Chapter 8

Summary and General discussion
MAIN FINDINGS

This thesis aimed to elucidate risk factors associated with a comorbid ODD diagnosis in individuals with ADHD, as well as the impact of a comorbid ODD diagnosis on neurocognitive and brain characteristics of individuals with ADHD. We hypothesized that (i) some of the previously reported characteristics reported to be associated with ADHD are in fact related to comorbid ODD, that (2) individuals with ADHD+ODD show the separate characteristics of both disorders, and that (3) individuals with ADHD+ODD show a double burden, reflected in larger impairments in domains that are implicated in both ADHD and ODD, compared with either of the disorders in singularity. Studying these hypotheses is of great importance since the aetiology and characteristics of this comorbid group are still poorly understood, even though the prevalence of a comorbid ODD diagnosis in individuals with ADHD is substantial and ranges from around 50% in the general population to up to 65% in clinical settings (American Psychiatric Association, 2013; Barkley, Anastopoulos, Guervemont, & Fletcher, 1992; Connor & Doerfler, 2008; Kuhne, Schachar, & Tannock, 1997). Moreover, individuals with both ADHD and ODD have a considerably worse prognosis than individuals with either one of the disorders, both in terms of an increased risk to develop other psychiatric disorders, as well as in terms of educational and vocational perspectives (Anderson & Kiehl, 2012; Loeber, Burke, Lahey, Winters, & Zera, 2000). We used a two-fold approach, studying risk factors and neurocognitive functioning in Part I, and studying brain characteristics in Part II. In the majority of our studies (except our review and meta-analysis [Chapter 4] and our study on structural connectivity [Chapter 6]), we compared three groups of extensively (endo)phenotyped individuals: Those with both an ADHD and ODD diagnosis, those with only an ADHD diagnosis, and a group of typically developing controls. Participants were selected from the NeuroIMAGE cohort (Von Rhein et al., 2015), which included a total of 1069 participants: 751 children from ADHD families and 318 children from control families. ADHD families consisted of participants in the ADHD-only or ADHD+ODD group and their biological brothers or sisters, control families consisted of participants in the control group and their biological brothers or sisters. For the exact number of included individuals per study and the specific aims and main findings, see Table 8.1 for an overview. The results of our studies are summarised below.

Part I – Risk factors & Neurocognitive functioning

In our study on risk factors (Chapter 2) and how these may differ between individuals with ADHD-only and individuals with ADHD+ODD, we found both overlapping and unique risk factors for the diagnostic groups. In addition to a high percentage of explained deviance (ranging from 58% to 62%), the sets of risk factors showed high specificity (95% and 98%) and sensitivity (87% and 80%) when differentiating between the control group and either the ADHD+ODD or the ADHD-only group, respectively. When differentiating between the ADHD-only and ADHD+ODD group, thus predicting the presence of comorbid ODD, the
explained deviance was 16%, the specificity 57%, and the sensitivity 90%. For both ADHD-only and ADHD+ODD, important risk factors were postnatal factors (adverse life events) and transgenerational influences (parental ADHD). However, adverse life events was an even stronger risk factor for the development of comorbid ODD in individuals with ADHD, than for the development of ADHD-only. Moreover, both postnatal adversities (socioeconomic status, deviant peer affiliation), and negative transgenerational influences (parental criticism) were additional factors, that were uniquely associated with the comorbid ADHD+ODD group. Finally, for the development of ADHD-only, maternal smoking was a unique factor. The reported risk factors were significant for all ages.

In terms of neurocognitive functioning a similar pattern of overlapping and unique characteristics for the diagnostic groups was found (Chapter 3). Both the ADHD-only group and the ADHD+ODD group were associated with impairments in cool EF (working memory) and temporal processing (time production). In addition, the ADHD+ODD group was associated with more extended impairments in cool EF (both working memory and inhibition) and in temporal processing (both time production and reproduction), as well as with a unique impairment in hot EF (emotion recognition). There were no unique neurocognitive correlates of ADHD-only. Since the diagnostic groups did not differ in their levels of ADHD symptoms, we can conclude that both findings on risk factors (Chapter 2) and neurocognitive functioning (Chapter 3) are presumably driven by the presence of comorbid ODD, rather than by ADHD.

Concluding, the findings of Part I of this thesis are in line with all three of our hypotheses, since it is clear that previous inconsistent findings on ADHD in terms of risk factors and neurocognitive functioning (hypothesis I), particularly in the domain of emotion recognition (see Chapter 3), may very well be due to the lack of studies that have taken the presence of comorbid ODD into account. Moreover, our findings suggest that individuals with ADHD+ODD show the features of both ADHD and ODD (hypothesis II), and that ADHD+ODD is associated with a double burden (hypothesis III) in terms of both a greater quantity of risk factors and more widespread neurocognitive impairments.

Part II – Brain characteristics

To understand the impact of a comorbid diagnosis of ODD on structural and functional brain characteristics associated with ADHD, it is important to unravel both the characteristics that are associated with ADHD+ODD and ODD itself. However, knowledge on brain characteristics associated with either ADHD+ODD or ODD in singularity is very limited. Therefore, we performed a systematic review and meta-analysis of neuroimaging in individuals with ODD and/or CD, in which we took the role of a comorbid ADHD diagnosis into account (Chapter 4). A total of 29 studies was included, of which 12 structural and 17 functional MRI studies. Involved structures were divided into functional areas related to either cool EF, e.g. the dorsolateral prefrontal cortex and the cerebellum (Prencipe et al., 2011; Rubia,
2011; Yang & Raine, 2009), or hot EF, e.g. the amygdala, anterior cingulate cortex, insula and orbitofrontal cortex (Crowe & Blair, 2008; Prencipe et al., 2011; Rubia, 2011). Taken together, our findings showed the involvement of some cool EF (e.g. precuneus), but predominantly hot EF (e.g. amygdala) associated brain areas in individuals with ODD/CD. Overall, ODD/CD compared with controls was related to smaller brain structures and hypoactivation in several areas. Importantly, we found the involvement of the amygdala and insula to be unique for ODD/CD compared with ADHD. These findings are in line with the behavioural difficulties observed in individuals with ODD and CD, among which difficulties in emotion processing and reduced self-control.

In our surface-based morphometry study (Chapter 5), we investigated the specific impact of a comorbid ODD diagnosis on structural abnormalities in individuals with ADHD, by comparing the two diagnostic groups and controls on grey matter volume, cortical thickness and surface area. We only found group differences in terms of grey matter volume, for which stepwise volumetric reductions in (mainly) frontal areas were present, with the largest reduction for the ADHD+ODD group followed by the ADHD-only group, including the lateral and medial orbitofrontal cortex, caudal middle frontal cortex and superior frontal gyrus. These findings suggest a double burden (greater severity) in abnormalities in areas that are associated with both ADHD and ODD. Additionally, the comorbid group showed unique reductions in grey matter volume in several other structures, such as the precuneus and pars triangularis. Interestingly, these structures were associated with ODD/CD in our meta-analysis (Chapter 4) as well, indicating that ODD, rather than ADHD, may carry the abnormalities in these regions in individuals with both ADHD and ODD. With respect to structural connectivity (Chapter 6), we compared an ADHD+ODD group to an ADHD-only group and found a similar stepwise pattern. Specifically, there was a double burden effect of comorbid ODD on white matter (WM) integrity in terms of lower fractional anisotropy (FA) in individuals with ADHD+ODD in the frontotemporal and striatal areas. Moreover, we found unique impairments in WM integrity for ADHD+ODD compared with ADHD-only in tracts in (orbito-) frontal areas. For both morphometry (Chapter 5) and structural connectivity (Chapter 6), our findings were largely unaffected by the level of ADHD symptoms, indicating that the larger abnormalities in the comorbid group are due to the combined diagnoses, rather than to more severe ADHD symptomatology.

In terms of functional brain characteristics associated with cool and hot EF (Chapter 7), we found that the ADHD-only group and the ADHD+ODD group were both associated with unique abnormalities in terms of neural correlates of cognitive performance. However, there was no evidence of a stepwise pattern or additive effect of ADHD and ODD in terms of abnormalities. During cool EF tasks that tapped into inhibition and working memory, the ADHD+ODD group showed altered activity in rather non-typical clusters including the precuneus, superior parietal, lateral occipital, and fusiform gyri (reduced), the paracingulate gyrus (reduced), and the pre- and postcentral gyri (increased) compared with
controls. Alternatively, the ADHD-only group showed alterations in the postcentral gyrus (increased) and supramarginal gyrus (reduced), the insula, caudate and thalamus (increased), and the cerebellum (reduced) compared with controls. For hot EF tasks, only the ADHD+ODD group showed alterations, reflected in increased activity in the frontal pole. Interestingly, on a behavioural level, only the ADHD+ODD group showed reduced performance in terms of both cool (inhibition and working memory) and hot (reward processing) EF. This may suggest that the observed functional abnormalities in the ADHD-only group may reflect compensatory mechanisms, resulting in normalized task performance. Lastly, in line with Chapter 5, the findings in terms of neural correlates were unaffected by the level of ADHD symptoms, again indicating that deficiencies in the ADHD+ODD group are driven by the presence of comorbid ODD.

Concluding, the findings of part II of this thesis are again largely in line with our hypotheses. Findings from Chapters 4, 5 and 6 show that previous inconsistent findings regarding ADHD may well be due to the lack of studies that take the presence of comorbid ODD into account (hypothesis I), since the ADHD+ODD group showed unique abnormalities that were not present in the ADHD-only group, such as a reduced grey matter volume in the precuneus. Moreover, ADHD+ODD was associated with a double burden, exhibited by larger as well as unique structural brain abnormalities (grey and white matter) compared with the ADHD-only group (hypothesis II and III). The findings from Chapter 7, on functional rather than structural brain characteristics, show a slightly different pattern, and are only in line with two of our hypotheses. Firstly, they show that previous inconsistent findings on functional brain imaging studies in ADHD may be explained by comorbid ODD, due to complementary associations between ADHD and ODD and brain activity (e.g. reduced activation associated with ADHD and increased activity associated with ODD for somatosensory areas, such as the postcentral gyrus). Secondly, although we hypothesised and found unique characteristics for the ADHD+ODD group, we unexpectedly found unique characteristics for the ADHD-only group as well. This unique pattern of activity of the ADHD-only group may be a reflection of the aforementioned compensatory mechanisms, although this needs further investigation. Finally, the functional imaging findings do not support our third hypothesis, since we did not find evidence of a double burden in the ADHD+ODD group, but rather unique patterns for the ADHD+ODD and the ADHD-only group.
### Table 8.1. Main findings

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| 2       | Identify risk factors and whether these differ for individuals with only ADHD and those with ADHD+ODD. | 82 ADHD+ODD  
82 ADHD-only  
82 TDC | Pre- and perinatal factors  
- Pregnancy duration  
- Birth weight  
- Maternal smoking  
Transgenerational influences  
- Parental ADHD  
- Parental warmth & criticism  
Postnatal factors  
- Parental SES  
- Adverse life events  
- Deviant peer affiliation | - Adverse life events and parental ADHD prove to be risk factors for both the ADHD+ODD and the ADHD-only group.  
- Adverse life events was an even stronger risk factor for the development of additional comorbid ODD.  
- Parental criticism, deviant peer affiliation, parental SES, and higher birth weight were unique risk factors for comorbid ODD.  
- Maternal smoking during pregnancy was a unique risk factor for the ADHD-only group  
Conclusion:  
- Individuals with ADHD+ODD show the unique features of both disorders.  
- ADHD+ODD is accumulation of deficits.  
- Previously reported risk factors for ADHD, may in reality be associate with comorbidd ODD. |
| 3       | Identify neurocognitive deficits and whether these differ for individuals with only ADHD and those with ADHD+ODD. | 82 ADHD+ODD  
82 ADHD-only  
82 TDC | Cool EF  
- Inhibition (stop task)  
- Working memory (digit span backwards)  
Hot EF  
- Reinforcement processing (temporal discounting task)  
- Reward and punishment sensitivity (rewarded motor timing task)  
- Emotion recognition (facial and vocal stimuli)  
Time Processing  
- Time production (motor timing task)  
- Time reproduction (time test task) | - Both the ADHD+ODD and the ADHD-only group showed impairments in working memory and time production abilities.  
- Impairments in inhibition, facial emotion recognition and time reproduction were unique for the ADHD+ODD group.  
Conclusion:  
- Individuals with ADHD+ODD show the unique features of both disorders.  
- ADHD+ODD is accumulation of deficits.  
- ODD carries substantial part of EF deficits observed in ADHD. |
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| 4       | Identify structural and functional brain abnormalities associated with ODD and CD, while taking ADHD into account. | Review & Meta-analysis of 12 structural MRI studies 17 functional MRI studies | Structural brain characteristics associated with ODD/CD | • ODD/CD is associated with both structural and functional abnormalities, irrespective of ADHD comorbidity.  
• Abnormalities in the amygdala are specific for ODD/CD, as compared to ADHD.  
• Besides the left precuneus, there was no evidence for abnormalities in typical cool EF related structures for ODD/CD.  
**Conclusion:**  
• Hot, and to a smaller extent cool, EF associated brain areas are involved in ODD/CD. |
| 5       | Identify structural brain abnormalities and whether these differ for individuals with only ADHD and those with ADHD+ODD. | 67 ADHD+ODD 243 ADHD-only 233 TDC | Structural brain characteristics  
• Grey matter volume  
• Cortical thickness  
• Surface area | • Both ADHD+ODD and ADHD-only showed structural abnormalities in areas crucial for attention, (working) memory, and decision-making. These areas included, in addition to total cortical and total grey matter volume, the parahippocampus, inferior parietal, caudal middle frontal, rostral middle frontal, lateral occipital, and precentral gyri and the isthmus.  
• ADHD+ODD was associated with step-wise larger abnormalities in the frontal lobes. These areas included the inferior parietal, caudal middle frontal, medial orbitofrontal, lateral orbitofrontal, and superior frontal gyri.  
• ADHD+ODD was associated with unique structural abnormalities in areas involved in social skills (empathy, self-awareness). These areas included the precuneus, medial orbitofrontal, rostral middle frontal, middle temporal gyri, and pars triangularis.  
**Conclusion:**  
• Individuals with ADHD+ODD show the unique features of both disorders.  
• ADHD+ODD is accumulation of deficits.  
• ODD carries a part of structural brain abnormalities observed in ADHD. |
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<td>6</td>
<td>Identify structural connectivity abnormalities and whether these differ for individuals with only ADHD and those with ADHD+ODD.</td>
<td>42 ADHD+ODD 117 ADHD-only</td>
<td>Structural brain characteristics • Fractional Anisotropy (FA) • Mean Diffusivity (MD)</td>
<td>ADHD+ODD was associated with lower FA in tracts important for social-emotional and cognitive skills. Conclusion: • ADHD+ODD is accumulation of deficits.</td>
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<td>7</td>
<td>Identify abnormalities in brain activity and whether these differ for individuals with only ADHD and those with ADHD+ODD.</td>
<td>Inhibition task 32 ADHD+ODD 78 ADHD-only 111 TDC, Working memory task 22 ADHD+ODD 66 ADHD-only 105 TDC, Reward anticipation task 22 ADHD+ODD 70 ADHD-only 76 TDC</td>
<td>Functional brain characteristics Cool EF tasks • Inhibition • Working memory Hot EF tasks • Reward anticipation</td>
<td>Behaviourally, only the ADHD+ODD group showed deficiencies. Different abnormal patterns of brain activation for ADHD+ODD and ADHD-only. • ADHD+ODD: ↓ self-reflection &amp; somatosensory related brain areas. • ADHD-only: ↑ &amp; ↓ motor &amp; somatosensory related brain areas. Conclusion: • ADHD+ODD and ADHD-only are associated with unique features in terms of functional brain activity.</td>
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Note. ADHD = Attention-Deficit/Hyperactivity Disorder; EF= Executive Functioning; ODD = Oppositional Defiant Disorder; SES = socioeconomic status; TDC = Typically Developing Controls.
General Discussion

Taken together, the studies in the current thesis provide strong evidence for substantial differences between individuals with only ADHD and those with ADHD and comorbid ODD in several domains in terms of both greater severity as well as unique characteristics, including risk factors, neurocognitive functioning, and brain characteristics. These findings are in line with clinical observations that individuals with both ADHD and ODD show poorer levels of educational, vocational and social functioning and have a poorer prognosis, among which an even further increased risk to develop other psychiatric disorders, compared with individuals with ADHD-only (Anderson & Kiehl, 2012; Kuhne et al., 1997; Loeber et al., 2000; Yoshimasu et al., 2012). Thus, our findings signify the importance of taking the presence of comorbid ODD into account in both research and clinical practice. This could help further clarify inconsistencies and provide a more accurate impression of the impairments related to (pure) ADHD, which currently seem to be overestimated due to not accounting for the presence of comorbid ODD in many of the previous studies.

Our findings to some extent explain heterogeneity in previous studies on ADHD, in line with hypothesis I. Strikingly, a large number of studies on ADHD does not control for comorbid ODD, while the findings of the current thesis suggest that those results may have been significantly influenced by comorbid ODD. Thus, previous studies on characteristics associated with ADHD, including risk factors, neurocognitive functioning, structural brain characteristics, and to a lesser extent functional brain characteristics, may have been tainted by comorbid ODD. This suggests that although ADHD does have a debilitating effect on the affected individual, this effect may be less dramatic than currently believed. For example, impairments in emotion recognition in individuals with ADHD may very well be associated with comorbid ODD, rather than ADHD. A recent review on facial emotion recognition in ADHD showed that 18 out of 26 studies reported impairments in facial emotion recognition for ADHD (Borhani & Nejati, 2018). However, except for one, all studies investigated samples with comorbidities such as ODD and CD. Of the total of four studies that did exclude comorbidities, three studies found no impairments in facial emotion recognition abilities in the ADHD group. This clearly indicates that the deficiencies in facial emotion recognition that are inconsistently linked to ADHD are probably carried by comorbidities such as ODD. This is in line with our finding that emotion recognition abilities were intact in the ADHD-only group and that emotion recognition deficiencies were driven by comorbid ODD (Chapter 3). This is also consistent with previous studies showing consistent impairments in emotion recognition when studying ODD samples (Matthys, Vanderschuren, Schutter, & Lochman, 2012). The influence of ODD on ADHD findings is also present in other domains of research, such as studies into structural brain characteristics (i.e. grey matter volume), where findings for the ADHD-only group in the current thesis are in line with the few studies available on individuals with only ADHD. For example, volumetric reductions in the frontotemporal regions have been reported to be not prominently associated with...
ADHD, but rather with the presence of comorbid CD (Stevens & Haney-Caron, 2012). Indeed, our findings show that structural deviations in terms of both brain volume (Chapter 5) and connectivity (Chapter 6) are larger and more widespread in the group with ADHD and ODD, than in the group with ADHD only. Taken together, findings from previous studies in ADHD samples that did not take comorbid ODD into account show an incomplete picture of the impairments in neurocognitive functions and related brain regions affected by ADHD, as the significant impact of comorbid ODD on the type and severity of impairments associated with ADHD is ignored. This has resulted in an overestimation of the risk factors associated with ADHD, and the different neurocognitive functions and brain regions affected by ADHD.

Moreover, we found evidence for a double burden, since we found a heightened level of neurocognitive and neuroanatomical impairments in the comorbid group, in line with hypothesis III. For example, we found a stepwise reduction in grey matter volume (ADHD+ODD < ADHD-only < controls) in Chapter 5, as well as a stronger deterioration of white matter structural connectivity for several brain areas in individuals with ADHD+ODD compared with individuals with ADHD-only in Chapter 6. We propose these findings to be related to the combination of impairments associated with ADHD and those associated with ODD. Since abnormalities in these frontal areas have been reported for both non-comorbid ADHD (Rubia, Alegria, & Brinson, 2014) and non-comorbid ODD/CD (Noordermeer, Luman, & Oosterlaan, 2016), this suggests an added impact of both disorders in areas that overlap between ADHD and ODD. Importantly, the larger abnormalities in terms of neurocognitive and neuroanatomical characteristics in the ADHD+ODD group could not be explained by the level of ADHD symptoms in any of our studies. The concept of a double burden of ADHD and ODD in individuals diagnosed with both disorders, rather than ADHD+ODD being a discrete disorder, is supported by studies into genetics that show a shared underlying factor. More specifically, it has been suggested that the comorbidity between ADHD and ODD is due to a shared genetic liability either operating directly, or indirectly through gene-environment correlations or interactions (Nadder, Rutter, Silberg, Maes, & Eaves, 2002). Consistent with this suggestion, the covariation among ADHD and ODD could be largely explained by a common genetic factor, that explained 57% of the total variance of an overarching latent externalizing behaviour factor (Tuvblad, Zheng, Raine, & Baker, 2009). This suggests that a common genetic influence lies at the base of both ADHD and ODD symptoms, and that the actual development of either or both of the disorders is additionally influenced by environmental factors, such as the factors we investigated (Chapter 2). Taken together, this indicates that ADHD and ODD have similar aetiologies, and the development of comorbid ODD is considerably driven by environmental factors.

In addition to larger neurocognitive and neuroanatomical impairments in the comorbid group, we also found more widespread impairments that were unique for the ADHD+ODD group, in line with hypothesis II. For example, unique impairments in emotion recognition abilities as well as unique volumetric brain reduc-
tions were present in the comorbid group, compared with the ADHD-only group. These findings were not only absent in the ADHD-only group, they also could not be accounted for by the level of ADHD symptoms, implying that the findings are specific for (comorbid) ODD. As such, individuals with ADHD and comorbid ODD appear to be affected by the impairing characteristics of both disorders.

Furthermore, the current thesis provides some insight into the maturational delay theory, one of the prominent theories on brain development in individuals with ADHD (Shaw et al., 2007). According to this maturational delay hypothesis, individuals with ADHD show a maturational lag in brain development compared with typically developing individuals. This maturational lag is most prominent in prefrontal regions and corresponds to a three year delay, with typically developing individuals attaining their peak cortical thickness at a younger age than individuals with ADHD (Shaw et al., 2007). Around (late) adolescence this delay decreases and the characteristics of the affected areas normalize towards the characteristics of typically developing adolescents. Contrary as to what expect based on that theory, we did not find effects of age (e.g. risk factors, Chapter 2) or an interaction of the assessed characteristics and age (e.g. structural brain characteristics, Chapter 5) in our studies. Thus, we found no evidence for a maturational delay. This is in line with a longitudinal study on neurocognitive functioning, that included largely the same individuals as those investigated in the current thesis (Van Lieshout et al., 2016). That study did not find evidence for a delay or later catch-up, but rather that the studied characteristics of ADHD are largely persistent. However, it must be kept in mind that the studies in the current thesis are not of a longitudinal nature, warranting further investigation (except for Chapter 2).

Finally, another implication of the current thesis is that, although the findings indicate a double burden in terms of risk factors, and neurocognitive and neuroanatomical impairments in individuals with ADHD and comorbid ODD, this was not true for the functional neural correlates, for which both diagnostic groups showed unique activation patterns in distinct areas. Granting that replication studies are needed, this suggests that abnormalities in grey and white matter morphology as well as neurocognitive functioning do not link linearly to abnormalities in neural functioning. This is in line with studies that relate structure and functioning in typically developing individuals showing that advanced computation models are necessary to link the two, and even those can only account for up to 35% of variance of functional characteristics (Breakspear, Jirsa, & Deco, 2010; Honey, Thivierge, & Sporns, 2010; Messé, Rudrauf, Benali, & Marrelec, 2014).
Clinical implications

First, our findings clearly indicate that early adverse life events are a risk factor for the development of ADHD and that their predictive value for the development of comorbid ODD in individuals with ADHD is even stronger. Additionally, parental criticism, socioeconomic status and parental ADHD were important, unique risk factors for the development of comorbid ODD. Our findings indicate that the presence of these risk factors may be prognostic for an increase in severity of outcomes at the level of clinical symptoms, cognitive functioning and brain morphometry and connectivity. Therefore, it is of importance that clinicians take these factors into account when assessing and treating individuals with ADHD. Since the development of comorbid ODD has a deteriorating effect on the functional outcome of individuals with ADHD, such as vocational and academic outcomes (Anderson & Kiehl, 2012; Kuhne et al., 1997), it is pivotal to start treatment in young children with ADHD and ODD symptoms, particularly when these risk factors are present, even when children do not (yet) meet diagnostic classification criteria for comorbid ODD. Since parental criticism was a unique risk factor for the development of comorbid ODD in individuals with ADHD, focussing on this aspect in young children with ADHD symptoms may be essential to have a preventive effect. The predictive role of parental criticism also adds to an increased insight into potential mechanisms of evidence-based interventions for ADHD (with and without comorbid ODD), such as parent training (“ADHD NICE guidelines,” 2018; Daley et al., 2014), that focus (among others) on preventing parents to be (overly) critical to the child. Similarly, our findings are in line with the effectiveness of interventions that focus on preventing deviant peer affiliation and support programs to help the individual to cope with adverse life events, such as the Dutch adaptation of the Coping Power Program, the so-called “Minder Boos en Opstandig” programme (Lochman et al., 2014; van de Wiel et al., 2007). This programme combines parent training to increase parenting skills with a child training to increase coping and prosocial skills of the child.

When ODD is present as comorbidity with ADHD, it is of importance to take the impairments of this group into consideration during the treatment of ADHD. Given the deteriorating impact of comorbid ODD on neurocognitive functioning of these individuals, our findings suggest to be extra alert on the clinical implications of neuropsychological impairments. An important finding of the current thesis is that emotion dysregulation was not associated with a diagnosis of ADHD, but rather with the presence of comorbid ODD. Since the presence of negative affect, an aspect of emotion dysregulation, has been reported to negatively affect treatment outcomes (Loeber, Burke, & Pardini, 2009), taking the presence of ODD into account in an early stage of the treatment is of importance. Although studies comparing different treatment approaches for individuals with ADHD exhibiting no or different comorbidities are scarce and sorely needed, one noteworthy study in which specific subgroups of ADHD in terms of their comorbidities, such as ODD, were investigated, further substantiates the importance of taking comorbidities into account. That study showed that treatment responses in an ADHD-only
sample and an ADHD+ODD sample differed markedly, in line with the expectation that emotion dysregulation negatively influences treatment response to psychoeducation or training (Reale et al., 2017), even though for ODD in itself behavioural treatment has been reported to be effective (Daley et al., 2014). Overall, although current guidelines are largely in line with our findings, those may benefit from a stronger focus on the presence of comorbid ODD in the primary stages of treatments as well.

Finally, an increasingly investigated method used to increase the efficiency of the diagnostic process with psychiatric disorders is machine learning (ML). By using machine pattern recognition techniques based on large datasets, ranging from questionnaire data to structural MRI data, this may result in a computer-aided diagnosis of, for example, ADHD. The ML field has already advanced from very time-consuming approaches to fast and fully automated approaches, especially for using structural MRI characteristics in trying to diagnose ADHD (Peng, Lin, Zhang, & Wang, 2013; Qureshi, Min, Jo, & Lee, 2016). Those faster approaches using extreme learning machine algorithms achieve ADHD prediction accuracies of 85 to 90%, with the most pronounced differences in the frontal lobes. The structural neuroimaging findings discussed in the current thesis may help advance this field even more. Since our findings (Chapter 4, 5 and 6) underline the dissimilarity in terms of structural brain characteristics in the clinical and general population diagnosed with either ADHD or ADHD and comorbid ODD, ML models that incorporate brain morphometry may be used to differentiate between pure ADHD and the more severe ADHD+ODD. Although in terms of grey matter volume our findings indicated small effect sizes over and above symptoms, with a $\eta^2$ ranging from .013 to .025 for the unique abnormalities, and from .010 to .020 for the stepwise reductions, future studies into sensitivity and specificity are warranted. Additionally, future studies using ML to classify individuals may benefit strongly from clear endophenotyping in terms of comorbidities present, further increasing correct classifications.

**Limitations and Research agenda**

While results from the current thesis are consistent, in order to advance our understanding of the aetiology of comorbid ODD, there also is a need for further research focussing on the characteristics of ODD itself. In order to gather more evidence for our hypothesis that ADHD+ODD is associated with a double burden of impairments of both ADHD and ODD, rather than a more separate (third) disorder, it is of crucial importance to study individuals with ODD-only. Although our findings indicate that characteristics of individuals with ADHD+ODD may be traced back to the presence of either ADHD or ODD, unique characteristics of this comorbid condition may be present as well. However, as of yet, neurocognitive and neural characteristics of ODD remain largely elusive, due to the lack of studies into non-comorbid ODD samples (with a few exceptions, for example see
A possible explanation for the lack of studies into ODD-only may be that the impact of this disorder on the individual is considered to be relatively insignificant, with a smaller negative impact on the individual's functional outcomes and prognosis compared with the more severe disorder CD (American Psychiatric Association, 2013; Loeber et al., 2009). Nevertheless, as explicated in the current thesis, the impact of ODD as a comorbidity is substantial. Thus, although a disorder in singularity may seem relatively manageable, the prognosis becomes considerably worse when it is present as a comorbidity. Furthermore, the current, limited knowledge on characteristics of ODD is largely tainted by the presence of CD in investigated samples. Although CD is related to ODD, CD is considered to be a more severe form of ODD and related to specific characteristics (American Psychiatric Association, 2013). For example, as opposed to a diagnosis of ODD, a diagnosis of CD includes aggression towards individuals or animals and a pattern of theft or deceit, but does not include emotion dysregulation (American Psychiatric Association, 2013; Loeber et al., 2009). Fortunately, in contrast to previous versions of the DSM, the current DSM-5 does allow both an ODD and a CD diagnosis to be given. This opened the possibility to not only more easily study ODD in singularity, but also to investigate whether the emotion dysregulation associated with ODD may have tainting findings in the CD field as well.

In line with the previous suggestion of more and better studies into the characteristics associated with pure ODD, it is of importance to further study both pure ADHD and ADHD+ODD as well. For pure ADHD, this may help better understand the aetiology and therewith improve treatment options for those who are diagnosed with ADHD-only. Moreover, it may explain why some individuals with ADHD do not respond to specific treatments while others do, such as medication or psychoeducation (Greenhill et al., 2006; Reale et al., 2017). Although most studies have reported that comorbidity of ODD does not affect treatment outcome of individuals with ADHD (Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008), some others studies seem to suggest otherwise, resulting in some inconsistency in the field (Kim, Sharma, & Ryan, 2015; Reale et al., 2017). For example, it has been reported that the level of ODD symptoms in individuals with ADHD is an important differentiating aspect in the prediction of methylphenidate treatment response, showing a poorer response of individuals with ODD symptoms to methylphenidate treatment (Kim et al., 2015). Another study on ADHD and specific subgroups in terms of comorbidities showed that treatment outcomes differed markedly between individuals with ADHD-only and those with ADHD+ODD, showing a poorer response to psychoeducation in the comorbid group (Reale et al., 2017). This further explicates the relevance of taking ODD into account, not only for further investigation and replication of our findings, but in treatment studies as well. This may eventually improve efficacy of treatment in ADHD and associated subgroups, as well as help to expand venues for interventions, and to possibly prevent the development of comorbid ODD.
In the current study, a categorical approach was used (i.e. presence or absence of a DSM diagnosis of ADHD or ODD), as we wanted to follow DSM diagnoses to increase comparability and replicability. Moreover, since a categorical approach is favoured over a continuum approach for adults, and we included young adults as well as children and adolescents, our categorical approach was most fitting (Faraone, Biederman, Doyle, et al., 2006; Faraone, Biederman, Spencer, et al., 2006; Lubke, Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009). While our findings were robust and did not suffer from the reduced power known to be associated with a categorical approach, further investigation using a dimensional approach would be useful as well. It has been reported that approximately 10% of school-aged children suffer from subthreshold ADHD, defined as not meeting full diagnostic criteria, but still showing a relatively high level of ADHD symptoms (Hong et al., 2014). Although these children do not meet the criteria needed for a diagnosis, they do show comparable functional impairments as individuals with an ADHD diagnosis, although those functional impairments are milder. Using a dimensional approach and therewith including the full spectrum of symptom severity, from typically developing individuals with just a few symptoms, to those with subthreshold levels of symptoms and those with a diagnosis and high levels of symptoms, should give an even more complete overview of the disorder. In addition, it is interesting to investigate how the findings of the current thesis relate to individuals suffering from subthreshold ADHD.

Since individuals with ADHD already show substantial heterogeneity by themselves (e.g. the different ADHD subtypes), it is important for future studies into characteristics of ADHD to assess extensively phenotyped participants, including a comprehensive psychiatric assessment of the included participants. As clearly shown by the findings of the current thesis, the impact of comorbid ODD on ADHD is substantial in several domains. Thus, only by extensive phenotypical assessments and accounting for these data in the analyses, will we be able to gain more insight into which characteristics truly relate to a specific disorder, and may ultimately be able to tailor both classification and treatment to specific subgroups, such as those with ADHD+ODD. In the future, this may lead to better and earlier detection of those children who are at an increased risk of more deteriorating long-term outcomes and thus improve their chances for a more positive long-term outcome.