CHAPTER 7
General discussion
The cubist Picasso painted his muse Dora Maar by merging different view points into one image. He understood that each perspective reflected one piece of her, but that it is impossible to recreate the complete synergy of a person or object as a whole. After all, there is more to people than meets the eye. The aim of this thesis was to apply Picasso’s cubist wisdom to the psychiatric disorder Attention-deficit/hyperactivity disorder (ADHD). In order to get more insight into consequences of living with ADHD, different view points were taken into consideration: the bird’s eye view (nature or neuropsychology of ADHD), the side view (expression of ADHD in the light of comorbidity), the frontal view (consequences of ADHD on behavior), and the crystal ball view (treatment options for ADHD). The studies described were carried out in adults with and without ADHD, and/or with comorbid depressive and/or anxiety disorders. In this chapter, the main outcomes are summarized, discussed and put into perspective. In addition, implications for future research studies are presented.

THE BIRDS-EYE VIEW: NEUROPSYCHOLOGY OF ADHD

The birds-eye view focused on the neuropsychology (or nature) of ADHD. Chapter 2 described the prevalence of executive functioning deficits in adult ADHD patients. Clinical executive functioning deficits were highly prevalent in adults with ADHD, and are grossly in line with numbers from earlier studies [16, 17]. Although executive functioning deficits are highly heterogenic in adults with ADHD [109], they remain stable over time [85]. When digging deeper into endophenotypes of ADHD, i.e., underlying characteristics (‘endo-’) for behavioral manifestations (‘phenotypes’), it was found that the continuous performance test (CPT) parameter Reaction Time Variability (RTV) had the largest objectively and subjectively measured sensitivity for ADHD medication efficacy. These findings mirror earlier CPT research where RTV was marked as a broad, underlying indicator of executive functioning deficiency, on a neuropsychological as well as behavioral level [20], thereby proposing an endophenotype for ADHD [337]. Inattentive symptoms profited more than hyperactive symptoms of ADHD medication. A recent genetic study of Sokolova et al. [338], suggests inattention as a driving factor for hyperactivity/impulsivity, which implies that improvements in attention may also diminish hyperactivity and impulsivity in ADHD. This was indeed reflected in our study findings, where the greatest improvements were found on parameters of inattention after use of methylphenidate, but smaller improvements were also found in hyperactivity and impulsivity. Furthermore, the positive relation between hyperactivity and inattention was replicated in
a smaller study among children with ADHD, where hyperactivity/impulsivity was found to increase the cognitive load in working memory (i.e., occupying attention capacity), instead of being related to an impairment in self-control mechanisms [20, 339].

From this study, it may be concluded that RTV seems an endophenotype for ADHD behavior. The search for endophenotypes of ADHD is of great importance, as it directly links underlying neuropsychological deficiencies to measurable, behavioral manifestations. In contrast, a lot of studies have relied on self- or other-reports of ADHD symptoms, which has led to discrepant prevalence rates of ADHD [340-342]. Likewise, most patients with ADHD find it hard to report on effects of ADHD medication [343]. The identification of endophenotypes of ADHD at a group level would not only increase the knowledge on etiology of ADHD [86], on a practical and individual level it may help to objectify effects of ADHD medication. Following our study results, future studies could focus on identifying responders to ADHD medication, and titrate and fine-tune the optimal ADHD medication dosage by looking at improvements on the RTV parameter.

Notably, not all CPTs are able to detect executive functioning deficits in adults with ADHD to the same degree, while problems with inattention, hyperactivity and impulsivity are core symptoms of the disorder. Moreover, executive functioning deficits are also prevalent among healthy controls [344]. An important explanation for differences in prevalence rates of executive functioning deficits among adults with ADHD concerns the difficulty to define and operationalize executive functioning. Nevertheless, RTV proved to be a parameter that was sensitive for ADHD medication effects across the two widely used objective CPTs we used in our study. For the generalizability of research findings in this field, it seems important to provide clear definitions regarding the parameters that are measured. Also, it should be taken into account that single cognitive performance tests are prone to measurement errors such as fluctuations in stress, motivation, and fatigue, and a mean test performance over multiple tests may increase reliability despite increased risk for dropout.
THE SIDE VIEW: COMORBID DEPRESSION, ANXIETY AND SLEEP DISORDERS

The side view places ADHD behavior in contrast with other psychiatric disorders that may be comorbid with ADHD. Chapter 3 described the association between severity of depression and comorbidity with ADHD symptoms, using a clinical staging model for depression. In a longitudinal cohort of anxiety and depression (NESDA study), the results showed that persons with a current depressive disorder had a 4.5 times greater odds to report clinical ADHD symptoms. Those with clinical ADHD symptoms had more severe depressive symptoms, more often had chronic depression, an earlier onset of depression, and comorbid anxiety disorders. Importantly, the prevalence of ADHD symptoms was related to the developmental phase of depression: the more severe the depression, the higher the prevalence of ADHD symptoms. More than 20% of persons with chronic depression had clinically relevant ADHD symptoms. It would be interesting to study the causality of this relationship. Although genetic alterations in dopaminergic and serotonergic pathways [129] and reward systems [183] were found in depression as well as ADHD, depressive symptoms may also develop as a result of undiscovered ADHD and co-occurring impairments on important areas of life [301].

This study was the first to give insight into the comorbidity of depression severity and ADHD symptoms, using a clinical staging model of depression. Diagnostically, the large overlap that was found between severe depression and ADHD symptoms is intriguing, considering the low treatment response rates that have been found in the group of persons with treatment-resistant depression. Following our study results, it seems worthwhile to investigate the possibility of a lifelong comorbid ADHD diagnosis in this patient group, as they might benefit from ADHD treatment.

Clinical staging models provide the opportunity to detect the presence of disorders in early stages, in order to prevent the disorder from becoming worse. It has been found that patients in early stages of an illness have better treatment response rates and an overall better prognosis [160, 345]. The use of clinical staging as a model for mental disorders is not yet validated [187], and the fluctuating course of depression may impede the use of one distinct staging model for depression [125, 178]. However, the clinical staging model for psychotic disorders has proven its value: it advanced the available treatment.
options, improved social and vocational functioning, and reduced the risk for recurrence of psychosis [346-348]. Furthermore, observations from cohorts on psychiatric disorders even advocate a different approach to diagnostics in psychiatry. Possibly, instead of determining the presence of a diagnosis at different time points, clusters of symptoms and syndromes could be identified, that gradually emerge and become less intense over time. In the future, clinical staging models may be used as a transdiagnostic tool for the development of psychiatric disorders, overarching mood and anxiety disorders, psychotic disorders, substance use disorders, or a combination of these disorders [345]. As a result, treatment options could be adjusted following the stage of the 'illness', providing early intervention options.

Our study contributes to the idea that considering the co-occurrence of symptoms can offer a new treatment approach by shifting the focus, i.e. from overt depression to covert inattention and hyperactivity/impulsivity symptoms. Since ADHD is relatively unknown among people with depression and anxiety, screening diagnostics and treatment of ADHD may improve depression severity and could positively influence the course of depression.

In Chapter 4, the comorbidity of ADHD symptoms in persons with depressive and/or anxiety disorders was studied in relationship to circadian rhythm sleep problems. The most important finding was that comorbid ADHD symptoms in depressive and/or anxiety disorders had odds ratios from 2.4 to 2.7 for all three parameters of circadian rhythm sleep disorders: extremely late evening type, delayed sleep phase syndrome, and short sleep on nights before work days. This implied that comorbid ADHD symptoms added to the risk of a disturbed circadian rhythm, independent from the known risk of depression and anxiety on circadian rhythmicity.

In contrast to earlier studies [200, 201, 229-231], predominantly problems with inattention appeared to be associated with circadian rhythm disturbances, and not hyperactivity/impulsivity. Possible explanations for the relationship between inattention and circadian rhythm disturbances may be that inattention induces a lack of sense of time, and hence late bedtimes and shorter sleep, or it may lead to rumination before falling asleep, causing longer sleep-onset times and delayed and shorter sleep. Furthermore, as discussed above, a recent study in genetics of ADHD implies that inattention drives hyperactivity/impulsivity [338]. From that perspective, hyperactivity/impulsivity may (also) mediate the relationship between inattention and circadian rhythm disturbances. Underlying
circadian rhythm disturbances are reflected in both the delayed sleep phase syndrome (chronic late sleep, late rise, and inability to go to bed earlier and to get up earlier in the morning) and in having an extreme late chronotype (the biologically entrained preference of timing of sleep). Both sleep patterns show a clear association with ADHD symptoms. A plausible consequence of both sleep patterns is a short sleep duration on work days, although short sleep duration may also be caused by working night shifts while the circadian rhythm in itself is not delayed. The direction of causality in the interrelationships between circadian rhythm sleep problems, depression and/or anxiety disorders, and ADHD symptoms deserve more research. Numerous studies however, implicate that circadian rhythm disturbances may be inherent to psychiatric disorders, including ADHD [40, 197, 227, 249, 250, 349]. Moreover, recent studies show that sleep disorders only persist into adulthood if ADHD persists [350], and vice versa that ADHD symptoms predict persistence of sleep problems [351]. Besides in ADHD, delayed sleep phase syndrome is highly prevalent in personality disorders, bipolar disorder, depression, anxiety disorders, and autism as well [206, 352-354]. The hypothesis of a shared etiology of (clusters of) symptoms is in line with genetic research where joint polymorphisms are found across psychiatric disorders [355]. Circadian rhythm disturbances have shown to cause various health conditions such as diabetes, cardiovascular disease, metabolic syndrome, immune suppression and even cancers on the long-term [216-218]. A broader investigation of symptom clusters across disorders could contribute to early detection, tailored treatment, and possibly prevention of certain health problems.

THE FRONT VIEW: BEHAVIOR OF ADHD

Viewing from the front, the consequences of ADHD on behavior are taken into account. In Chapter 5, the short and long term effects of methylphenidate use on tobacco consumption and nicotine craving were investigated. In correspondence with prior studies, we found that more than half of our ADHD patient sample smoked, in contrast to 25% of the general population. Both after two weeks and after three months of using methylphenidate for ADHD symptoms, patients reported a slight increase in the number of consumed cigarettes, and experienced more nicotine craving, especially in the group of light smokers.
Our study findings contradict the self-medication hypothesis, which postulates that nicotine and methylphenidate have comparable effects on the reward system of the brain [54, 293]. Following this hypothesis, it was expected that tobacco and nicotine consumption would decrease after treatment with methylphenidate. The adverse relationship between nicotine and methylphenidate could be explained by the aspect of addiction and habitual disruption, that both cannot be extinguished with the use of methylphenidate. Our findings implicate that smokers with ADHD need to be informed about the risk of increased craving for nicotine when starting methylphenidate treatment. A possible way to deal with this undesirable interaction may be to use nicotine patches or bupropion, an dopaminergic agent licensed for smoking cessation to reduce the physical aspects of craving as a new and healthy routine that may interrupt the unhealthy habit of smoking. However, in our study the negative effect of methylphenidate on smoking appeared to stabilize over time. It would be interesting to study the effect of methylphenidate on a longer term beyond three months, in order to see whether the increase in tobacco and nicotine consumption is permanent or just temporary.

Chapter 6 compared driving behavior between persons with and without ADHD, using healthy controls from the general population. In line with prior studies, persons with ADHD had a relative higher risk for (speeding) citations and (self-inflicted) vehicular crashes [55, 56]. Likewise, persons with ADHD rated their driving behavior as less safe compared to healthy controls without ADHD. Nevertheless, when compared to other risk factors for unsafe driving, such as younger age, male gender, high levels of hostility and anxiety, and high alcohol use, having an ADHD diagnosis did not increase the risk for impaired driving any further. Although these risk factors often accompany ADHD, they are nonspecific to ADHD, as they are found in the general population as well. The risk of an ADHD diagnosis on driving behavior thus deserves to be refined. Having an ADHD diagnosis did increase the odds for three or more vehicular crashes. Our findings conflict with the results of large population-based study in Canada, where ADHD was not related to an increased risk for vehicular crashes when other risk factors were taken into account [356]. This discrepancy may arise from different methodologies and cutoffs regarding vehicular crashes.

A note to our findings was the lack of any effects of ADHD medication on driving behavior. Several studies however have shown that ADHD medication has a positive effect on driving on the road, improving attention during driving, and
diminishing hyperactivity [316-320]. Likely, the ADHD patients who participated in our study were in the first phase of treatment just after assessment, and not yet adequately titrated to a dosage of medication to fully suppress ADHD symptoms during driving.

Based on the research about ADHD and risky driving behavior and outcomes, the current Dutch regulations for having a driving license when diagnosed with ADHD are very strict. First of all, an extra driving test and a psychiatric evaluation are needed before a driving exam can take place, and secondly, a re-evaluation after three or five years is often required. The costs for extra driving tests and psychiatric evaluations must be paid by patients themselves. When put into perspective, these regulations seem overdone since no extra tests or evaluations are needed when a person (with or without ADHD) drinks too much alcohol, has extreme anxiety, or gets aggressive behind the wheel, without getting into trouble. Our study shows that some of these factors may increase the risk for unsafe driving even more than ADHD. For improvement of road safety, driving instructors should screen for persons at risk for unsafe driving, giving information about drinking while driving, anger management skills, and tips on how to overcome anxiety, into the driving lessons.

**METHODOLOGICAL CONSIDERATIONS**

**Measurement of ADHD in adults**

In our studies using data from the Netherlands Study of Depression and Anxiety (NESDA) (Chapter 3 and 4), ADHD symptomatology was cross-sectionally measured as a comorbid condition to depression and anxiety disorders. Clinical ADHD symptoms were studied at one time point using the Conners Adult ADHD Rating Scale (CAARS; [179]), a self-report questionnaire on presence DSM-IV criteria of ADHD in the past months. By adding extra questions regarding childhood symptoms, some information about chronicity of symptoms could be determined. Several self-reported measures on adult ADHD symptoms have shown high internal consistency, moderate to high concurrent validity compared to other raters, and sufficient test-retest reliability [189, 357-359]. Moreover, the CAARS has shown modest sensitivity to malingering and excellent specificity for ADHD [360], implying reliable data for ADHD in our studies. However, the recollection of childhood ADHD symptoms may be hindered by memory problems [361], are sensitive to underreporting, and are influenced by mood [189, 362, 363]. Also, there is the fear of over-diagnosis in ADHD, nevertheless, to
date, no such evidence has been found [364]. In order to thoroughly investigate and diagnose ADHD in adults, the administration of a structured interview by a clinician and collateral information by close relatives or those who knew the person as a child, is essential. There are several diagnostic interviews for ADHD in adults such as the Adult ADHD Clinical Diagnostic Scale (ACDS) [365], the Conner’s Adult ADHD Diagnostic Interview for DSM-IV (CAADID) [366], the Brown Attention-Deficit Disorder Scale (BADDs) diagnostic form [367], and the semi-structured Diagnostic Interview for ADHD in adults (DIVA 2.0) [97].

The remaining studies in this thesis (Chapter 2, 5 and 6) included adults who were diagnosed with ADHD using the DIVA 2.0 [97], at the PsyQ Department and Expertise Center on Adult ADHD. The DIVA 2.0 is based on the DSM-IV criteria of ADHD. DIVA 2.0 asks about the presence of ADHD symptoms in adulthood as well as childhood by using concrete and realistic examples that are typical ADHD behaviors. Also chronicity of ADHD symptoms and significant clinical or psychosocial impairment on five areas of life (i.e., work/education, relationships and family, social contacts, free time/hobbies, and self-confidence/self-image) due to these symptoms are investigated. The DIVA 2.0 was found to have an excellent accuracy for diagnosing adult ADHD, had a good concurrent validity compared to the CAADID [368], and had a good discriminative validity (sensitivity 90%, specificity 73%) [369].

**Sample size**

In NESDA (Chapter 3 and 4), the number of persons with clinical ADHD symptoms in the group with lifetime depression and/or anxiety was quite small (n=181), and the ADHD-only group was too small (n=2) to compare with other groups. Nevertheless, even in these small samples strong associations were found between severity of depression, circadian rhythm sleep disturbances and ADHD symptoms. Ideally the results of our studies should be replicated in a large study comprising a considerable group of people with ADHD, without depression or anxiety disorders. However, it should be noted that this group may be hard to find, considering the high level of comorbidity in adult ADHD [22].

Our study concerning executive functioning deficits (Chapter 2) comprised a relatively small sample size of 22 adults with ADHD. According to the power analysis, this sample size should be enough to be able to find an effect for methylphenidate on parameters of continuous performance tests, using a cross-over design. Indeed, individual differences on executive functioning
deficits were found even in this small sample, which illustrates the strength of a within-subjects study method. Methylphenidate effects were also found in a large cross-over studies among 77 children with ADHD [370], but so far cross-over studies among adults with ADHD using objective tests all had a small sample size [371-374]. For the generalizability of neuropsychological impairments in adults with ADHD, future studies should study executive functioning in larger samples.

Cross-sectional analyses
Some study designs in this thesis only allowed for cross-sectional analyses instead of longitudinal analyses (Chapters 3, 4, and 6), which impedes drawing conclusions about causality of relationships. Despite the strong relationship between severity of depression and ADHD symptoms, it could not be disentangled whether severe depression caused symptoms that mirror ADHD, or whether undiscovered ADHD may have caused depressive symptoms. The same holds true for the association between circadian rhythm sleep disturbances and ADHD symptoms. Yet, there are indications that sleep disturbances may be inherent to ADHD [350, 351]. In the interest of causality, the development of depression and circadian rhythm sleep disturbances should be investigated in children with and without ADHD, using regular follow-ups. With regards to driving behavior and ADHD, our study assessed driving at only one time point. Many studies have found that ADHD is related to unsafe driving [55, 56] and direct causality of adverse driving outcomes may be hard to investigate, as our study illustrated that multiple factors may play a role. Longitudinal follow-up studies in teens and adults with and without ADHD taking into account several other risk factors such as alcohol use, anxiety, hostility/aggression may provide more insight into the association between driving and ADHD.

The crystal ball view: treatment of ADHD
Looking into the future of living with ADHD, the European consensus statement on diagnosis and treatment of adult ADHD has stated the ingredients for optimal treatment of ADHD in adults [60]. Regarding pharmacological treatment options, the highest efficacy rates are found for stimulant medications. In this thesis the effect of ADHD medication – and in particular the stimulant methylphenidate – was tested in two studies, namely on executive functioning deficits (Chapter 2) and on smoking behavior (Chapter 5). Chapter 2 showed that methylphenidate effectively improved executive functioning deficits
on objective tests and subjectively diminished ADHD symptoms, mainly on parameters concerning attention. These results underline the beneficial effects of the stimulant methylphenidate on core symptoms of ADHD. On the other hand, Chapter 5 illustrated an undesirable side effect of methylphenidate, as our naturalistic follow-up study among adults with ADHD showed that methylphenidate use increased tobacco and nicotine use, and nicotine craving on the short (two-weeks) and long term (three-months). The most common side effects of methylphenidate include headaches, insomnia, nervousness (due to an increased heart rate), nausea, abdominal pain, and dry mouth. However, an increased craving for tobacco and nicotine has not been studied well yet. Most side effects disappear when medication is used over a longer period of time. It is important to study whether the impact of methylphenidate on smoking behavior is only temporary, like most side effects mentioned above, by assessing the association between methylphenidate use and smoking behavior over a longer period of time. If the negative association between methylphenidate use and smoking remains stable over time, patients should be made aware of this side effect, and increased smoking may be obviated by means of nicotine patches or other treatment options for smoking cessation.

Stigma on ADHD

Generally speaking, for most people to have ADHD in the 21st century may seem a benign and mild disorder. Also, symptoms of ADHD are recognizable for many of us. We all experience moments of inattention or feel distracted, have hyperactive and restless moments and initiate one thing after another, or make impulsive decisions that we afterwards regret. On the one hand, one could say that this aspect of recognition could lead to more social acceptance of ADHD as a diagnosis. After all, although we may smile about those moments of inattention, hyperactivity and impulsivity among ourselves, we also realize that it must be exhausting and impairing to live with continuous ADHD symptoms 24/7. On the other hand, in reality patients with ADHD often do not feel recognized or understood by others about the impact of this disorder on their lives. It is not surprising that the average age of referral for diagnosis and treatment at the PsyQ adult ADHD department in The Hague, The Netherlands, is at 35 years of age. The threshold for seeking psychiatric help for ADHD symptoms appears to be high. However, eventually getting the diagnosis puts the lives of adults with ADHD into perspective about the choices they made. Learning to deal with experiences of failure has left its mark, and may lead to overthinking life events that could have been prevented if ADHD was diagnosed earlier in life. It
is important to pay attention to the process of acceptation of the diagnosis and – to some extent – mourning, in order to stimulate improvement of the negative self-image. Furthermore, getting the diagnosis of ADHD offers an explanation for experiences of failure in the past. ADHD behaviors are not traits that are inherent to the person themselves, rather symptoms of inattention and hyperactivity/impulsivity are explained by a disorder that influences the ‘control system’ of the brain. This insight offers adults with ADHD an opportunity to re-evaluate life events and put them into perspective, taking away the feeling of self-blame. Friends and family of the person with ADHD may not understand why getting an ADHD diagnosis is so important, as the person seemingly has had a fine life without this ‘label’. However, recent studies from Semeijn and Michielsen have shown that it is never too late to get a diagnosis of ADHD: almost 3% of older adults above age 60 have ADHD [375, 376]. Importantly, they reported a lower quality of life, including more often divorce, a lower income, more comorbid anxiety and depressive disorders, more social problems and serious conflicts, more loneliness, and a worse physical health [156, 377-379]. There is fear for over-diagnosis (‘everybody has ADHD nowadays’) and medicalization (‘pills solve it all’), leading to a stigma and counteraction for ADHD patients in daily life. Regrettably, this seems to limit the opportunities for ADHD patients even more.

We hope that this thesis contributes to a more Picasso-like view on ADHD in adults. Despite the apparently mild symptoms of inattention, hyperactivity and impulsivity, many patients with ADHD experience serious deficits in executive functioning, which among others alters driving abilities, and they encounter several comorbid disorders such as depression and circadian sleep problems. Despite positive effects of methylphenidate as a treatment for core symptoms of ADHD, undesirable side effects concerning increased smoking deserve further investigation. Altogether this shows, that there truly is more to ADHD than meets the eye.