The development of depression in children and adolescents with ADHD

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General Introduction

Overview

Attention Deficit/Hyperactivity Disorder (ADHD) is a major and a common childhood-onset mental health problem that is yet to be fully understood. One yet unresolved problem – amongst the plethora of questions that plague scientific enquiry into this elusive disorder – is the development of depression in many but not all affected individuals with ADHD. This thesis is aimed at clarifying some of the issues related to the development of depression in children and adolescents with ADHD. This chapter begins with a brief introduction into the origins of the term 'ADHD' and its definition. This is followed by a short discussion of one defining characteristic of ADHD: the development of multiple comorbidities. Next, the existing literature on depressive comorbidity in ADHD is presented and the context of the main scientific question of this thesis is introduced. Further, goals of this thesis are described and the respective chapters dealing with each of these are outlined.

Definition and evolution of the term ADHD

Attention Deficit/Hyperactivity Disorder or the more commonly used abbreviation, ADHD, is a mental health disorder that begins early in childhood. ADHD is often defined, as the name suggests, by the presence of hyperactive, impulsive and inattentive symptoms in multiple settings for at least six months, which are excessive in comparison to other children of the same age (American Psychiatric Association 2013). The earliest descriptions of ADHD have dated past back to the mid-eighteenth century. Back then, this disorder was poorly understood, and incorrectly classified as a 'moral defect' or a 'discipline problem'. Between the eighteenth century and the early twentieth century, not much progress was made in the understanding of ADHD. The first version of the DSM appeared in 1952, but did not recognize the disorder at all. It was only in the second version (DSM-II) in 1968 that ADHD was considered as a mental health disorder. The DSM-II labelled the disorder as 'hyperkinetic-impulse disorder' and did not include the inattention dimension. By 1980, a newer version of the DSM (DSM-III) arrived that included both the hyperactivity/impulsivity and the inattentive dimensions in its definition of ADHD.

Between the introduction of the DSM-III in 1980 and now, the conceptualisation of ADHD has undergone further changes. For example, while the DSM-III labelled the disorder as 'attention deficit' either with or without hyperactivity, the revised version in 1987 (DSM-III-R) did not subdivide the

disorder based on presence or absence of hyperactivity. Instead the DSM-III-R included hyperactivity as a core symptom. The next version, the DSM-IV, classified ADHD into three subtypes – hyperactive/impulsive, inattentive, and combined. The most recent changes were made in 2013, with the introduction of DSM-5, which changed one of the diagnostic criteria: a diagnosis of ADHD now requires symptoms to have arisen by the age of 12 instead of 7 years as in previous DSM versions.

More changes to the diagnostic criteria of ADHD may be expected in the future. One example would be that symptoms of sluggish cognitive tempo (SCT) may be included in the diagnostic criteria. SCT is a symptom complex characterised by day dreaming, drowsiness, sluggishness, and decreased activity (Fassbender, Krafft, & Schweitzer, 2015; Barkley 2014; Penny, Waschbusch, Klein, Corkum, & Eskes, 2009), and is present in many children with ADHD. It is correlated with inattentive symptoms and therefore often considered an integral symptom of ADHD (Carlson & Mann 2002; Garner, Marceaux, Mrug, Patterson, & Hodgens, 2010; McBurnett, Pfiffner, & Frick, 2001). Others point out that SCT also occurs in individuals without ADHD and may thus better be considered a separate disorder (Lee, Burns, Snell, & McBurnett, 2014; McBurnett et al., 2014; Wilcutt et al., 2014; Leopold, Bryan, Pennington, & Willcutt, 2015). Another criticism of the current diagnostic criteria concerns the emphasis the DSM puts on categorical definitions of ADHD and symptom score cut-offs to diagnose the disorder (Coghill & Sonuga-Barke, 2012), which ignores studies that have shown that symptoms of hyperactivity/impulsivity and inattention lie along a continuum and that the symptom severity of children with a diagnosis of ADHD ranges from moderate to severe levels (Lubke, Hudziak, Derks, van Bijsterveld, Boonsma, 2009; Polanczyk, 2014; Hudziak, Achenbach, Althoff & Pine, 2007; Kraemer, 2007). Future changes to the conceptualisation of ADHD may include replacing or complementing the categorical diagnoses with dimensional measures (Kraemer, 2007). These two examples of possible future changes in the DSM illustrate the heterogeneity of ADHD, which is one of the reasons that ADHD is difficult to define.

The changing definitions of ADHD complicate sampling for research, clinical decision making, diagnosis and initiation of therapy. Further, the conceptualisation of ADHD is complicated by the fact that individuals with ADHD may differ in characteristics such as presence or absence of SCT and symptom severity, and that several subgroups may exist in the ADHD population. Such considerations challenge not only clinical judgements but also research, as the changing standards have added to the heterogeneity in literature. Despite these concerns, it is well-established that ADHD is associated with significant distress and reductions in quality of life. It is also well-known that the symptoms of ADHD merely do not explain the full range of impairments that occur in affected individuals. Rather, impairments are unrelated, to a large extent, to the symptom severity or treatments received. Key among

the distress and impairments involved in ADHD is the emergence of comorbid mental health conditions over time (Pliszka, 1998; Pliszka, 2000).

Comorbid disorders

ADHD is diagnosed in 4-9% of children world-wide, of whom 30-50% have developed additional mental health problems by adolescence (Angold, Costello, & Erkanli, 1999; Biederman, Newcorn & Sprich, 1991). Amongst adults with ADHD, about 80% suffer from at least one comorbid condition, while about 50% have two or more comorbid disorders (McGough et al., 2005; Meinzer, Pettit, Viswesvaran, 2014). An individual with only ADHD, without comorbidity, is thus the exception rather than the norm (Jensen et al., 2011). Comorbidities lead to difficulties in assessing impairment levels, clinical judgements, and treatment decisions (MTA Cooperative Group, 1999; Pliszka, 2003), and inevitably increase problems in daily functioning (Biederman et al., 1991). Amongst all comorbid disorders, the occurrence of oppositional defiant disorder (ODD) and conduct disorder (CD) are the most common, affecting 30-50% and 25-35% of all children respectively (Angold et al., 1999; American Psychiatric Association, 2013; Jensen, Martin & Cantwell, 1997). Apart from ODD and CD, autism spectrum and learning disorders are also common, albeit both show a wide heterogeneity in rates across studies: between 20-70% of children with ADHD show symptoms of learning disorders, while 10-90% have symptoms of autism spectrum disorders (American Psychiatric Association, 2013; Jensen et al., 1997; Pliszka, 1998; Pliszka, 2000; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Further, anxiety disorders are present in 25-30%, and mood disorders in 10-30% of children with ADHD (Angold et al., 1999; Biederman et al., 1991).

Comorbidity of ADHD and depression

To date, most studies have investigated the associations of ADHD with learning problems, ODD and CD. Fewer studies are present on the association of ADHD with anxiety and autism spectrum disorders. Of all ADHD comorbidities, the association with depression has been studied the least (Deault, 2010). Consequently, there is a lack of information on the mechanisms through which depression develops in individuals with ADHD (Steinberg & Drabick, 2015). The development of depression is associated with impaired social, emotional, cognitive and academic functioning of children with ADHD (Meinzer at al., 2014). Comorbid depression also leads to impairments in adulthood and to increased risks for substance misuse, social functioning problems, cognitive functioning difficulties, suicidal attempts, risky behaviour, and occupational difficulties (Bramham et al., 2012; Michielsen et al., 2013; Semeijn et al., 2015). In addition, the development of depression impairs the ability of affected individuals to perceive their symptoms and estimate their impairment levels (Bramham et al., 2012). This may negatively affect their

decision to seek professional help and also impair quality of life. Taken together, it is imperative that this comorbid condition be examined in-depth.

The lack of knowledge regarding the ADHD-depression association hampers timely and adequate intervention. Furthermore, treatment regimens for individuals with ADHD and comorbid depression are currently ill-established. The rule of thumb in these cases is to treat whichever of the two (ADHD or depression) is associated with higher severity (Daviss, 2008). This approach is often ineffective and requires changes to management protocols to adequately tackle the risks of deteriorating functioning associated with comorbid depression (Daviss, 2008). The optimum route to take involves preventing the development of depression in children and adolescents with ADHD. For this it is important to recognise or anticipate its occurrence in vulnerable groups. Identification of the correlates of comorbid depression in children and adolescents with ADHD is, however, an ongoing task.

Until recently, the association of ADHD with depression was considered an epiphenomenal co-occurrence, based on the idea that all psychiatric conditions are correlated and the occurrence of a single comorbidity can be predicted from the common co-occurrence of all other mental health problems (Angold et al., 1999). Recent research has shown that this view may not be true; individuals with ADHD are likely to show higher rates of depression than those without ADHD even after controlling for other comorbid conditions (Biederman et al., 2008; Meinzer et al., 2013).The co-occurrence of ADHD and depression may also be explained as an overlap in diagnostic criteria of the two disorders, such as concentration problems and sleep difficulties. This view too has been countered by studies that show associations between ADHD and depression after excluding overlapping symptoms (Biederman, Mick, & Faraone, 1998a; Biederman, Faraone, Mick, & Lelon, 1995; Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995). In short, the relationship of ADHD with depression is not merely a spurious association, but a genuine comorbid association that has been established by several studies (Biederman et al., 1991; Meinzer et al., 2015; Meinzer et al., 2014).

Several explanations have been floated for the association of ADHD with depression. These include: (i) sharing of common vulnerabilities by ADHD and depression, leading to a simultaneous increase in risk for developing both disorders; (ii) increased risk for depression attributed by ADHD, and; (iii) existence of a separate disorder type. These three hypothesized rationales for the ADHD-depression association are further explained below.

First, previous studies indicate that ADHD and depression share common vulnerabilities that may lead to their co-development (Biederman et al., 1991).[1] For example, genetic factors such as the 5-HTTLPR, 40-basepair (bp) Variable Number Tandem Repeat (VNTR) of DAT1, and 48-bp VNTR of DAT1 may underlie both ADHD and depression by way of their effects on the serotonergic and dopaminergic pathways (Gatt, Burton, Williams, & Schofield, 2015; Meinzer et al., 2014). Variation in reward responsivity may be another common underlying factor for both ADHD and depression: depression is associated with blunting of responses to potentially rewarding stimuli (Forbes, 2009; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008) and ADHD is associated with reduced neural activation during reward anticipation (Scheres, Milham, Knutson, & Castellanos, 2007; Stark et al., 2011). One study reported poor hedonic responsivity in both ADHD-inattentive subtype and depression (perhaps due to repeated social or academic failures) and suggested that it was a common factor, the development of which is associated with both ADHD and depression (Meinzer, Pettit, Leventhal, & Hill, 2012). These vulnerability factors explain only part of the ADHD-depression association though, and are based on a few studies. Moreover, the 'common vulnerability factor' explanation does not clarify why some individuals with such vulnerability factors escape development of one disorder, nor does it explain the absence of any (known) common vulnerabilities in many individuals with both ADHD and depression. Clearly, further research is needed to understand how common factors lead to the development of ADHD and depression, as well as to detect more such vulnerability factors. This, however, is not a topic of study for this thesis.[2]

Second, the co-occurrence of the two problems is attributed to an increased risk for depression induced by ADHD (Meinzer et al., 2014). The pathway from ADHD to depression is more plausible than the reverse pathway from depression to ADHD (Ostrander & Herman, 2006). However, information on the mediators involved in this pathway is currently limited (Deault, 2010; Meinzer, 2015; Seymour et al., 2012; Steinberg et al., 2015). One of the aims of this dissertation includes understanding some of the mediators involved in the pathway from ADHD to depression.

[1] While these common vulnerability factors are present early on, and some may even be present right since birth, the development of ADHD precedes the onset of depression, which is the age-norm for presentation of these disorders.

[2] To conduct this type of research, one would want to determine the genetic profile that explains both disorders. Such work needs to be done in very large samples, and cannot be done in the TRAILS sample on its own. It should be added that the success of such genetic work has been rather limited for psychiatric disorders so far. Moreover, the common environmental risk factors must be determined early on, prior to the development of ADHD, and be tracked continuously up to the development of depression in order to determine the relationships of such common factors to both disorders. This is not possible in TRAILS due to the age range of the sample studied, which was recruited only after the development of ADHD.

Third, some researchers have proposed that ADHD with depression constitutes a separate and new disorder type (Meinzer et al., 2014). To define a new disorder, this hypothesised disorder must have no semblance to another existing disorder type. In case of ADHD-depression, aetiology, correlates, and consequences of the combined condition must be uniquely identifiable as compared to ADHD alone or depression alone. Current guidelines on the identification and definition of a new disorder type, distinct from existing disorders, require to determine its validity as a uniquely identifiable phenomenon (Milich et al., 2001; Widiger & Clark, 2000). Criteria for determining the validity of a hypothesized new disorder were first established by Emil Kraepelin (Widiger et al., 2000) and later modified by Cantwell and Baker (1988), and Feighner et al. (1972). According to these criteria, a six-step procedure should be followed to establish validity of a disorder, including: (i) a description of features of the disorder; (ii) a clinical description of the disorder using physical and neurological features; (iii) laboratory studies; (iv) family psychopathology and family interaction studies; (v) follow-up and characterization studies, and (vi) treatment outcome studies. It is generally agreed that more of these approaches indicate unique featurs, the stronger is the evidence to support a disorder classification (Milich et al., 2001; Widiger et al., 2000). Based on the above-mentioned criteria, there is a scarcity of useful information to determine whether ADHD-depression constitutes a separate disorder. A few cluster analytic studies found no evidence for a subgroup with combined ADHD and depressive symptomatology, showing that it may be difficult to delineate the combined condition from ADHD alone (Nigg, Goldsmith, & Sachek, 2004; Pauli-Pott, Dalir, Mingebach, Roller, & Becker, 2014; Wilens et al., 2002). Of note is that studies do show an aggregation of ADHD and depressive symptoms in affected families. That is, unaffected parents and siblings of children with ADHD are more likely to be depressed than families of children without ADHD (Bhatia, Nigam, Bohra, & Malik, 1991; Grigoroiu-Serbanescu, et al., 1991; Mick, Biederman, Santangelo, & Wypij, 2003). Although such a familial aggregation may suggest the presence of a separate disorder type, it is insufficient evidence by itself (Feighner et al., 1972). A second aim of this thesis is to further explore the validity of the ADHD-depression disorder, with a particular focus on the first of the above-mentioned criteria: characterization of individuals affected with the both ADHD and depression to see whether this combination could qualify as a separate disorder. Evidence for classification of ADHD-depression as a separate disorder would be delivered if it could be shown that individuals affected with the combined condition show unique qualitative characteristics that differ from cases of ADHD without depression and depression without ADHD, which are not merely their sum of the characteristics seen in the two component disorders (Rutter, 1978).

Summarizing, knowledge of the ADHD-depression relationship is still lacking in many respects, and at least two major issues remain to be tackled. First, it is still unclear whether co-occurring ADHD

and depression constitutes a separate disorder type. Second, the mechanisms through which depression may develop in individuals with ADHD are not clear. In particular, mediators and moderators of the pathways from ADHD to depression are to be further determined.

Goals of this thesis

This thesis aims at: a) characterising adolescents with ADHD and comorbid depression, and; b) identifying mediators of the pathways from ADHD to depression. To achieve these goals, I conducted a number of studies, which are described in the following chapters of this thesis. First, I assessed and compared the cognitive functioning of adolescents with ADHD and comorbid depression to that of adolescents with only ADHD, only depression and neither ADHD nor depression (chapter 2). Second, I compared the family functioning characteristics of adolescents with ADHD and depression to that of adolescents with either disorder alone or no disorders (chapter 3). Third, the role of comorbid ODD/CD and anxiety disorders as mediators of the ADHD-depression pathway was explored (chapter 4). Fourth, I studied the effects of peer functioning difficulties on the risk for depression (chapter 5). Fifth, the pathways from ADHD through peer difficulties to depression were examined in-depth in a narrative review (chapter 6). This thesis ends with a summary of the evidence gathered from all above-mentioned studies, followed by a discussion that puts these results in context of information from existing research findings, deliberates on the translation of these research findings to practical use, and suggests avenues for future investigations (chapter 7). Results from this research will assist in the early identification of individuals at risk for comorbid depression, clarify processes leading to comorbid depression, and add to our understanding as to whether or not ADHD plus depression constitutes a separate disorder, and thereby improve understanding of the ADHD-depression association.

Framework of studies

Studies included in this thesis were carried out using data from the TRacking Adolescents' Individual Lives (TRAILS) cohort. The TRAILS cohort is a notable and well-characterised sample of adolescents, who have been followed-up repeatedly, for a period of over twelve years now (Oldehinkel et al., 2015). This cohort provides a sound framework to reach the goals outlined previously. Thus far, studies on the associations of ADHD and depression have utilised cross-sectional samples. The longitudinal nature of the TRAILS cohort stands to provide additional information on the ADHD-depression relationship, especially on the pathways that lead from one disorder to the other.

TRAILS included participants from the general population (population cohort) as well as clinically referred subjects (clinical cohort; referral only in part for ADHD). Most studies described in

this thesis used data from the general population sample of TRAILS, with the exception of chapter 5 that included participants from both the population and clinical cohort. Much of the ADHD literature is based on information from referred samples, and little is known of this disorder in the general population (Daviss, 2008; Meinzer et al., 2013). Clinically referred participants, who tend to have high symptom severity, multiple comorbidities and functional impairments, are the norm in ADHD-related research. Thus, use of the TRAILS population cohort will provide new and more balanced information on ADHD and its characteristics in the general population.

Diagnoses of ADHD and depression in the TRAILS participants were made using criteria of the DSM-IV (American Psychiatric Association, 1994; Kessler et al., 2004; Wittchen, Robins, Semler, & Cottler, 1993). For ADHD, the criteria required presence of hyperactivity/impulsivity symptoms and/or inattentive symptoms by the age of 7 years. For assessments of depression, lifetime diagnoses of depressive disorders were used (please see table A for the complete DSM checklist of symptoms). As all participants were 19 years at the time of the last assessment, the development of comorbid depression up to only this time-point was assessed. Although it is certainly possible that comorbid depression developed (and will develop) later in these participants with age, the likelihood of such an occurrence is probably much less than in (late) adolescence. A recent study showed that the development of depression in individuals with ADHD reaches peak levels at 18 years of age, and that the risks thereafter reduce dramatically (Meinzer et al., 2015). Hence, the studies in this thesis give a fairly inclusive picture of individuals with ADHD and comorbid depression.

Table A DSM checklist of symptoms for ADHD and depression

DSM symptom checklist
ADHD
I] Inattention (six of the following nine symptoms must have been present in at least two settings for a minimum of six months for a diagnosis of ADHD-inattentive subtype)
Often does not give close attention to details or makes careless mistakes in schoolwork, work or other activities
Often has trouble keeping attention on tasks or play activities
Often does not seem to listen when spoken to directly
Often does not follow through on instructions and fails to finish schoolwork, chores or duties in the work place (loses focus, gets sidetracked)
Often has trouble organizing activities
Often avoids, dislikes, or doesn't want to do things that require sustained metal effort
Often loses things necessary for tasks or activities
Is often easily distracted
Is often forgetful in daily activities
II] Hyperactivity (six of the following nine symptoms must have been present in at least two settings for a minimum of six months for a diagnosis of ADHD-hyperactive impulsive subtype)
Often fidgets with hands or feet or squirms in seat when sitting still is expected
Often gets up from seat when remaining in seat is expected
Often excessively runs about or climbs when and where it is not appropriate
Often has trouble playing or doing leisure activities quietly
Is often "on the go" or often acts as if "driven by a motor"
Often talks excessively
Often blurts out answers before questions have been finished
Often has trouble waiting one's turn
Often interrupts or intrudes on others
Additional criteria for ADHD diagnosis: - Age of onset at or before 7 years - Presence of at least 6 inattentive and six hyperactive symptoms for a diagnosis of ADHD-combined subtype - Clear evidence of clinically significant impairment in social, academic, or occupational functioning - Determining that the symptoms are not better accounted for by another mental health disorder
Major depressive disorder
Depressed mood or a loss of interest or pleasure in daily activities for at least two weeks
Presence of at least 5 out of the following nine specific symptoms[3]: - Depressed mood or irritable most of the day - Decreased interest or pleasure in most activities, most of the day, each day - Significant weight change (5%) or change in appetite - Insomnia or hypersomnia - Change in activity levels such as psychomotor agitation or retardation - Fatigue or loss of energy - Guilt/worthlessness

[3] For minor depression must have at least two but not five of the nine symptoms listed

- Diminished ability to think or concentrate, increased indecisiveness - Suicidal thoughts
Additional criteria: - Mood represents a change from person's baseline - Symptoms cause significant impairment in functioning - Screening for conditions that may mimic or co-exist with major depressive disorder (substance abuse, medical illnesses, mania, hypomania, bipolar disorder, schizophrenia, schizoaffective disorder, bereavement)
Dysthymic disorder
Depressed mood most of the day, for more days than not, for at least two years
Presence of two or more of the following symptoms: - Poor appetite or overeating - Insomnia or hypersomnia - Low energy or fatigue - Low self-esteem - Poor concentration or difficulty in decision-making - Feeling of hopelessness
Symptoms cause significant impairment in functioning