical interviews with a psychiatrist, school reports, including the Conner's Global Index Teacher (CGI-T) version questionnaire (Conners, Sitarenios, Parker, & Epsteins, 1998a, 1998b), the Diagnostic Schedule for Children (DISC) version IV (Shaffer, Fischer, Lucas, Dulcan, & Schwab-Stone, 2000), and the Conner's Global Index Parents Version (CGI-P, Conners et al., 1998a, 1998b), which were completed by parents. The diagnoses were made using *DSM-IV* criteria. Within our sample, 53.6% of the children suffered from the combined type of ADHD, 32.3% were of the inattentive type, and 11.6% were of the hyperactive type.

Exclusion criteria included having an IQ of less than 70 on the Wechsler Intelligence Scale for Children-III (Weschler, 1991) or a diagnosis of pervasive developmental disorder, Tourette's syndrome, and/or psychosis. Children who had a previous intolerance or allergic reaction to MPH were also excluded. Although 41.2 % of the children in our sample had been on some medication sometime in the past, all medication was stopped for 2 weeks before the start of our clinical trial.

Clinical Trial

The participants were subjected to a double-blind, placebo-controlled, two-week, crossover, randomized MPH trial that was approved by the ethics board of the Douglas Institute. Written informed consent was given by the parents. All children also agreed to participate. After baseline assessment, children randomly received either placebo or 0.5 mg/kg of MPH adjusted to body weight and divided into 2 equal doses (morning and noon) during a period of 1 week. The participants were crossed over during the second week. The capsules given were prepared by a pharmacist who was not involved in the clinical evaluations.

Laboratory measures were taken before and at least 45 min after the administration of MPH or placebo, on the third or fourth day of each week. These measures reflected acute response to MPH. Children were assessed on the Restricted Academic Situation Scale (Barkley, 1990), which quantifies behavior such as being off task, vocalizing, playing, fidgeting, or being off seat during the exercise. They were also asked to complete the Conners' Continuous Performance Task (Conners, 1995) that measures sustained attention and impulse inhibition control. Furthermore, they were assessed on the Clinical Global Impression Scale (National Institute for Mental Health, 1985), which evaluates the severity of illness.

The CGI-T and CGI-P forms were handed out to the participants' teachers and parents to obtain an overview of their behavior at school and at home. Parents evaluated their children on the Sunday of each week, and teachers evaluated children on the Friday of each week.

Before revealing the hidden drug code, the research team proceeded to quantify the response to treatment of each participant with the results of the preceding measurements. The response was quantified on a 4-point Likert scale, which included responses on a scale of 1 to 4 (1 = *no* to 4 = *large*). The response was determined as a consensus clinical response (CCR) given by at least two child psychiatrists, a psychologist, and research assistants. The CCR takes into account multiple measurements and settings. The nonresponders and those who responded mildly were placed in a "poor responders" (PR) group, whereas those who responded moderately or largely were grouped as "good responders" (GR). Those in the GR group showed improvement in at least two settings.

A more detailed description of our diagnostic methods and our clinical trial can be found in Grizenko, Bhat, Schwartz, Ter-Stepanian, and Joober (2006).

Other Parameters Assessed

Comorbidity was assessed by using the DISC-IV questionnaire and was confirmed by clinical interviews.

We evaluated the stress experienced by the participants' mothers during their pregnancy using the Kinney Medical and Gynaecological Questionnaire (McNeil, Cantor-Graae, & Sjöstrom, 1994) . The answers were then scored using the McNeil–Sjöstrom Scale (McNeil & Sjöstrom, 1995). A scale of 1 to 3 based on the *DSM-III* and *DSM-III-R* Axis IV was then used to analyze the stress experienced during pregnancy. For example, "1" represented no stress at all. Moderate stress, such as important financial difficulties or marital problems, was given a score of "2." Stress such as the sudden death or incarceration of a spouse was considered severe and given a score of "3." All accounts of stress were corroborated through a separate interview with a significant Other, whether a spouse or a parent. For a more detailed account of how stress levels during pregnancy were assessed and analyzed, see Grizenko et al. (2008).

Mothers reported whether they smoked or consumed alcohol during their pregnancies. Mothers were also asked for the birth weight of their child. This information was verified with an obstetrical report.

All molecular genotyping was done using PCR amplification and resolution of different alleles on agarose gels. We examined the 3' VNTR of the SLC6A3 gene (DAT), the DRD4 VNTR, as well as the biallelic 5-HTTLPR (Joober et al., 2000; Steiger et al., 2007).

Data analyses

For categorical variables, we compared ADHD subtypes using simple cross-tabulations and calculated significance using χ^2 tests. For continuous variables, analysis of variance (ANOVA) was used. We also used a logistic regression to examine the relationship between the 5-HTTLPR genotype and pregnancy stress on ADHD subtypes.

Results

We first started by comparing all three ADHD subtypes according to demographic parameters and symptomatology (see Table 1). The combined and inattentive subtypes differed on every parameter except on CBCL internalizing *t*-test score. However, the combined and hyperactive groups were similar on all parameters, except for age at baseline and Child Behavior Check List (CBCL; Achenbach, 1991) internalizing *t* score. Furthermore, the hyperactive group differed from the inattentive group on all parameters, except on CBCL internalizing *t* score and CGI-P baseline score.

We combined the ADHD/C and ADHD/H subtypes for the purpose of statistical analysis. The new ADHD combined/hyperactive group (ADHD/CH) was, therefore, compared to the ADHD/I group. Our results can be seen on Table 2. We found that both groups differed significantly on levels of CD (with more CD in the ADHD/CH group, $p = .001$) but not on levels of ODD ($p = .626$), generalized anxiety ($p = .798$), and the presence of a major depressive episode ($p = .693$).

We compared both groups based on CCR treatment response. The ADHD/CH group showed a significant difference with the ADHD/I group. In fact, 74.1% of ADHD/CH were good responders, compared to only 62.2% for the ADHD/I group ($p = .021$).

A marginally significant difference emerged between both subgroups ($p = .061$) when comparing the level of pregnancy stress experienced by the mothers of the participants. In fact, both groups differed significantly in the "moderate" category of pregnancy stressors (17.4% for ADHD/I versus 30.9% for ADHD/CH, $p = .019$) but not in the "none" or "severe" categories.

There was no significance when comparing the two groups on the amount of participants' mothers who smoked or consumed alcohol during pregnancy ($p = .347$ and $p = .970$, respectively). No significance was equally found when comparing mean birth weight for both groups in grams ($p = .742$)

Finally, we compared the two subgroups on the basis of genotype with the DAT and DRD4 VNTRs and the 5-HTTLPR. For the DAT gene, we found 6 alleles with 3, 7, 8, 9, 10, and 11 repeats, respectively. The genotypes observed were 3/10 (1.6%), 7/10 (0.4%), 8/10 (0.4%), 9/9 (8.2%), 9/10 (37.4%), 9/11 (0.4%), 10/10 (34.2 %), and 10/11 (2.3%). We used only the 9/9, 9/10, and 10/10 genotypes due to their predominant prevalence. These genotypes did not depart from the Hardy–Weinberg distribution ($p = .910$) and were statistically equally distributed between subtypes ($p = .167$).

For the DRD4, we found 6 alleles with 2, 3, 4, 5, 7, and 8 repeats, respectively. The genotypes observed were 2/2 (0.5%), 2/3 (1.4%), 2/4 (8.9%), 2/7(1.9%), 3/4 (3.8%), 3/7 (1.9%), 4/4 (46.0%), 4/5 (1.4%), 4/7 (28.0%), 4/8 (0.5%), 7/7 (4.7%), 7/8 (0.5%), and 8/8 (0.5%). We used only the 4/4 and 4/7 genotypes due to their prevalence and because previous studies have associated the 4- and 7- repeat alleles to ADHD (Faraone et al. 2005). The 4/4, 4/7, and 7/7 genotypes respect the Hardy–Weinberg distribution ($p = .991$), but no significance was found when comparing subtypes ($p = .883$).

For the 5-HTTLPR, we compared both subtypes using the biallelic version of the gene, that is, the S (short) and L (long) alleles. We observed the S/S genotype (22.9%), as well as the S/L (45.1%) and the L/L (32.0%) genotypes. The Hardy–Weinberg equilibrium was respected ($p = .655$). Significance emerged ($p = .002$) when comparing both subtypes for these genotypes. We found that the major difference lay with the L/L genotype (more in the ADHD/CH group, 39.2% for ADHD/CH vs. 17.4% for ADHD/I, $p < .001$) and S/L genotype (less in the ADHD/CH group, 39.8% for ADHD/CH vs. 54.7% for ADHD/I, $p = .022$; for S/S, $p = .211$).

Lastly, we ran a logistic regression for our male probands only, using a forward, step-by-step approach and successively entering the 5-HTTLPR genotype, pregnancy stress (in Yes/No categories, with "moderate" combined with "severe"), the interaction between the latter and 5-HTT genotype and, finally, age. The ADHD/CH subtype was the outcome measure. Age loaded significantly ($p = .003$, $df = 1$, Exp(B) = 0.766), as did the interaction between the L/L genotype and the "Yes" category of stress ($p = .005$, $df = 1$, Exp(B) = 8.427). Having both the L/L genotype and a history of stress during pregnancy confers an 8.4 times higher risk for developing ADHD/CH.

Table 1
Demographics Across ADHD Subtypes

	Inattentive	Combined	Hyperactive	Statistic	Degrees of Freedom (*df*)	*p* Value[a]
N (%)	120 (32.3)	199 (53.6)	43 (11.6)		—	
Age at baseline (*SD*)	9.6 (1.8)	8.9 (1.7)	8.0 (1.5)	$F = 14.6$	2, 359	<.001
Post hoc I > C > H		C versus I		$t = –3.4$	359	.001
		C versus H		$t = 3.2$	359	.002
		H versus I		$t = 5.2$	359	<.001
Male/Female (%)	85/35 (70.8 / 29.2)	166/33 (83.4 / 16.6)	38/5 (88.4 / 11.6)	$X^2 = 9.6$	2	.008
Post hoc C, H > I		C versus I		$X^2 = 7.1$	1	.008
		C versus H				.418
		H versus I		$X^2 = 5.3$	1	.022
Income groups[b] (*SD*)	4.72 (1.52)	4.05 (1.60)	3.97 (1.68)	$F = 7.1$	2, 339	.001
Post hoc I > C, H		C versus I		$t = –3.6$	339	<.001
		C versus H				.793
		H versus I		$t = 2.5$	339	.012
CBCL internalizing T-Score (*SD*)	63.8 (10.8)	65.2 (10.1)	60.6 (8.9)	$F = 3.5$	2, 349	.031
Post hoc C > I, H		C versus I				.244
		C versus H		$t = 2.6$	349	.010
		H versus I				.089
CBCL externalizing T-Score (*SD*)	64.8 (11.4)	71.9 (8.3)	70.2 (8.7)	$F = 20.2$	2, 349	<.001
Post hoc C, H > I		C versus I		$t = 6.3$	349	<.001
		C versus H				.308
		H versus I		$t = –3.1$	349	.02
Conner's Parents Baseline (*SD*)	70.5 (11.3)	76.6 (10.3)	73.6 (9.7)	$F = 12.6$	2, 352	<.001
Post hoc C, H > I		C versus I		$t = 5.0$	352	<.001
		C versus H				.096
		H versus I				.095
Conner's Teachers Baseline (*SD*)	65.6 (12.9)	72.4 (11.5)	73.2 (10.9)	$F = 12.8$	2, 328	<.001
Post hoc C, H > I		C versus I		$t = 4.8$	328	<.001
		C versus H				.739
		H versus I		$t = –3.4$	328	.001

Note: X^2 for Chi-square, F for ANOVA, t for T-test.
a. Significance was set at $p = .05$.
b. Income groups in five categories (1 for < Can$6,000, 2 for Can$10-$20,000, 3 for Can$20-$30,000, 4 for Can$30-$40,000 and 5 for > Can$40,000). The numerical value of each category was taken as a scale value.

Discussion

The results obtained are consistent with previous findings, when comparing all three ADHD subtypes for mean age at baseline, male/female ratio, and CBCL symptomatology. The ADHD/I group had a higher mean age than the ADHD/C group, which had a higher mean age than the ADHD/H group. This is similar to findings by Lahey et al. (1994) and can be explained in that hyperactive children tend to be more disruptive at home and at school and are thus referred at an earlier age for treatment. The ADHD/I group also included more women than both the ADHD/C group and the ADHD/H group. This is in keeping with results obtained by Biederman et al. (2002). On the level of symptomatology, the ADHD/C group had the highest mean internalizing and

Table 2
Differences Between the Inattentive and Combined/Hyperactive Subtypes

	Inattentive	Combined/Hyperactive	Test statistic (X^2)	Degrees of Freedom	p Value[a]
DISC Conduct Disorder, Y/N (%)	9/111 (7.5/92.5)	50/187 (21.1/78.9)	10.7	1	.001
Treatment Response, Y/N (%)	74 / 45 (62.2 / 37.8)	177 / 62 (74.1 / 25.9)	5.3	1	.021
Level of Pregnancy Stress (%)		Overall	5.6	2	.061
None	48 (55.8)	88 (45.3)	2.6	1	.106
Moderate	15 (17.4)	60 (30.9)	5.5	1	.019
Severe	23 (26.8)	46 (23.7)	0.3	1	.587
5-HTTLPR alleles (%)		Overall	12.7	2	.002
S/S	24 (27.9)	38 (21.0)	1.6	1	.211
S/L	47 (54.7)	72 (39.8)	5.2	1	.022
L/L	15 (17.4)	71 (39.2)	12.7	1	<.001

Note: X^2 for Chi-square.
a. Significance was set at $p = .05$.
b. This value was calculated by substracting Conner's Parents score during the placebo week from the score during the treatment week, thus giving an idea of treatment response.
c. This value was obtained with the same method as presented in b.

externalizing scores. This is also consistent with findings by Faraone et al. (1998) who concluded that the ADHD/C group presented more symptoms than other children diagnosed with ADHD.

The ADHD/H group has proven to be problematic for many authors. A recent study by Lahey, Pelham, Loney, Lee, and Willcutt (2005) has suggested, based on a prospective study of 118 ADHD patients of all three subtypes, that ADHD/H may be a developmental precursor of ADHD/C. They found, just as we did, that ADHD/H first presents at a younger age with fewer inattention symptoms. These findings and the many significant differences between the ADHD/H group and the ADHD/I group are what led us to combine the ADHD/C group and the ADHD/H group for the purposes of statistical analysis.

When comparing the new ADHD/CH group to the ADHD/I group on the level of comorbidity, we found that the ADHD/CH group had a higher frequency of CD. Indeed, Faraone et al. (1998), Gaub and Carlson (1997), and Wolraich et al. (1996) all found that levels of CD were significantly higher in the ADHD/C group. However, they also found similar results for ODD, which we did not reproduce. Gaub and Carlson (1997) and Wolraich et al. (1996) both exclusively used teacher reports to establish presence of comorbidity. One could argue that these results cannot truly be compared with ours, which were also based on observations by the participants' mothers. Bauermeister et al. (2005) and Faraone et al. (1998), however, also used the reporting of participants' mothers in their study and they also found higher rates of ODD in ADHD/C children.

In regards to treatment response, our results bring support to other studies that compared ADHD subtypes. Similar to Barkley, DuPaul, and McMurray (1990), the ADHD/CH group had more good responders than the AHDD-I group. Our findings are, however, different from those of Kopecky, Chang, Klorman, Thatcher, and Borgstedt (2005) who reported that ADHD/I children benefit more than ADHD/C children from MPH when asked to complete the Tower of Hanoi test. The fact that Kopecky et al. (2005) only measured treatment response with the Tower of Hanoi and that their sample was quite small (34 controls and 41 children with ADHD) may explain this difference.

No differences were found across subgroups for the DAT alleles or the DRD4 alleles. Nevertheless, we did find a strong association of the L/L genotype of the 5-HTTLPR with the ADHD/CH group. This is consistent with previous findings associating the L/L genotype with hyperactive symptoms (Curran et al., 2005). The fact that the levels of S/S genotype in our sample are similar across subgroups is also in keeping with previous research. Grevet et al. (2007) reported that the presence of an S allele leads to more symptoms of inattention. As both subgroups suffered from inattention, it seems logical that no difference was found between them for the presence of the S/S genotype, which consists of a double allele associated with inattention.

At the level of pregnancy stressors, we found that a moderate level of stress was highly associated with ADHD/CH. However, there were no subgroup differences when considering a severe level of stress. This may be because girls were overrepresented in the severe

category as compared to their frequency in the other two groups (p = .011). Their presence in the "severe" category may explain the lack of difference between subtypes in this category, as we noticed that there were more girls in the ADHD/I group than in the ADHD/CH group. Gender, therefore, seems to be confounding the results in the category of highest stress. This is what led us to examine the relationship between the 5-HTTLPR genotype and pregnancy stress in male probands. We found that young age was negatively associated with the diagnosis of ADHD/CH and that a combination of the L/L genotype and stress during pregnancy lead to an 8 times higher risk of ADHD/CH. This may be one of many possible mechanisms linking stress to genotype in the development of ADHD/CH.

No significant differences were found between subgroups when comparing birth weight and maternal smoking and alcohol consumption during pregnancy. It is true that reviews such as Linnet et al. (2003) have found little evidence for the association of alcohol consumption during pregnancy and the development of ADHD. Nonetheless, the case for association of maternal smoking during pregnancy and ADHD is strong. We believe that the reason maternal smoking was similar across subtypes and the reason there were no differences in dopamine genes may lie in the composition of our ADHD/I group. As argued by Hartman, Willcutt, Rhee, and Pennington (2004), and originally described by Lahey et al. (1988), there may in fact be two groups that make up the current *DSM-IV* ADHD/I subtype: a group of children with "sluggish cognitive tempo" as well as a group of patients with subclinical ADHD/C. The subclinical ADHD/C group within the ADHD/I group may in fact be masking the true differences between the SCT group and the ADHD/C group. Nonetheless, we must caution that ADHD is a polygenic disorder with multiple etiologic factors and it is possible that ADHD/I and ADHD/CH share certain genetic and etiological factors. We believe that more research is needed to identify and compare the SCT group to the ADHD/CH group. Such research could provide more significant results and a stronger case for redefining the ADHD *DSM-IV* subgroups into new, distinct disorders.

The strengths of our study are the reliable way in which the diagnosis of ADHD and subtypes were done, using parent/child interviews and teacher and parent reports, and the blind and controlled evaluation of therapeutic response. One of the limitations lies in genotyping. We are missing data for certain participants who did not want to give blood or whose parents did not consent to genotyping. Also, because genetic data have been collected in a consistent manner in the last 9 years, we have not genotyped the 5-HTTLPR according to its triallelic form including the S, L_A, and L_G alleles but rather according to the earlier accepted bialelic form, with the S and L alleles (Steiger et al., 2007). Another limitation is that we only administered a total dose of 0.5mg/kg twice a day. Using varying doses may have enabled us to see the different effects of both small and larger doses. Lastly, it is important to note that our sample of participants were clinically referred, and thus not population based.

In summary, this study has shown that the inattentive subtype of ADHD is different from the combined/hyperactive subtype on many parameters including age, gender distribution, severity of symptoms, and comorbidity. Furthermore, the subtypes differ significantly on treatment outcome, with the combined/hyperactive subgroup presenting a higher frequency of good responders. When examining possible etiological factors linked to the development of ADHD, this study shows that more children with the combined/hyperactive subtype had a history of moderate stress during their mother's pregnancy. Lastly, our study found a higher frequency of the L/L genotype of the 5-HTTLPR in the ADHD/CH group. These findings raise the possibility that the ADHD/CH and ADHD/I subgroups may in fact be two separate disorders. A better understanding of the differences between subtypes may help physicians make clearer diagnoses, establish a clearer treatment plan, and predict more accurate prognoses in children with ADHD.

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