CHAPTER 1
General introduction
“There is more to people than meets the eye”. This wisdom is what the colorful Pablo Picasso was trying to convey, with the cubist portrait of his muse Dora Maar. Picasso realized that persons or objects can be simultaneously looked at from numerous angles and in multiple spatial and temporal dimensions, all reflecting one small piece of the person or object as a whole. Despite the fact that all different perspectives give information about the person or object, it is impossible to recreate the complete synergy of a face or object. Or to put it in Aristotle’s words: “The whole is more than the sum of its parts”. These principles also hold true for the investigation of psychiatric disorders. In this thesis Picasso’s cubist wisdom is applied to the highly heritable, neurobiological disorder Attention-Deficit/Hyperactivity Disorder (ADHD) [1], by taking into consideration different viewpoints of lifestyle in ADHD: the bird’s-eye view (nature), the side view (expression), the front view (consequences), and the crystal ball view (treatment) (see Figure 1).

**FIGURE 1.** Different viewpoints on adult ADHD. Black arrows indicate the direction of the relationship investigated in this thesis.
The birds-eye view enables us to fly above ADHD behavior and look into the underlying principles (i.e., endophenotypes) of ADHD behavior. In our study, neurocognitive functioning was observed at time the behavior took place. The side view places ADHD behavior next to other disorders that may influence behavior, i.e. comorbidity. That way, the relative impact of ADHD behavior can be put into perspective. From a front view, we take a look at ADHD on a behavioral level. In line with this viewpoint, we examined lifestyle of ADHD patients in specific situations and compared that to the behavior of other populations. And last, the crystal ball view looks toward the future of ADHD, by highlighting the pharmacological and psychological treatment options when living with ADHD. This thesis sheds light on the nature, expression and consequences of living with ADHD, as there is more to ADHD than meets the eye.

**ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)**

ADHD is characterized by behavioral symptoms of inattention, hyperactivity and/or impulsivity. As ADHD has a childhood onset, it indicates that some symptoms of ADHD were already present before the 12th year of age [2]. The symptoms of inattention and/or hyperactivity/impulsivity cause significant dysfunctioning in important areas of life, such as work and education, relationship and family life, social contacts, free time or hobbies, and self-confidence and self-image. ADHD is depicted by many as a childhood disorder that ‘resolves’ in adulthood. However, ADHD often has a chronic course: 65% of cases with childhood ADHD continue to experience ADHD symptoms into adulthood [3], and as much as 90% of cases report dysfunctioning of these symptoms in adulthood [4]. ADHD is associated with disrupted dopaminergic and noradrenergic transmission in the brain [5, 6]. Genome wide association studies have identified mainly dopaminergic candidate genes to be associated with the occurrence of ADHD [7]. The neurotransmitter dopamine serves as the inhibitor or ‘brake’ of responses to stimuli, which influences the control over cognitions, emotions and behaviors. Because of the supposed relative deficiency of dopamine in the brain, ADHD is often labeled an inhibition disorder. Worldwide, ADHD is prevalent in 4 to 12% of children [8, 9] and cross-national prevalence estimates for adults average at 3 to 4% [10, 11]. In the Netherlands, 3 to 5% of children [8, 12] and 5% of adults meet criteria for a diagnosis of ADHD [11].
THE BIRD’S EYE VIEW: THE NEUROPSYCHOLOGY OF ADHD

Research has indicated that the brain volume of ADHD children is structurally 5% smaller when compared to children without ADHD, and these differences continued throughout childhood and adolescence [13]. Furthermore, from fMRIs, SPECT, and PET scans the ADHD brain shows less activity in the dorso-anterior cingulated cortex, globus pallidus, caudate nucleus, dorso-lateral prefrontal cortex, and the cerebellum [14]. Moreover, the white matter connectivity between frontal, striatal, and cerebellar networks appears disrupted, causing impairment in information flow and integration [15]. Not surprisingly, about 40% of adults with ADHD experience difficulties in executive functioning [16, 17]. These are the control functions of the brain where novel and complex information is coordinated and organized in the frontal lobes. Executive functions determine goal-directed actions and behavior, eliminate distractions, coordinate tasks step-by-step and verify effects, take into account past experiences and future expectations, and apply any necessary corrections of errors in the meantime. Neuropsychological tests have indicated that ADHD patients experience executive functioning difficulties in the areas of working memory, inhibition, delay aversion, decision making, timing, and response variability [18-20].

Short-acting methylphenidate, the first-choice type of pharmacological treatment in ADHD in The Netherlands, has been found to improve executive functioning in children and adults with ADHD, however, these neurocognitive improvements were only weakly related to behavioral measures of executive functioning [17, 21]. Chapter 2 describes the effects of a long-acting methylphenidate on objective parameters of executive functioning and subjective measures of ADHD, resulting from a randomized, placebo-controlled cross-over study.

THE SIDE VIEW: COMORBID DEPRESSION, ANXIETY AND SLEEP DISORDERS IN ADHD

Three-quarter of ADHD patients experience comorbid disorders, of which depressive disorders, anxiety disorders, sleep disorders, and addictions are the most prevalent [22]. The large-scale National Comorbidity Survey Replication, a mental health survey aiming at estimating the prevalence rates and correlates of DSM disorders in the U.S., showed that 20% to 50% of adults with ADHD had any kind of comorbid mood disorder, of which 19% had major depressive disorder
(MDD), 13% had dysthymia, and 21% had bipolar disorder [10]. Anxiety disorders occurred in 25% to 40% of adults with ADHD [10]. Specifically, social phobia is prevalent in 29% of cases, 23% has other phobias, and 9% has a generalized anxiety disorder. Approximately one-third of patients with an anxiety disorder has ADHD, of which patients with social phobia show the highest prevalence of comorbid ADHD (39%) [23]. Depressive and anxiety disorders often co-occur [24] and both are often comorbid with ADHD [10]. For instance, there are similarities in genetic polymorphisms [25], neurobiological underpinnings [26, 27], and behavioral overlaps between depression and ADHD [28]. It is unknown how severity of depression relates to the prevalence of ADHD symptoms. In Chapter 3, this relationship was studied using a clinical staging approach in a large cohort of 2,053 people with lifetime depression and controls.

Another important conformity between depressive, anxiety disorders and ADHD, is the co-occurrence of sleep problems. Children with ADHD more often have bedtime resistance, chronic sleep-onset insomnia, difficulty waking up in the morning, nightmares, increased nocturnal activity and a disturbed sleep architecture [29, 30]. A delayed sleep is reported in 73% of children with ADHD [30]. In adults with ADHD, 78% have a late chronotype and sleep-onset difficulties [31], they have a lower sleep quality, have difficulty getting up in the morning [32], and report increased daytime sleepiness [33]. Several studies have indicated that these sleep disorders can be largely explained by disturbances of the circadian rhythm [34]. The circadian rhythm, or biological clock, regulates important physiological processes such as body temperature, heart rhythm, sleep pattern, need for food and drinks, sensitivity to medication, and secretion of hormones [35]. The biological clock is located in the suprachiasmatic nuclei and in most people reflects a 24-hours rhythm. The circadian rhythm is hereditary but is influenced by exogenous sun light, tides, climate, and social environment. From all exogenous time indicators, also called Zeitgebers, light is one of the most important factors impacting the sleep-wake cycle [36]. Light down-regulates the sleep hormone melatonin. In the short term, disruptions of the circadian rhythm have been linked to emotional and behavioral problems like irregular sleep, inattention problems, disturbed eating pattern, gastrointestinal symptoms, loss of energy, headaches, agitation, and mood swings [37-39]. Phase shifts can be measured in saliva of melatonin onset [31], body temperature [40], and levels of activity [41, 42]. In psychiatric disorders, there is an increased prevalence of circadian rhythm disturbances when compared to the normal population. On the long term, disturbances of the circadian rhythm increase
the risk for obesity [43], cardiovascular diseases, and cancer [44-46]. Therefore, **Chapter 4** reports a study on the role of ADHD symptoms in the occurrence of circadian rhythm sleep disorders in depressive and anxiety disorders, in order to possibly prevent severe health problems.

**THE FRONT VIEW: ADHD BEHAVIOR**

Next to the mental and physiological health problems in ADHD and the comorbidity with depressive and/or anxiety disorders described above, behavior of ADHD patients has been related to an unhealthy lifestyle. Among others, this is reflected in the numbers on smoking and driving behavior. ADHD patients have a higher smoking prevalence of up to 46% compared to controls (twice as high), more often present with nicotine dependency [47, 48], start smoking at an earlier age, are more likely to progress from incidental to regular smoking [49], and have more difficulty quitting smoking [50], which may be due to a tendency to sensation seeking behavior [51], comorbid conduct disorder [48], genetic predisposition for smoking [52], or self-medication [53]. Following the dopamine-deficit hypothesis, nicotine acts on dopamine receptors and influences the reward system of the brain, inducing stimulation of inhibitory processes. To some extent, nicotine and ADHD medication thus have comparable effects on the brain, as both increase the dopamine availability in the ADHD brain, and suppress ADHD symptoms [54]. In this thesis, we were interested in this self-medication effect of methylphenidate on smoking behavior. While it was expected that the use of methylphenidate would ‘take over’ the dopamine-inducing role of nicotine and thereby decrease tobacco consumption, the results from our prospective, observational pilot study showed the opposite: ADHD patients reported an increase in smoking after using methylphenidate. These controversial results were the reason to conduct a large scale study aiming at investigating the acute and long-term effects of methylphenidate use on smoking behavior, nicotine consumption, and nicotine craving, of which the results are described in **Chapter 5**.

ADHD patients are also at increased risk for adverse driving outcomes and more often drive unsafe when compared to people without ADHD [55, 56]. On the one hand this appears to be attributable to the core symptoms of ADHD: problems of inattention may lead to missed road signs and impulsivity may lead to switching lanes without looking. On the other hand, deficits in executive functioning also play a great role in the relationship between ADHD and unsafe
driving [57, 58]. People with ADHD have problems selecting information and stimuli from their environment, so that most stimuli reach them, making it hard to select those that are relevant [19, 59]. The same situation applies for driving. Behind the wheel, many stimuli attract the drivers attention: a car joins the traffic from the right, the driving speed needs to be adjusted to traffic, unexpected events may occur such as accidents or a severe rainstorm, drivers need to keep looking in their mirrors, and there may also be a passenger in the car talking to the driver while the radio is on. Those suffering from ADHD more often have traffic citations, a higher likelihood of license suspension, experienced and caused more vehicular crashes, and more often drive without a license, when compared to people without ADHD [55, 56]. But how does an ADHD diagnosis relate to other factors that are known to influence driving as well, such as anxiety, use of alcohol, or aggression? When comparing ADHD patients with controls, which factors add to the risk for unsafe driving? The risk profiles for adverse driving outcomes and unsafe driving among 330 adults with ADHD and 330 controls were described in Chapter 6.

THE CRYSTAL BALL VIEW: TREATMENT OF ADHD

Considering the clear neurobiological origin of ADHD, it is a highly treatable disorder. The European consensus statement on diagnosis and treatment of adult ADHD recommends a combination of pharmacological and psychological treatment [60]. In 50% to 70% of cases, the core ADHD symptoms are successfully treated with psychostimulant medication [61], of which methylphenidate and dexamphetamine are the most commonly used forms. Both are considered first choice pharmacological treatments of ADHD in Europe. The dopamine agonist methylphenidate inhibits the re-uptake of the neurotransmitters dopamine and noradrenalin by the presynaptic cell, a process that is assumed to be accelerated in the brain of ADHD patients [62]. By the inhibition of dopamine reuptake, the dopamine stays available in the synaptic cleft for a longer period of time, so that signals of inhibition can be transmitted to the postsynaptic cell [63]. Dexamphetamine also aims at increasing the availability of dopamine and noradrenalin in the synaptic cleft, but the mechanism of action is by increasing the presynaptic release of these neurotransmitters [64]. In ADHD, stimulants increase the control over cognitions, emotions and behaviors, by which concentration may improve, hyperactivity diminishes, impulsivity may be inhibited, and irritability decreases. Figure 2 displays the mechanisms of action of methylphenidate (left) and dexamphetamine (right) on the ADHD brain.
Other stimulant preparations that have been studied less often in ADHD are mixed-amphetamine salts, dexmethylphenidate and lis-dexamphetamine, which are all long-acting formulations that have a longer duration of action. It is expected that long-acting release preparations will increase compliance to ADHD medication, by less frequent dosing schedules, resolving daily instability due to frequent rebound effects [67, 68].

Five non-stimulant medications that have been shown to be effective for treatment of ADHD are 1) Atomoxetine, a highly specific noradrenergic re-uptake inhibitor [69]; 2) Bupropion, an antidepressant and anti-smoking medication that selectively inhibits neuronal re-uptake of noradrenaline and dopamine [70]; 3) Tricyclic antidepressants, that inhibit the re-uptake of noradrenaline [71]; 4) Modafinil, anti-narcoleptic medication that inhibits the re-uptake of dopamine by blocking the dopamine transporter [64]; and 5) Guanfacine, a centrally working alpha-2 agonist and anti-hypertensive drug. Other non-pharmacological treatments for ADHD consists of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) or psychological (neurofeedback, cognitive and behavioral treatment) interventions, but the efficacy of these treatments on the core symptoms of ADHD needs further investigation [72-74].

Effective psychological treatment in adult ADHD mainly includes coaching and cognitive behavioral therapy (CBT). Psychological treatment focuses on
reinforcement of a positive self-image and includes the restructuring of negative cognitions and behaviors, learning cognitive skills like planning, organization, and dealing with distractions, learning emotion regulation techniques, and coping with comorbid disorders such as depressive and anxiety disorders, sleep problems, and addictions [75]. CBT can be provided individually, in groups and/or online.

In this thesis, only the effects of a long-acting psychostimulant (methylphenidate) – the pharmacological treatment of first choice in ADHD – were tested using objective measures (see Chapter 2), as well as subjective measures of ADHD behavior (see Chapter 6).

DATA USED IN THIS THESIS

The Netherlands Study on Depression and Anxiety (NESDA)
The studies investigating the comorbidity between severity of major depressive disorder and ADHD symptoms, and depressive and/or anxiety disorders, and ADHD symptoms in relationship to circadian rhythm sleep problems, were performed using data from the Netherlands Study on Depression and Anxiety (NESDA). The NESDA study is an ongoing longitudinal cohort study examining the course and consequences of depressive and anxiety disorders [76]. Participants were recruited from community, primary care and secondary mental health care, in order to represent various health care settings and stages of psychopathology. NESDA was established in 2004 and comprised 2,981 participants at baseline, of which 2,596 men and women took part in the two-years follow-up, and 2,402 participated in the four-years follow-up (respectively 87% and 81% of the baseline sample).

Department and Expertise Center Adult ADHD
For the other three studies on executive functioning, smoking behavior after methylphenidate treatment, and driving behavior in adults with ADHD compared to controls, data were collected among patients at the PsyQ Program Adult ADHD, and analyzed at the PsyQ Expertise Center Adult ADHD. The Expertise Center Adult ADHD aims at developing knowledge through scientific research, spreading knowledge through education and courses, publishing in (inter)national journals, putting new knowledge on websites and in newsletters, presenting at (inter)national symposia, and by implementing new knowledge in the training of professionals in The Netherlands and abroad [77]. The PsyQ
Program and Expertise Center Adult ADHD have obtained the Top Clinical Mental Health Care quality mark (TopGGZ) from the minister of health, which refers to excellent provision of specialized mental health care for patients with serious complicated mental health problems, doing applied clinical research, and educating and training professionals about new knowledge on diagnosis and treatment of ADHD.

**OUTLINE OF THIS THESIS**

The general purpose of this thesis is to examine lifestyle in ADHD from four different viewpoints: the bird’s-eye view (nature), the side view (expression), the frontal view (consequences), and the crystal ball view (treatment).

**Chapter 2** describes specific neuropsychological deficits in adults with ADHD, and investigates their sensitivity to treatment with long-acting OROS-methylphenidate.

**Chapter 3** examines whether the prevalence of clinical ADHD symptoms is related to the severity of depression by using a clinical staging approach in an epidemiological cohort. Analyses were based on the NESDA 4-year follow-up data.

**Chapter 4** elucidates the role of ADHD symptoms on the relationship between circadian rhythm sleep problems and depressive and/or anxiety disorders, using data from the 2-year follow-up of NESDA.

**Chapter 5** reports on the short- and long-term effects of methylphenidate use on tobacco consumption, nicotine consumption and nicotine craving in adults with ADHD.

**Chapter 6** presents comparisons between adults with ADHD and healthy controls regarding the prevalence and predictors of adverse driving outcomes and unsafe driving behavior using questionnaires, in order to specify which individuals are most at-risk.

Finally, **Chapter 7** summarizes and discusses the main findings of the studies described in this thesis.