Chapter 1

Introduction

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) occurs in approximately 5% of school-aged children (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision [DSM-IV-R]; American Psychiatric Association, [APA], 2000). ADHD is characterised by excessive motor activity, inattentiveness, and impulsivity (APA, 2000). Children with ADHD frequently meet the criteria for at least one additional diagnosis, referred to as comorbidity (Angold Costello, & Erkanli, 1999). Comorbidities may include oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorder, depression, developmental coordination disorder (DCD) and reading disorder (RD) (Gilger, Pennington & DeFries, 1992; Jensen et al., 2001).

Among psychiatric disorders, ADHD is frequently associated with RD (Kronenberger & Dunn, 2003). RD, also referred to as dyslexia, is defined as an unexpected, persistent failure to acquire efficient reading skills, despite conventional instruction, adequate intelligence, and socio-cultural opportunity (APA, 2000). RD alone occurs in approximately 5% of school-aged children (APA, 2000). Research estimates the comorbidity of RD in children with ADHD between 18 - 45% (Dykman & Ackerman, 1991; Mayes & Calhoun, 2006; Semrud-Clikeman et al., 1992; Wisniewska, Baranowska & Wendorff, 2007). These estimates differ slightly for boys and girls: in a large American community sample, 51% of the boys with ADHD also met criteria for RD and 46.7% of the girls with ADHD met criteria for RD (Yoshimasu et al., 2010). The comorbidity of ADHD in a referred RD population has been found to be 18 % for girls and 42 % for boys (Willcutt & Pennington, 2000). Another study found that 36% of the subjects with RD met also the criteria for ADHD (Gayán et al., 2005). These numbers indicate that the comorbidity between ADHD and RD occurs far more often than would be expected by chance.

ADHD and RD are both highly heritable (Willcutt, Betemann et al., 2010; Willcutt, Pennington et al., 2010). Several family and twin studies have demonstrated that the *comorbidity* between RD and ADHD may be due to common genetic factors (Gayán & Olson, 2001; Willcutt, Pennington & DeFries, 2000). Genetic correlations between RD and hyperactivity symptoms range between r_g=.37-.40, r_g=.43-.70 between RD and inattention symptoms, and r_g=.43-.63 between RD and total ADHD symptoms (Willcutt, Pennington, Olson & DeFries, 2007). There is evidence of chromosomal regions that are associated with an increased risk of being affected with both ADHD and RD (Gayán et al. 2005; Zhou et al., 2008). Gayán et al. (2005) found evidence for linkages in the chromosomes region 14q32, 13q32 and 20q11 in families with RD and ADHD problems. The chromosome locus 1p36 may harbour a quantitative trait affecting both inattention and RD (Zhou et al., 2008). In addition, there is evidence that the ADRA2A gene may play a role in susceptibility for both ADHD and RD (Stevenson, Pennington, Gilger, DeFries & Gillis, 2005). These results point to a partially overlapping genetic basis of ADHD and RD. However, results are not clear and indicate

various loci susceptible for this comorbidity. The identification of shared genes of ADHD and RD and comorbid ADHD+RD is currently being pursued. An alternative approach to studying the association of ADHD with RD is to examine the overlap of these two disorders in terms of their neurocognitive functioning.

Neurocognitive functions

In this study, we will attempt to unravel the origin of comorbidity between ADHD and RD by studying the specificity and/or overlap in neurocognitive deficits between these disorders. Neurocognitive functions refer to functions as language, memory and executive function and may serve as endophenotypes. Endophenotypes are supposed to mediate the relationship between a genetic predisposition of a disorder (genotype) and disease symptoms of that disorder (phenotype) (Gottesman & Gould, 2003). Like biochemical or brain markers, neurocognitive functions may have this intermediate role and could serve as endophenotypes. By focusing on endophenotypes, it may be possible to identify susceptibility genes for a disorder. Endophenotypes are considered to be less genetically complex than phenotypes, since they are aetiologically closer to the disease genes than phenotypes (Almasy & Blangero, 2001; Castellanos & Tannock, 2002). Endophenotypes may therefore be more useful in exploring different pathways leading to a disorder, than clinical phenotypes (Waldman, 2005). One criterion for a suitable endophenotype is that it is associated with the clinical manifestation of the disorder (phenotype). To aid in the search for suitable endophenotypes of ADHD, RD and comorbid ADHD+RD in order to unravel the origins of the comorbidity between ADHD and RD, we search in this thesis for specific and overlapping neurocognitive functions in ADHD and RD. Specific neurocognitive functions may help in the distinction of ADHD from RD, whereas overlapping neurocognitive functions between ADHD and RD may point to common aetiologic factors.

Double dissociation design

To study the overlap and specificity in neurocognitive functions between ADHD and RD more systematically, a double dissociation design may be useful. A double dissociation refers to the separateness of two disorders on two contrasting domains. A double dissociation between ADHD and RD would be supported if ADHD and RD exhibit contrasting profiles on two distinct domains that are supposed to be characteristic for either ADHD or RD (Pennington, Groisser & Welsh, 1993; Willcutt, Pennington, Olson, Chhabildas & Hulslander, 2005). If the two disorders could be separated on two distinct domains, this would be evidence that ADHD and RD have distinct aetiologies. If, however, a double dissociation does not occur between ADHD and RD, it could be concluded that ADHD and RD have a common aetiology. Thus, studies employing a double dissociation design may help identify potential overlapping neurocognitive deficits in ADHD and RD, and what neurocognitive variables could dissociate ADHD from RD.

Including a comorbid ADHD+RD group in studies with a double dissociation design could aid in unravelling the origins of the combination of ADHD and RD. The comorbid group may be characterised by a combination of the deficits of the single diagnosis groups. In contrast, more severe or distinct deficits in the comorbid group than in the single diagnosis groups could indicate that the combination of ADHD and RD is a distinct clinical condition differing from single clinical conditions of ADHD and RD. Thus ideally, studies that test the overlap and specificity of neurocognitive deficits in ADHD and RD include four groups: a group of children with ADHD only, a group of children with RD only, a comorbid group that include children that have both ADHD and RD, and a control group.

Neurocognitive findings in RD

When using the double dissociation design, it is essential to study known characteristic neurocognitive deficits of a particular disorder. Impairments that have been assumed to be uniquely associated with RD are: reading deficits, rapid naming deficits and phonological impairments. However, reading deficits have also been found in ADHD, although of a less severe nature than in RD (Ghelani, Sidhu, Jain & Tannock, 2004). Although rapid naming often has been associated with RD, deficits in rapid naming also occur in children with ADHD (Ghelani et al., 2004; Shanahan et al., 2006; Tannock, Martinussen & Frijters, 2000; Rucklidge & Tannock, 2002). Rapid naming refers to the skill to name as quickly as possible sequentially presented alphanumerical (letters, digits) and non-alphanumerical stimuli (colours, objects). Some studies indicate that the group of children who have comorbidity of ADHD and RD have a different profile on rapid naming than the single diagnosis of ADHD and RD.

Deficits in phonological processing are hypothesised to lie at heart of the reading deficits in RD and are uniquely found in RD (Snowling, 2000). Phonological processing refers to processing of the sound structure of oral and written language (Wagner, Torgesen & Rashotte, 1994). Studies that compared phonological processing in ADHD and RD showed that phonological processing deficits are limited to RD (Gooch, Snowling & Hulme, 2010). Phonological processing deficits are suggested to reflect impaired auditory temporal processing, referring to the temporal processing of auditory information such as speech stimuli (such as phonemes) and non-speech stimuli. Both ADHD and RD have been associated with impaired auditory temporal processing (Breier, Fletcher, Foorman, Klaas & Gray, 2003).

There is evidence of overlap in impairments in rapid naming in ADHD and RD, suggesting a common pathway of ADHD and RD. Phonological deficits, in contrast, are uniquely seen in RD and not in ADHD, which suggest a possible route to distinguish these two disorders.

Neurocognitive findings in ADHD

We will study neurocognitive deficits that have frequently been found characteristic for ADHD, such as in executive functioning (Pennington & Ozonoff, 1996) and intra-individual variability in reaction times (IIV) (Castellanos & Tannock, 2002). Executive functions include

those functions that are needed for goal directed behaviour, such as planning, monitoring, and flexibility (ability to change one's actions) (Pennington & Ozonoff, 1996). Additional executive functions include inhibition (ability to stop an action or response) and working memory (holding information online). Although children with ADHD have difficulties in all these areas of executive functioning, they exhibit deficits especially in inhibition and working memory (Barkley, 1997; Martinussen, Hayden, Hogg-Johnson & Tannock, 2005).

Executive function deficits are not limited to ADHD but also occur in children with RD (Chiappe, Hasher & Siegel, 2000; Donfrancesco, Mugnaini, & Dell'Uomo, 2005; Helland & Asbjørnsen, 2000; Roodenrys, Koloski & Grainger, 2001). Deficits in inhibition have been shown in RD (Purvis & Tannock, 2000; Willcutt et al., 2005), and there is evidence for deficits in working memory in both ADHD and RD. A meta-analysis found that both spatial and verbal working memory are affected in both ADHD and RD (Martinussen et al., 2005).

IIV refers to the phenomenon that reaction times can fluctuate during a task, thus someone can have relatively slow or fast reaction times compared to his other reaction times on a particular task. Especially, children with ADHD are considered to have occasional extremely slow responses compared to children without ADHD. Although IIV has been considered to be impaired uniquely in ADHD (Castellanos & Tannock, 2002; Klein, Wendling, Huettner, Ruder & Peper, 2006; Vaurio, Simmonds & Mostofsky, 2009), there is evidence that comorbid RD in ADHD has a differential effect on IIV (Williams, Strauss, Hultsch, Hunter & Tannock, 2007). Williams et al. (2007) compared children with ADHD with children with ADHD+RD, RD and normal controls found that increased IIV is not limited to ADHD but was also associated with RD. The comorbid group had a unique profile of increased IIV compared to the single groups on all and slow trials which suggest that comorbid RD in ADHD leads to unique deficits of increased IIV (Williams et al., 2007).

Taken together, these results indicate that impairments in inhibition, working memory, and IIV have not only been found in ADHD but also in RD. Hence, there is a suggestion in the literature that ADHD and RD show overlap in some executive dysfunctioning.

Three hypotheses about comorbidity

Based on a double dissociation method, three hypotheses on the origins of the comorbidity between ADHD and RD have been suggested in the literature: the *phenocopy hypothesis*, the *cognitive subtype hypothesis* and the *common aetiology hypothesis.* All three hypotheses are discussed hereafter.

The *phenocopy hypothesis* proposes that one disorder may lead to a copy of the symptoms but not of the whole syndrome of the other disorder (Pennington et al., 1993). For example, frustrations during reading in children with RD may lead to symptoms of inattention and hyperactivity. Phenotypically or clinically, these children show the symptoms of both ADHD and RD. However, these children do not show the underlying characteristics of ADHD such as

a particular brain or neurocognitive deficit associated with ADHD, but only impairments in endophenotypes associated with RD. The *cognitive subtype hypothesis* suggests that children with both ADHD and RD have a distinct form or more severe form of ADHD or RD than children with either disorder alone (Rucklidge & Tannock, 2002). Children with only RD could be dissociated from children with only ADHD. The *common aetiology hypothesis* suggests that ADHD and RD have common genetic origins, explaining why no double dissociation is found between ADHD and RD (Willcutt et al., 2005). According to this theory, children with ADHD, RD and children with ADHD+RD show common deficits.

Evidence for the three comorbidity hypotheses

The *phenocopy hypothesis* has been supported in a study of Pennington et al. (1993). They found a double dissociation between ADHD and RD: only children with ADHD exhibited executive functioning problems and only children with RD exhibited difficulties in phonological functioning. The comorbid group predominantly had the neurocognitive profile of the RD group. The results of Pennington et al. (1993) have been partly replicated in a study by Närhi and Ahonen (2000). In that study, the comorbid group exhibited naming deficits like the RD group. However, the comorbid group did not differ from the ADHD, RD or control groups in executive functioning. Other studies failed to support the *phenocopy hypothesis* (Nigg, Hinshaw, Carte & Treuting, 1998; Rucklidge & Tannock, 2002; Willcutt et al., 2001).

There is evidence that the comorbid ADHD+RD group shows different neurocognitive deficits than the combined deficits associated with both ADHD and RD. A significant interaction between ADHD and RD on one or more measures tapping neurocognitive deficits associated with ADHD and RD would support the *cognitive subtype hypothesis*. Individuals with both ADHD and RD were found to be more impaired than individuals with a single diagnosis of ADHD or RD in terms of executive functioning and phonological functioning (Willcutt et al., 2001), rapid naming (Bental & Tirosh, 2007; Rucklidge & Tannock, 2002), verbal working memory (Bental & Tirosh, 2007) and verbal long term memory (Kaplan, Dewey, Crawford, & Fisher, 1998).

Evidence for the *common aetiology hypothesis* was provided by Willcutt et al. (2005), who found evidence that children with ADHD, children with RD and children with ADHD+RD had overlapping deficits in inhibition, processing speed and verbal working memory. Since the three groups had overlapping deficits, Willcutt et al. (2005) concluded that RD and ADHD share common aetiological factors. Overlapping deficits in processing speed between ADHD and RD have been confirmed in a study of Shanahan et al. (2006).

All three hypotheses receive empirical support, although they are not mutually exclusive. It can only be concluded that the origins of comorbidity of ADHD and RD thus far remain unclear. One reason for the contradicting findings is that the three hypotheses are based on the assumption that ADHD and RD could be distinguished through a single neurocognitive

deficit. Pennington (2006) proposed a multiple deficit model, since there is increasing evidence that the aetiology of heterogeneous and complex developmental disorders such as ADHD or RD, is multifactorial and involves the interaction of multiple risk and protective factors, which can be either genetic or environmental. Consequently, comorbidity of heterogeneous developmental disorders such as ADHD and RD is to be expected because of shared aetiological and cognitive risk factors (Pennington, 2006). This multiple deficit model suggests that ADHD, RD and the comorbid condition may result from a different combination of neurocognitive deficits, some shared and some not shared. This may lead to the rejection of a single cognitive deficit model and lead to the conclusion that the overlap of more than one neurocognitive dysfunction produces the comorbidity between ADHD and RD (McGrath et al., 2010; Willcutt, Betemann et al., 2010; Willcutt, Pennington et al., 2010).

This thesis is aimed at elucidating which neurocognitive functions are shared and which are not shared between ADHD and RD, by using a double dissociation design.

Treatment Options

Overlap in neurocognitive impairments between ADHD and RD, possibly indicative for shared aetiological factors in ADHD and RD, may suggest that treatments that are effective in either ADHD or RD, may also be effective in the other disorder. However, despite their high comorbidity ADHD and RD are treated with distinct treatments (Kaiser, Hoza & Hurt, 2008; Shaywitz, Gruen & Shaywitz, 2007). Studies into the effectiveness of one treatment for both ADHD and RD are few. ADHD may share a constitutional inefficiency in the conversion of essential fatty acid precursors to unsaturated fatty acids (Stevens et al., 1995) with RD and dyspraxia (Stordy, 2000), which suggest that supplementation of polyunsaturated fatty acids may be an effective treatment in both children with ADHD and children with RD. There is limited evidence that supplementation of polyunsaturated fatty acids is effective in children with ADHD (Sinn, Bryan & Wilson, 2008) and in children with specific learning disorders (Richardson & Puri, 2002),

In addition, there is some evidence that methylphenidate (MPH), shown to be an effective treatment in ADHD, improves reading performance in children with ADHD and children with ADHD and RD (Bental & Tirosh, 2008; Keulers et al., 2007). These findings suggest that MPH may be effective in both ADHD and RD. In this thesis, we will describe the effects of a pharmacological alternative for MPH, atomoxetine, in both ADHD and RD. Atomoxetine is an effective pharmacological treatment of ADHD and acts as a noradrenaline reuptake inhibitor (Liu et al., 2008).