Affect modulation of methylphenidate in patients with Attention Deficit Hyperactivity Disorder

Bottelier, M.A.

Link to publication

Creative Commons License (see https://creativecommons.org/use-remix/cc-licenses):
Other

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 2

Comorbid depression and anxiety symptoms in children and adolescents with ADHD

Hyke G.H. Tamminga — Bianca E. Boyer
Marco A. Bottelier — Saskia van der Oord
Liesbeth Reneman — Hilde Geurts

Submitted
Chapter 2 Comorbid depression and anxiety symptoms in children and adolescents with ADHD

Abstract
Children with ADHD are at increased risk of developing depression and anxiety. However, previous studies on this co-occurrence have not accounted for stimulant use, while animal and human studies suggest a role of stimulants in the development of depression and anxiety.

In the present study we first assessed self-reported depressive and anxiety symptoms in stimulant naïve boys (10 - 17 years) with (n = 74) and without ADHD (n = 58), and, second, compared the age-trajectory of comorbid symptoms in naïve (n = 30) and prior medicated (n = 51) boys with ADHD (12 - 17 years). Effects of age, ADHD diagnosis, and medication use were analyzed cross-sectionally, in regression analyses with self-reported depressive symptoms on the Children’s Depression Inventory (CDI) and anxiety symptoms on the Screen for Child Anxiety Related Emotional Disorders (SCARED) rating scale as dependent variables.

The ADHD group reported more depressive symptoms than controls, but groups were similar on anxiety symptoms. Furthermore, prior stimulant use was not associated with comorbid symptoms of depression and anxiety.

The results support both a genetic and early developmental explanation of depressive comorbidity in ADHD. When replicated, these findings could be reassuring to therapists, parents and clients who are deciding on the use of stimulant medication for ADHD.

Introduction
ADHD is a neurodevelopmental disorder affecting approximately 5 to 10% of children (Faraone et al., 2003; Polanczyk et al., 2007). In addition to impairment caused by core symptoms of inattention, and/or hyperactivity and impulsivity, individuals with ADHD often have comorbid disorders. In ADHD, levels of depression and anxiety and the risk of a lifetime comorbid diagnosis are significantly higher as compared to ‘typically developing’ (TD) individuals (Angold et al., 1999; Biederman et al., 2006; Blackman et al., 2005; Chronis-Tuscano et al., 2012; Guttmann-Steinmetz et al., 2010; Larson et al., 2011; Lavigne et al., 2009; Ostrander and Herman, 2006; Roy et al., 2014) In a childhood study with a clinically referred sample, comorbid Major Depression Disorder (MDD) was present in 24% of children with ADHD (Spencer., et al. 2000). Although studies with community samples show lower rates than studies with clinical samples, rates of comorbidity are still higher in ADHD as compared to TD (depression: 9 - 14% in ADHD as opposed to 1 - 2% in TD, anxiety: 15 - 35% in ADHD as opposed to 2 - 15% in TD; Blackman et al., 2005; Larson et al., 2011) (Pliszka, et al., 1999).

In late childhood and early adolescence, levels of depression and anxiety are age-dependent, with increasing age being associated with an overall increase in depression (Costello et al., 2011, 2003; Saluja et al., 2004) and anxiety (increase of panic disorder and agoraphobia, decrease of separation anxiety disorder, specific phobias, and social phobia; (Copeland et al., 2014; Costello et al., 2011). Differences in development of (comorbid) depression and anxiety between ADHD and TD already occur at a young age (Lavigne et al., 2009). As onset of comorbid depression and anxiety generally follows onset of ADHD, co-occurrence has been suggested to be related to both negative environmental interactions (after a history of failure and punishment, more depressive symptoms develop(Ostrander and Herman, 2006; Schatz and Rostain, 2006) and to shared genetic components (Biederman et al., 1992; Cole et al., 2009). In adults with ADHD, comorbidity seems more extensive than in children with ADHD. For example, a cohort study revealed that 38.3% of an ADHD group met criteria for MDD and 47.1% met criteria for any anxiety disorder in the last 12-months, as opposed to 11.1% and 19.5% of a control group(Kessler et al., 2006). Knowledge regarding comorbid depression and anxiety in ADHD is of importance, as these comorbidities may influence the course of ADHD, as well as the outcome and treatment response (March et al., 2000), (Spencer, 2006b). For example, children with multiple comorbid anxiety disorders have poorer daily functioning and parent-reported quality of life as compared to children with ADHD only (Schierras and Lycett, 2015) and children with ADHD and MDD are at a high risk of suicide attempts (Chronis-Tuscano et al., 2012). As such, it is important to know how ADHD and depression and anxiety are related.
Children and adolescents with ADHD are often treated with psychostimulants (Hodgkins et al., 2013). However, previous studies on the co-occurrence of ADHD and depressive or anxiety symptoms have not considered the potential confounding effects of medication history on comorbidity. This is surprising, as both animal and human studies suggest that having a history of stimulant medication is associated with the development of a depression- and anxiety-like state, presumably due to cellular alterations in reward pathways in the brain (Bolaños et al., 2008; Carlezon William A et al., 2003; Wiley et al., 2009). For example, (normal) Sprague-Dawley rats treated with MPH during adolescence showed more depressive- and anxiety-like behaviour in adulthood than saline vehicle-treated control rats. In line with this, although not controlled for baseline levels of ADHD, children who had received pharmacological treatment for ADHD were more likely to meet MDD criteria than children with ADHD who had not received pharmacological treatment, and duration of treatment was associated with this increased risk (Jerrell et al., 2014). Furthermore, the children initially randomized to pharmacological treatment in the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study study had higher rates of anxiety or depression diagnosis at six year follow-up, as compared to children initially receiving behavioral treatment and community care, although this effect was not observed at later follow-up (Molina et al., 2009). On the other hand, Smalley and colleagues (Smalley et al., 2007) showed significant comorbid depression and anxiety in stimulant naïve adolescents with ADHD in a cohort study, suggesting that these disorders also co-exist without the influence of stimulants. Some studies take this even further by suggesting a protective effect of stimulant use. A retrospective study (Daviss et al., 2008) of ADHD revealed that individuals without a history of comorbid MDD reported earlier initiation of stimulant treatment than individuals with a history of comorbid MDD, which authors interpret as a potential protective effect of stimulant use. In addition, a cohort study, monitoring children newly diagnosed with ADHD, demonstrated that duration of stimulant treatment in children was related to depression, with a reduced comorbidity risk with longer treatment duration (Lee et al., 2015). Although contrasting, these findings emphasize the importance of taking medication status into consideration in ADHD comorbidity research, as it could well be that previous findings on comorbidity have been affected by medication history.

Therefore, the present cross-sectional study aims to determine the relationship between ADHD diagnosis, (prior) stimulant use, age, and depressive and anxiety symptoms in boys between the ages of 10 to 17 years. Two studies were executed. Study 1 evaluated whether having an ADHD diagnosis moderates the relationship between age and depressive/anxiety symptoms between the ages of 10 to 17 years. In order to exclude possible (short- or long-term) influences of pharmacotherapy, this study included stimulant naïve boys between the ages of 10 to 17 years with a clinical diagnosis of ADHD, and a TD group of a similar age.

The second study examined whether having a history of stimulant use moderates the relationship between age and depressive and anxiety symptoms, comparing a stimulant naïve and a medicated sample of male adolescents aged 12 to 17 years with ADHD (ADHD- and ADHD+).

Following the hypothesis that both shared genetic components and negative environmental interactions (Davis et al., 2008) contribute to the development of depressive and anxiety comorbidity in stimulant naïve boys with ADHD, we expected increased depression and anxiety in the ADHD group as compared to the TD group. In addition, we expected an interaction between age and ADHD diagnosis for depressive symptoms (a stronger increase in depressive symptoms with increasing age for the ADHD group in comparison to the TD group), and an interaction between age and ADHD diagnosis for anxiety symptoms (showing stable or increasing anxiety symptoms in the TD group, and a stronger increase in anxious symptoms with increasing age for the ADHD group). Given the conflicting evidence in the literature, we did not formulate specific expectations regarding the relationship between stimulant use and comorbidity, however, a different trajectory of anxiety and depression in ADHD- and ADHD+ adolescents could imply a role of stimulant medication in the development of comorbid depression and anxiety in ADHD.

Methods

Participants

In Study 1, we included a male stimulant naïve ADHD group (n = 74) and TD group (n = 58) aged 10 to 17 years. In Study 2, we included boys aged 12 to 17 years who were stimulant naïve (ADHD-; n = 30), or had a history of stimulant treatment (ADHD+; n = 51). For both studies, participants with an estimated IQ < 80 and/ or a history of major medical or neurological trauma or illness were excluded. Participants with ADHD were recruited through child and adolescent psychiatry outpatient clinics. They either had been diagnosed previously, or were diagnosed at the intake of the study with ADHD (IT, HI or CT) by experienced clinicians, based on the DSM-IV-TR (APA, 2000). Children and adolescents with ADHD were included only when their clinical diagnosis was confirmed with a structured interview (Diagnostic Interview Schedule for Children [NIMH DISC-IV; Ferdinand & Van der Ende, 1998] parent- or self-report). In addition, the ADHD- group had never used stimulants and was seeking treatment for ADHD related impairment. ADHD+ participants were eligible when parents reported that children used stimulant medication currently and had taken medication compliantly in the past four weeks. Treatment was discontinued 24 hours before the assessment of depressive and anxiety symptoms, as the adolescents also participated in neuropsychological
testing for which they needed to be stimulant free at the time of testing (Boyer et al., 2014). The TD group was recruited through typical schools. Exclusion criteria were a clinical psychiatric diagnosis of ADHD or ASD, and scoring above the 90th percentile on the parent DBD (Oosterlaan et al., 2000). For participants aged 17 years, DBD norms for 16-year olds were applied, as norms for 17 year olds were not available.

**Group selection**

ADHD - Parents of the ADHD groups were approached through their child’s clinician at child and adolescent psychiatry outpatient clinics¹. Before entering the studies, caregivers and participants aged 12 years or older gave written informed consent, and children younger than 12 years gave verbal informed consent. All children and adolescents filled out the SCARED and CDI, and were tested with the Block Design and Vocabulary subtests of the WISC-III-R (Kort et al., 2002), in order to estimate IQ. Parents were interviewed using the DISC-IV and filled out the DBD rating scale.

TD - Fifty-eight TD children were recruited through regular schools throughout the Netherlands. Parents of TD children and adolescents received a letter through school asking for their cooperation. After giving informed consent, procedures were the same as described for the ADHD group, except no DISC-IV interview was administered.

### 4.2.3 Inclusion materials

The DISC-IV (Ferdinand & Van der Ende, 1998) is a structured interview based on DSM-IV (APA, 1994) and ICD-10 (World Health Organization, 1993) criteria. The ADHD section of the DISC-IV was administered by one of the researchers or a trained research assistant in order to verify the clinical diagnosis and determine the ADHD subtype.

The DBD (Oosterlaan et al., 2000) is a questionnaire assessing parent reported externalizing symptoms in children aged 6 to 16 years. The DBD comprises 42 items reflecting core symptoms of inattention (9 items), hyperactivity/impulsivity (9 items), oppositional defiant disorder (ODD; 8 items), and conduct disorder (CD; 16 items). Parents indicate the frequency of the child’s externalizing behavior. Responses range from not at all, a little, pretty much to very much and are scored with 0, 1, 2, or 3 respectively. Good internal consistency was shown for the subscales inattention, hyperactivity/impulsivity, and oppositional defiant disorder (ODD; 8 items), and scoring above the 90th percentile on the parent DBD (Oosterlaan et al., 2000). For participants aged 17 years, DBD norms for 16-year olds were applied, as norms for 17 year olds were not available.

¹The majority of the children (aged 9-12 years) were asked to participate in an RCT with medication treatment (Bottelier et al., 2015) Some of the children, and all of the adolescents (aged 12-17 years), were included in an RCT with cognitive behavioral therapy (Boyer et al., 2015) Questionnaires were administered before the start of treatment.

**Dependent measures**

The Children’s Depression Inventory (Kovacs, 1985; Timbremont and Braet, 2001) is a self-report measure of childhood depression. The CDI was designed for children aged 7 to 17 years and comprises 27 items. Each item is formulated as three statements, from which the respondent chooses the one that best reflects his/her thoughts and feelings in the last two weeks. The total score ranges between 0 and 54, as statements are scored as 0, 1 or 2, with a higher total score indicating more depressive symptoms. Internal consistencies of $\alpha = .85$ and $\alpha = .86$ have been found in nonclinical and clinical samples respectively (Timbremont and Braet, 2001).

The Screen for Child Anxiety Related Emotional Disorders (Muris et al., 2007) is a self-report questionnaire, screening for symptoms of childhood anxiety. It was designed for children aged 7 to 19 years and gives an indication of the presence of the following anxiety disorders: panic (13 items), social phobia (7 items), obsessive-compulsive (9 items), posttraumatic stress (4 items), generalized anxiety (12 items), and specific phobias [i.e. animal (3 items), medical (7 items), and situational (5 items)]. Children and adolescents indicate whether they experience the symptom never or seldom, sometimes, or often (scored 0, 1, or 2 respectively). Good internal consistency ($\alpha = .92$) was shown with a non-clinical, normative sample of $n = 1011$ (Muris et al., 2007).

**Statistical analyses**

In both Study 1 and Study 2, we conducted two linear, forced-entry regression analyses, one with the raw total CDI score and one with the raw total SCARED score as the dependent variable. Predictor variables in Study 1 analyses were age (continuous), ADHD diagnosis (dichotomous: yes/no) and the interaction between age and ADHD diagnosis. In Study 2, age (continuous), prior stimulant use (dichotomous: yes/no), and the interaction between age and prior stimulant use were entered as predictors. In order to determine whether an additive differential effect of age and ADHD diagnosis was present, and to account for multicollinearity, the predictors age and ADHD diagnosis were entered in the first model, and age x ADHD diagnosis was added in the second model. Given the number of comparisons and the conservativeness of a Bonferroni correction, we used the Hochberg (1988) modification of the Bonferroni correction to account for multiple comparisons. This resulted in alphas ranging from .004 to .05 for observed $p$-values ordered sequentially from smallest to largest. We looked for outliers and adjusted these values to the next highest score plus one (Field, 2009) in order to reduce their influence on the regression model (for SCARED $n = 1$ outlier with value 100
was adjusted to a value of 79). Assumptions of linearity and multicollinearity were met. In order to meet the assumption of normality of the standardized residuals, data was square root transformed (Study 1) and log transformed (Study 2) for the depression analysis, and log transformed (Study 1) for the anxiety analysis, which normalized the skew (D = 0.062, \( p = .200 \), D = 0.081, \( p = .200 \), and D = .061, \( p = .200 \) respectively). All statistical analyses were done with Statistical Package for the Social Sciences version 20 (SPSS/IBM 2011).

**Results**

**Descriptives**

Even though age was entered as a continuous variable in the main analyses, we compared the younger (aged 10 - 11 years, \( n = 28 \)) and older stimulant naïve ADHD groups (aged 12 - 17 years, \( n = 46 \)) on ADHD symptoms and diagnostic subtypes, to determine whether our sample characteristics were in line with the literature. We assigned children from the age of twelve to the older group, as children in the Netherlands generally make the transition from middle to high school at the age of twelve. We applied independent samples t-tests to normally distributed data and Mann-Whitney tests to not normally distributed data. The younger and older children differed significantly in the type of ADHD diagnosis on the DISC, with relatively more children in the older group meeting criteria for the IT (\( \chi^2 = 11.146, df = 2, p = .004 \)), as can be seen in Table 5.1. This is consistent with the development of ADHD symptoms over time, with a decline in inattentive and especially hyperactive/impulsive symptoms during adolescence (Biederman et al., 2000) However, younger and older children did not differ significantly in parent-reported inattentive (U = 558.0, \( z = -0.036, p = .72 \)), hyperactive/impulsive (t(68) = 1.83, \( p = .072 \)), ODD (U = 590.0, \( z = 0.024, p = .98 \)) and CD symptoms (U = 547.50, \( z = -.61 \)) on the DBD. In addition, the age groups did not differ in CDI Total Score (t(71) = -1.228, \( p = .23 \)) and IQ (U = 747.00, \( z = 1.713, p = .09 \)), but the younger age group did show a higher SCARED Total Score as compared to the older age group (U = 435.5, \( z = -2.208, p = .03 \)).

### Table 2.1 | Diagnostic subtypes of ADHD in younger and older stimulant naïve children.

<table>
<thead>
<tr>
<th></th>
<th>Aged 9 - 11</th>
<th></th>
<th>Aged 12 - 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISC-IV IT</td>
<td>12</td>
<td>43%</td>
<td>37</td>
</tr>
<tr>
<td>DISC-IV HI</td>
<td>1</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>DISC-IV CT</td>
<td>15</td>
<td>53%</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>100%</td>
<td>46</td>
</tr>
</tbody>
</table>

Note: DISC=Diagnostic Interview Schedule for Children; IT=inattentive subtype; HI=hyperactive/impulsive subtype; CT=combined subtype.

The stimulant naïve ADHD and TD group were comparable in mean age and IQ. As expected, the ADHD group scored higher on DBD symptoms of inattention, hyperactivity/impulsivity, ODD and CD (see Table 4.2).

### Table 2.2 | Characteristics of the stimulant naïve ADHD and TD children and adolescents.

<table>
<thead>
<tr>
<th>ADHD</th>
<th>TD</th>
<th>Statistics(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>n</td>
</tr>
<tr>
<td>Age</td>
<td>11.9 (1.5)</td>
<td>74</td>
</tr>
<tr>
<td>IQ</td>
<td>105.0 (16.0)</td>
<td>72</td>
</tr>
<tr>
<td>DBD(^a) Inatt</td>
<td>21.1 (4.5)</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>13.3 (6.8)</td>
<td>71</td>
</tr>
<tr>
<td>ODD</td>
<td>6.2 (5.1)</td>
<td>71</td>
</tr>
<tr>
<td>CD</td>
<td>1.8 (3.0)</td>
<td>71</td>
</tr>
<tr>
<td>CDI</td>
<td>8.7 (4.9)</td>
<td>74</td>
</tr>
<tr>
<td>SCARED</td>
<td>25.5 (16.7)</td>
<td>74</td>
</tr>
</tbody>
</table>

Note: ADHD=Attention Deficit Hyperactivity Disorder; TD=Typically Developing children; IQ=estimated IQ; DBD=Disruptive Behavior Disorders scale; Inatt=inattention; Hyp/Imp=hyperactive/impulsive; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; CDI=Children’s Depression Inventory Total Score; SCARED=Screen for Child Anxiety Related Disorders Total Score.

\(^a\)raw score, \(^b\)Mann-Whitney Test, \(*p<.05, **p<.01, ***p<.001\)
The ADHD- and ADHD+ group were comparable in IQ and DBD symptoms of hyperactivity/impulsivity, ODD and CD (see Table 5.3). However, the ADHD+ group was older, and their parents reported less DBD symptoms of inattention. In the ADHD+ group, 13 participants used short-acting MPH (n = 1 once daily, n = 9 twice daily, n = 3 three times daily), 36 participants used long-acting MPH, and 2 used dexamphetamine (n = 2 twice daily). The daily dosage of MPH ranged between 10 and 90 mg, with a mean dosage of 33.41 mg (SD = 17.04, n = 41). Dosage was not significantly associated with the number of depressive and anxiety symptoms (r = -.06, p = .73 and r = .16, p = .33 respectively). No information was available about the duration of stimulant treatment.

Table 2.3 | Characteristics of the prior medicated and stimulant naïve adolescent Comorbidity in stimulant naïve boys (Study 1)

<table>
<thead>
<tr>
<th></th>
<th>ADHD+</th>
<th>ADHD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>14.5 (1.3)</td>
<td>13.4 (1.2)</td>
</tr>
<tr>
<td>IQ</td>
<td>105.9 (18.2)</td>
<td>106.0 (14.5)</td>
</tr>
<tr>
<td>DBD</td>
<td>Inatt</td>
<td>16.4 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Hyp/Imp</td>
<td>8.7 (6.5)</td>
</tr>
<tr>
<td></td>
<td>ODD</td>
<td>5.8 (4.3)</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>0.8 (1.6)</td>
</tr>
<tr>
<td>CDI</td>
<td>10.2 (5.8)</td>
<td>9.3 (4.0)</td>
</tr>
<tr>
<td>SCARED</td>
<td>20.8 (14.1)</td>
<td>20.9 (10.2)</td>
</tr>
</tbody>
</table>

Statistics:
- U = 411.00, z = -3.46***
- U = 750.00, z = 0.37, ns
- t = -2.73, df = 75**
- t = 0.86, ns
- t = -0.11, ns
- t = 1.46, ns
- t = -0.04, df = 78, ns

Note: ADHD=Attention Deficit Hyperactivity Disorder; ADHD+=prior medicated ADHD group; ADHD-=stimulant naïve ADHD group; IQ=estimated IQ; DBD=Disruptive Behavior Disorders scale; Inatt=inattention; Hyp/Imp=hyperactive/impulsive; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; CDI=Children’s Depression Inventory Total Score; SCARED=Screen for Child Anxiety Related Emotional Disorders Total Score.

Table 2.4 | Regression analysis with age and ADHD diagnosis predicting depressive symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI</td>
<td>B</td>
<td>SE B</td>
</tr>
<tr>
<td>Age</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>ADHD diagnosis</td>
<td>0.65</td>
<td>0.14</td>
</tr>
<tr>
<td>Age * ADHD</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>R²</td>
<td></td>
<td>0.17</td>
</tr>
</tbody>
</table>

Note: CDI=Children’s Depression Inventory; ADHD=Attention-Deficit Hyperactivity Disorder

Comorbid depression and anxiety symptoms in children and adolescents with ADHD

Comorbidity in stimulant naïve boys (Study 1)

Depressive symptoms in ADHD- and TD boys aged 10 to 17 years

The total number of children that completed the CDI was 131. The linear regression analysis on square root transformed data revealed that in the first model, age and ADHD diagnosis together explained a significant proportion of variance in CDI scores (F(2, 128) =12.661, p < .001, R² = .165). ADHD diagnosis significantly predicted CDI scores (β = .379, t (130) = 4.662, p < .001 respectively); having an ADHD diagnosis was associated with an increase in depressive symptoms. Following correction for multiple comparisons (α = .005), age was not a significant predictor (β = .198, t (130) = 2.433, p = .016). The second model, incorporating the interaction term age x ADHD diagnosis, did not add to the first model (ΔF(1, 127) = 0.051, p = .821, ΔR² = .001). Table 5.4 and Figure 5.1 present the relationship between age, ADHD diagnosis, and depressive symptoms.
Comorbid depression and anxiety symptoms in children and adolescents with ADHD

Anxiety symptoms in ADHD- and TD boys aged 10 to 17 years
A total number of 132 children completed the SCARED rating scale. The linear regression analysis on log-transformed data revealed that the first model with age and ADHD diagnosis did not explain a significant proportion of variance in SCARED scores ($F(2, 129) = 2.529, p = .084, R^2 = .038$). The second model, adding the interaction term age x ADHD diagnosis, did not add to the first model ($\Delta F(1, 128) = 1.168, p = .282, \Delta R^2 = .009$). Although the Mann-Whitney test showed that the younger ADHD group had more anxiety symptoms than the older ADHD group, the regression analysis showed that age and ADHD diagnosis, and the interaction between age and ADHD diagnosis, did not predict anxiety symptoms. Figure 4.2 and Table 4.5 present the relationship between age, ADHD diagnosis, and anxiety symptoms.

Note: SCARED= Screen for Child Anxiety Related Emotional Disorders, ADHD=Attention-Deficit Hyperactivity Disorder.

Table 2.5 | Regression analysis with age and ADHD diagnosis predicting anxiety symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>SE B</th>
<th>Model 2</th>
<th>SE B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.02</td>
<td>0.02</td>
<td>-0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>ADHD diagnosis</td>
<td>0.09</td>
<td>0.06</td>
<td>0.52</td>
<td>0.41</td>
</tr>
<tr>
<td>Age * ADHD</td>
<td>0.14</td>
<td>0.03</td>
<td>0.80</td>
<td>0.00</td>
</tr>
<tr>
<td>R^2</td>
<td>.04</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F $\Delta R^2$</td>
<td>2.53</td>
<td>1.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: SCARED= Screen for Child Anxiety Related Emotional Disorders, ADHD=Attention-Deficit Hyperactivity Disorder.

*log transformed dependent variable, \('n=132\).

*significant value (predictor specific thresholds after Hochberg correction: $\alpha=.03$ for the interaction term, $\alpha=.02$ for age, and $\alpha=.01$ for ADHD diagnosis).
Comorbidity in medicated boys (Study 2)

Depressive symptoms in ADHD+ and ADHD- boys aged 12 to 17 years

The total number of adolescents completing the CDI was 81. A linear regression analysis on log transformed data from an ADHD+ and ADHD- group revealed that the first model with age and medication group did not explain a significant proportion of variance in CDI scores ($F(2, 78) = 1.274, p = .285, R^2 = .032$). The incorporation of the interaction-term in the second model did not add to the first model ($AF(1, 77) = .781, p = .380, \Delta R^2 = .010$; see Appendix 5.1). Thus, age and medication use did not predict the number of depressive symptoms.

Anxiety symptoms ADHD+ and ADHD- adolescents aged 12 to 17 years

The total number of adolescents completing the SCARED rating scale was 80. A linear regression analysis on normal data from an ADHD+ and ADHD- group revealed that the first model with age and group did not explain a significant proportion of variance in SCARED scores ($F(2, 77) = .051, p = .950, R^2 = .001$). Incorporating the interaction-term in the second model did not add to the first model ($AF(1, 76) = .517, p = .647, \Delta R^2 = .007$; see Appendix 4.2). Age and medication use did not predict the number of anxiety symptoms.

Exploratory analyses

As some anxiety disorders (separation anxiety disorder, specific phobias, social phobia) have been reported to decrease, and others (panic disorder and agoraphobia) have been reported to increase with increasing age (Costello et al., 2011), these effects might have counteracted each other. Thus, we created a dependent variable omitting the SCARED items regarding anxiety disorders that decrease with increasing age in the general population (35 items remaining) and tested the predictive value of age and ADHD diagnosis or medication group in the first model and of the interaction term in the second model. Neither the models in Study 1 predicted anxiety ($F(2, 129) = 1.919, p = .15$, and $F(3, 128) = 1.611, p = .19$), nor the models in Study 2 ($F(2, 77) = .214, p = .81$, and $F(3, 76) = 0.358, p = .78$) predicted anxiety.

Discussion

The aim of the two present studies was to determine the relationship between depressive and anxiety symptoms, ADHD diagnosis, and prior stimulant use in child and adolescent boys. In the primary study we incorporated a unique sample of stimulant naïve child and adolescent boys with ADHD (aged 10-17 years). The results showed more depressive symptoms in the stimulant naïve ADHD group as compared to the TD group. As reported previously for boys (Costello et al., 2011) an age effect was not evident for depressive symptoms, thus, older boys generally did not show more depressive symptoms than younger boys. With reference to the other group, neither group demonstrated an increase of depression with increasing age. Furthermore, levels of anxiety were similar in the stimulant naïve ADHD and TD group, and no age effects or differences in age effects between groups were observed. In the second study, we compared stimulant naïve to prior medicated boys with ADHD (aged 12 - 17 years). Importantly, depressive or anxiety symptoms were not related to prior stimulant use. To sum up, the present study shows increased levels of self-reported depressive symptoms, but not anxiety symptoms, in stimulant naïve boys aged 10 to 17 years with ADHD. In addition, comparable levels of depression and anxiety were observed in boys aged 12 to 17 years with and without a history of stimulant use.

The association between ADHD diagnosis and depressive symptoms in stimulant naïve participants, observed in Study 1, combined with the lack of a relationship between stimulant use and depression, observed in Study 2, suggest that having a history of stimulant use is not associated with the development of depressive comorbidity in ADHD. This extends previous research showing co-morbidity in a cohort study with stimulant naïve adolescents with ADHD (Smalley et al., 2008). Furthermore, we did not observe accumulation of co-morbidity symptoms with increasing age in ADHD as compared to TD. This finding was coherent with a study showing comparable comorbidity levels in medicated school-aged boys and adolescents with ADHD (Biederman et al., 1998). However, accumulation of comorbidity symptoms could be expected if depression would (in part) follow from ongoing negative environmental interactions, which are more prevalent in ADHD (Ostrander and Herman, 2006). Thus, the results are in line with hypotheses of shared genetic components for ADHD and depression or early environmental influences (Biederman et al., 1992; Cole et al., 2009), but not with ongoing effects of environmental interactions or prior use of stimulant medication.

As for anxiety, we observed a comparable level of symptoms across ages, diagnostic status, and medication status, suggesting that ADHD and prior stimulant use do not affect anxiety, even though elevated anxiety levels have consistently been described in male medicated ADHD groups as compared to TD groups (Angold et al., 1999; Biederman et al., 2006; Guttmann-Steinmetz et al., 2010; Larson et al., 2011). In part, this could be in line with the fact that we studied the present occurrence of anxiety symptoms, as opposed to lifetime diagnosis of anxiety disorders, which is evaluated in the majority of studies. Symptoms of specific disorders, such as separation anxiety, decrease drastically from childhood to early adolescence, and the normal levels of anxiety in the present study could be in line with the fact that we focused on current symptoms. As for depression, the lack of age-depend-
ency might be explained by the inclusion of boys only, while the age-dependency of anxiety is more consistent in girls than in boys (Cope
eland et al., 2014).

Several alternative interpretations for the present findings were explored. For example, the lack of a relationship between anxiety and age could be due to counteracting of separate anxiety disorders decreasing and increasing with increasing age (Costello et al., 2011). Furthermore, one might argue that comorbid disruptive disorders explain comorbid depressive symptoms (Nigg et al., 2004). Also, an overlap between ADHD and depression on items of the CDI (e.g., concentration problems; Hoza et al., 1993) could explain the difference in depressive symptoms between the stimulant naïve ADHD and TD group. We therefore conducted separate analyses, omitting SCARED items that decrease with increasing age, incorporating ODD symptoms into the predictive model, and omitting CDI items regarding concentration, school accomplishment and finishing homework. None of these approaches altered the present conclusions (ODD and CDI analyses available from first author upon request).

Remaining caveats could well be that we, first of all, combined participants recruited for two different types of treatment studies within a cross-sectional design. However, the young group (mainly consisting of participants from the medication trial) and old group (mainly consisting of participants from the trial with behavioural treatment) in Study 1 were comparable in parent reported age of ADHD symptom onset, in ODD and CD symptoms, and the observed shift in diagnostic subtypes (from combined to inattentive) with increasing age is in line with the literature (Biederman et al., 2000). Nevertheless, recruitment bias cannot be ruled out as the treatment goals of the original children and adolescent studies differed (respectively medication and cognitive behavioral therapy). Second, several factors limit the findings of Study 2. The time off-medication at assessment was 24 hours only, while questions in the depression questionnaire apply to the past two weeks. Thus, a longer period of time off-medication would be optimal in determining potentially lasting effects of MPH, however, this is ethically and practically challenging. Furthermore, we did not document the duration of stimulant use in the ADHD+ group, hence, we only know they received stimulant treatment for at least four weeks prior to discontinuation for assessment. Also, the current dosage was quite low (mean dosage of 33.41 mg), however, a study demonstrated that the additional effect of increasing the MPH dosage over 10 mg was marginal in children aged 12-17 years (Smith et al., 1998). Even though this indicates that sensitivity to stimulants might be higher during adolescence as compared to childhood, the effects of higher dosing on comorbidity need to be determined, preferably in a study in which treatment duration is documented and, if ethically possible, following a longer off-medication interval. A third limitation is that we included a clinical sample of boys, limiting the generalizability of the conclusions to girls and non-clinical samples, and evaluated current symptoms instead of the lifetime occurrence of comorbid disorders. Studies with TD children reveal higher levels of depression and anxiety and an (steeper) age-related increase in girls as compared to boys (Costello et al., 2011, 2003). Regarding comorbidity in ADHD, results are less consistent, but most reveal a higher risk of internalizing problems in girls as compared to boys (Gershon, 2002; Romano et al., 2005; Yoshimasu et al., 2012), for null findings see (Abikoff et al., 2002; Gaub and Carlson, 1997). Nevertheless, many studies have revealed increased mood comorbidity in boys with ADHD, which underlines the importance of the current study. Finally, we observed only small effects and large variance, suggesting that other predictors, not included in our model, contribute to comorbid levels of depression and anxiety in ADHD. Other factors associated with the level of comorbidity in ADHD might be, for example, parenting behaviour and psychopathology, social functioning, and emotional lability (Karustis et al., 2000; Ostrander and Herman, 2006; Seymour et al., 2012; Sobanski et al., 2010). Unfortunately, we did not assess all of these factors in the present study, but we did take the age trajectories of different anxiety disorders, the role of oppositional behavior, and overlap between the CDI and ADHD symptoms into account.

In summary, the present study shows increased levels of self-reported depressive symptoms, but not anxiety symptoms, in stimulant naïve boys aged 10 to 17 years with ADHD, and comparable levels of depression and anxiety in stimulant naïve and prior medicated boys aged 12 to 17 years with ADHD. These findings are in line with hypotheses of shared genetic components for ADHD and depression, or early environmental influences, and do not support a role of stimulant medication in the development of depression and anxiety. Thus far, the role of stimulant use on mood and affect in humans has received little attention, while it is relevant to know whether stimulants affect the development of comorbidity, as scientific consensus and guidelines on the treatment of ADHD depend on such knowledge.

Hence, limitations of the present study should be kept in mind and the findings should be replicated in order to adequately conclude a lack of stimulant effects on the development of depression and anxiety. For future research, it would be of interest to prospectively determine the effect of stimulants on the development of depression and anxiety, preferably in a randomized, placebo-controlled trial.
## Appendices chapter 2

### Appendix 2.1 | Regression analysis with age and stimulant use predicting depressive symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.02</td>
<td>.19</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Stimulant use</td>
<td>-0.02</td>
<td>0.06</td>
<td>-0.3</td>
<td>0.54</td>
<td>0.63</td>
</tr>
<tr>
<td>Age * stimulant use</td>
<td></td>
<td></td>
<td></td>
<td>-0.04</td>
<td>0.05</td>
</tr>
</tbody>
</table>

R²: .03
F: .04

\( \alpha \) = .04 for stimulant use, \( \alpha \) = .03 for the interaction term, and \( \alpha \) = .02 for age.

### Appendix 2.2 | Regression analysis with age and stimulant use predicting anxiety symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
</tr>
<tr>
<td>Age</td>
<td>-0.36</td>
<td>1.14</td>
<td>-0.04</td>
<td>-1.54</td>
<td>1.99</td>
</tr>
<tr>
<td>Stimulant use</td>
<td>0.28</td>
<td>3.21</td>
<td>.01</td>
<td>-23.80</td>
<td>33.63</td>
</tr>
<tr>
<td>Age * stimulant use</td>
<td>1.75</td>
<td>2.43</td>
<td>.98</td>
<td>&lt; .01</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

R²: < .01
F: .05

\( \alpha \) = .05 for stimulant use, \( \alpha \) = .04 for age, and \( \alpha \) = .03 for the interaction term.
Chapter 2

Comorbid depression and anxiety symptoms in children and adolescents with ADHD


Chapter 2
Comorbid depression and anxiety symptoms in children and adolescents with ADHD


