CHAPTER 7

Summary and Discussion
Predicting Clinical Outcome in Children with ADHD
Is there a Role for Neurocognitive Functioning?

The aim of the current thesis was to advance our knowledge of the course of Attention-Deficit/Hyperactivity Disorder (ADHD), and the role of neurocognitive functioning in ADHD behavior and overall functioning, using longitudinal information from individuals with ADHD-combined type (ADHD/C), their unaffected siblings and controls. Participants were included from the Dutch part of the International Multicenter ADHD Genetics (IMAGE; baseline) and NeuroIMAGE (follow-up) projects. Specific aspects such as age and pharmacological treatment were taken into account in an attempt to capture the complex relationship between neurocognitive and behavioral functioning using a longitudinal sample. This thesis was written with both a descriptive and a predictive perspective as (a) the course of ADHD symptoms (symptom change and persistence rates), comorbid problems and functional impairment was described, as well as the course of neurocognitive functioning, and (b) ADHD outcomes (ADHD symptom severity and symptom change, overall functioning and comorbid problems) were predicted from behavioral and neurocognitive characteristics using information from baseline and follow-up.

In the next sections, the main results from each chapter of this thesis will be summarized (see also Table 7.1 for an overview). Subsequently, we will discuss the findings on the course of ADHD and its neurocognitive characteristics, to what extent ADHD outcomes can or cannot be predicted, and will try to draw some conclusion regarding specific models in which the course of ADHD and the role of neurocognitive functions were described earlier. In addition, clinical implications will be discussed. This chapter will finish with a discussion of strengths and limitations of the studies of this thesis and future recommendations will be provided.
Summary of the Main Findings

In chapter 2, a systematic overview of studies that investigated the predictive value of neurocognitive functioning for prospective ADHD was provided. Relevant studies published between 1990 and 2011 were included. Based on eighteen studies there was no evidence that either automatically controlled (requiring little mental effort; lower level), or more consciously controlled (requiring high levels of mental effort; higher level) neurocognitive functions differentiated ADHD persistence from remittance; overall, both persisters and remitters showed weaker performance than typically developing controls, although the effect was smaller for remitters. Further, neurocognitive functions measured in childhood were able to predict ADHD a few years later, regardless of the type of neurocognitive function. Our findings do not support the model of Halperin and Schulz (2006), which suggests a stronger maturation of more consciously controlled neurocognitive functions in ADHD remitters. Further, several neurocognitive functions seem to be useful to prospectively differentiate individuals with ADHD from controls in childhood.

In the other chapters (3-6) in this thesis, we investigated participants from the IMAGE and NeuroIMAGE cohort. In chapter 3 and 4, affected siblings (ADHD/C) were included. Additionally, in chapter 5 and 6, unaffected siblings and control children were included, thereby covering the full ADHD spectrum from no to severe symptom levels. In chapter 4-6, identical neurocognitive measures were investigated (i.e. verbal working memory, temporal processing [including timing and variability], reaction time speed, and motor control). In chapter 4, this battery was extended by measures of visuo-spatial working memory, motor and cognitive inhibition. We could not include those particular measures at follow-up, as these measures were adjusted for use in the Magnetic Resonance Imaging (MRI)-scanner at follow-up (visuo-spatial working memory, motor inhibition), or differences between ADHD and control children appeared to be due to differences in baseline task (e.g. speed) differences instead of higher order cognitive functioning (cognitive inhibition). Please see Table 7.1 for details on participant and study characteristics of each chapter.

In chapter 3, we investigated the course of ADHD/C from childhood/adolescence into (late) adolescence/young adulthood, and additionally studied a full set of potential predictors for ADHD outcomes over a six-year interval. Although symptom severity decreased, persistence rates were indisputably high: the vast majority of participants had a persistent Diagnostic and Statistical Manual (DSM)-5 diagnosis (86.5%), independent of age. The greater part of ADHD persisters still met combined type criteria (51.4%). Only a very small amount (5.1%) of the participants fully remitted from the disorder. However, since only about half of the sample was functionally impaired at outcome, prognosis is generally rather favorable. Moreover, comorbidity rates (Oppositional Defiant Disorder [ODD], Conduct Disorder [CD]) decreased
strongly over time, and mood- and anxiety disorders were virtually non-existent following strict criteria (1-3%), indicating that overall outcome was better than baseline functioning. The large majority of participants (> 90%) had taken stimulants at some point in time. These findings indicate that although ADHD diagnoses strongly persist, a steady decrease in ADHD and comorbid symptoms is observed and functional impairments attenuate in a substantial proportion. Predictive variables explained up to 20% of variance in our outcome measures: Higher ADHD symptom severity and higher parent-reported impairment prospectively predicted higher ADHD symptom severity and lower overall functioning. A current ADHD diagnosis of (one of) the parent(s) contributed to the prospective prediction of higher ADHD symptom severity, while the child being younger prospectively predicted lower overall functioning. Continued pharmacological treatment had no beneficial impact on ADHD outcomes or overall functioning. In addition, higher cumulative intake of medication until follow-up predicted worse outcomes in terms of ADHD severity, probably explained by a confounding effect where more severe cases had a higher chance of taking medication. Findings on predictors suggest that some variables (e.g. severity, family history for the disorder) may be important risk factors, however, the largest part of variance remains unexplained, needing further investigation.

This was done in chapters 4-6, in which the prospective predictive value of neurocognitive functioning (chapter 4) and the relationship between longitudinal characteristics of neurocognitive functioning (chapter 5 and 6) for ADHD outcomes were investigated. As our review in chapter 2 showed that studies with a larger follow-up interval (i.e. >3 years) and a broader age range (i.e. age > 12 years) are absent so far, we aimed to fill this gap in chapter 4, in which we investigated baseline neurocognitive predictors of ADHD outcomes, using a broad array of neurocognitive measures. These neurocognitive predictors were derived from component scores for eight domains: Working memory, motor inhibition, cognitive inhibition, reaction time variability, timing, information processing speed, motor control, and intelligence. The results revealed that better working memory predicted lower ADHD symptom severity, and less reaction time variability predicted better overall functioning, with a small percentage of explained variance (3-5.6%). Our neurocognitive predictors were significant over and above baseline behavior (e.g. ADHD symptoms), and neurocognitive functions together with ADHD behavior explained a higher percentage of variance compared with models with behavioral or neurocognitive measures alone. The models were independent of age, gender and pharmacological treatment. Finding only few predictive neurocognitive functions with small predictive value challenges the role of neurocognitive functioning in the outcome of ADHD and is in line with findings from chapter 2.

In chapter 5, we investigated the neurocognitive course in multiple domains in ADHD affected as well as unaffected siblings and controls, and subsequently tested whether
this course mapped onto dimensional ADHD outcomes at follow-up. It appeared that affected and unaffected siblings trended to, or fully caught up with performance levels of controls at follow-up on four (44.4%) and five (55.6%) of the nine dependent variables, respectively. Within this trending pattern, only measures of time production, motor control, and an overall measure of neurocognitive functioning showed a full catch-up. In contrast, performance in remaining key neurocognitive measures (i.e. verbal working memory, variability in responding, but also intelligence) remained impaired at follow-up. Importantly, in terms of the predictive value, the course of neurocognitive functioning generally was not related to ADHD outcomes, suggesting that improvement or deterioration of neurocognitive functioning does not translate one-to-one into (ADHD) behavior. Findings indicate not just a maturational delay, but suggest more complex models. Also, the etiological link between neurocognitive deficits and ADHD outcomes in adolescents and young adults is questioned and appear in line with findings of chapter 2 and 4.

As the predictive value of neurocognitive functioning was limited in chapter 2, 4 and 5 with only small effect sizes, in chapter 6 a novel person-based approach was taken to capture heterogeneity and developmental aspects in ADHD, by identifying homogeneous longitudinally informed neurocognitive subgroups. We then examined whether these homogeneous subgroups would link to ADHD outcomes. This was done in individuals with ADHD/C, their unaffected siblings and controls, using neurocognitive measures at two time points. Latent class analysis (i.e. detecting latent neurocognitive subgroups based on patterns of associations between the included neurocognitive measures) revealed three longitudinally stable, mainly quantitatively different neurocognitive subgroups, one characterized by overall weak (inaccurate slow) performance, another by a fast yet accurate performance and a third group showing an overall average profile. As expected, the inaccurate slow subgroup had the worst clinical outcomes at follow-up, with a higher odds ratio for having an ADHD diagnosis at follow-up (3.10, 95% CI [2.05, 4.69]) and 2.21, 95% CI [1.32, 3.70]) compared to the overall average subgroup and the fast yet accurate subgroup respectively. In terms of clinical applicability of the findings, an overall weak neurocognitive profile is reason for concern, since it is a less common phenomenon in control children, clearly increases the odds for a persistent form of ADHD and may even index a risk for late onset ADHD in children at familial risk for ADHD. In addition, our findings suggest that this overall weak profile is a relatively stable neurocognitive profile with apparently very few children showing relative improvements over time. Including the overall weak profile in clinical practice for ADHD as an indicator could increase the accuracy of prognosis and (very tentatively) may even be useful in early detecting of siblings at risk for developing late-onset forms of the disorder. Future studies are needed to examine this issue in clinical practice.
General Discussion

The Course of ADHD Symptoms and Neurocognitive Functions: A Matter of Delay?

Following the maturational lag hypothesis mentioned in the Introduction section, one would expect that at a certain developmental stage, ADHD symptoms should decrease to the level of typically developing controls. Also, it is suggested that due to maturation, underlying deficits (for example neurocognitive deficits, but note that this statement is also based on another hypothesis, assuming a certain association between neurocognitive functioning and behavior) would remit together with remitting symptoms; development is “just” delayed, not qualitatively different. Our results provide some important insights regarding the question whether ADHD is a matter of maturational delay. One of them is the strong persistence rate of initially combined-type ADHD (86.5%) until young adulthood that we have observed in chapter 3. This persistence rate is one of the highest reported thus far; even higher than the 70% persistence rate that was found in the study of Langley and colleagues (2010), which included children with all types of ADHD ≤ 13 years at baseline. This finding contrasts with the hypothesis that with maturation, children with ADHD catch up in their behavior with equal-aged typically developing peers.

An explanation for our high persistence rate may be that we included only children with ADHD/C, a subtype that includes more symptoms to fulfill DSM-criteria compared to the other subtypes. Also, adolescents meeting combined type criteria at baseline may be considered as relatively more severely affected compared to younger children meeting these criteria as these adolescents could have been remitted yet but apparently did not. If the suggestion that the baseline inclusion of only the most ADHD severe subtype may have led to a higher persistence rate is correct, special attention should be drawn to these adolescents with ADHD/C in clinical practice compared to the other subtypes. Being adolescent and still fulfilling criteria of the combined type may indicate a certain risk for persisting behavioral problems. The relative stability of ADHD observed in this thesis is especially important given that the adolescent brain develops strongly during the transition from puberty into adulthood, marked by increased reward seeking activities leading to problematic decision-making processes (Geier, 2013). In combination with ongoing symptoms of ADHD, this may have unfavorable effects on academic, health, and social outcomes, or may lead to adverse outcomes such as offending behavior. Consistent with this view is that more than 50% of the ADHD persisters is still significantly functionally impaired at outcome, indicating that indeed, functioning is importantly compromised still in adolescence and young adulthood. Taken together, our results indicate that in children with combined type ADHD, the course of ADHD symptoms generally is not, or at least not only, understood by a delayed maturation in childhood and adolescence.
While persistence rates are high, ADHD symptoms decreased significantly (chapter 3), which is in line with other studies that show that 15% versus 65% remain symptomatic at age 25 depending on the definition of persistence (Faraone, Biederman, & Mick, 2006). Almost 10% of all participants with ADHD/C decreased in symptom levels to the extent that they now fell in the category of subthreshold ADHD, and half of all ADHD persisters attained an inattentive (majority) or a hyperactive/impulsive (minority) subtype diagnosis instead of a combined subtype. This difference in persistence in terms of meeting full DSM-criteria versus persistence in terms of symptom levels evidently illustrates the difference between a continuous and a dichotomous approach, which is consistent with the findings in the earlier mentioned comprehensive meta-analysis (Faraone et al., 2006). It is possible that with further aging, symptoms may further decrease and eventually lead to remittance. However, given the prevalence rates of ADHD in adults (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009) and the high persistence rates and compromised overall functioning that we observed in 50% of participants in young adulthood, remittance perhaps is not cut out for every individual and clearly is not yet set for a large proportion in adolescence and young adulthood. Taken together, looking at the continuous level, a general pattern of decrease in symptom severity is observed which may be in accordance with a maturational delay hypothesis, however, this decrease is so small that an indisputably high number of children remains fulfilling ADHD criteria and compromised overall functioning, suggesting a maturational delay alone is not sufficient to explain these ongoing problems.

Of note, a relevant issue in the discussion on persistence and remittance of ADHD symptoms is to what extent comorbid problems persist over time. In chapter 3, we have demonstrated that the rate of comorbidities, in the form of oppositional, conduct, mood and anxiety disorders decreased over time, which is particularly notable compared to most other studies showing higher rates of comorbidities (Biederman, Newcorn, & Sprich, 1991), but is also evident compared to the clearly persisting pattern of ADHD. The course of comorbid problems seems to differ from that of ADHD symptoms, by showing a stronger decrease. This stronger decrease in comorbid problems may suggest that separate mechanisms are involved in the decrease of comorbid problems as opposed to the stronger persistence of ADHD symptoms. Alternatively, a ‘U-shape’ development may exist, in which ADHD symptoms emerge first, followed by comorbid problems, and with time (or maturation), the comorbid problems remit first, followed by a decrease in ADHD symptomatology. When such a mechanism is at work here, that may indicate that the stronger decrease in comorbid problems in our sample could predict the further decrease of ADHD symptoms in time.

Our results so far do not confirm that a maturational delay in ADHD is apparent in (most) individuals with ADHD/C. In an attempt to further understand pathophysiological mechanisms that may increase our insight into the course of
ADHD, many studies have investigated neurocognitive functions (e.g. Frazier, Demaree, & Youngstrom, 2004; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Pauli-Pott & Becker, 2011; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), some of them also from a longitudinal perspective (e.g. Barkley & Fischer, 2011; Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014; Mick et al., 2011; Rajendran, Rindskopf, et al., 2013; Rajendran, Trampush, et al., 2013; Vaughn et al., 2011), or by studying neurocognitive functions in adults with ADHD (Bálint et al., 2009; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Bridgett & Walker, 2006; Hervey, Epstein, & Curry, 2004; Schoechlin & Engel, 2005). We extended this knowledge in chapter 5 by investigating the course of a broad range of neurocognitive functions over a six-year follow-up interval, from which one interesting point clearly withstands. The majority of functions in unaffected and affected siblings showed a trending pattern into the direction of normalization (time reproduction, time production variability, reaction time speed) or even fully caught-up with performance levels of controls (time production, motor control, aggregated neurocognitive functioning). Importantly, however, for remaining functions that were suggested key domains in ADHD (e.g. working memory, reaction time variability), the initial gap in performance between (un)affected siblings and controls remained over time. Our findings confirm results reported in other studies regarding patterns of neurocognitive normalization in ADHD for some functions (Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005; McAuley, Crosbie, Charach, & Schachar, 2014; Miller, Loya, & Hinshaw, 2013), while other functions show partial normalization and some functions remained impaired (Hervey et al., 2004; Mostert et al., 2015). No clear pattern emerged regarding the type of functions that did and did not show normalization. For example, we could not clearly differentiate between lower (more automatically controlled) or higher (requiring a high level of effort) order functions or otherwise (Halperin & Schulz, 2006). Nevertheless, we can conclude that findings do not entirely fit the hypothesis of a maturational delay, as three important neurocognitive functions (verbal working memory, variability in responding and intelligence) remained impaired when all participants reached adolescence and young adulthood. This is confirmed by the lack of a significant effect of age on patterns of catch-up, which would have been evident following the maturational lag hypothesis as it assumes that an individual would show a ‘growth spurt’ leading to normalization at a certain developmental stage. So for both the behavioral as for the neurocognitive data, evidence does not support the suggestion that ADHD is ‘only’ a matter of delay, at least not for most of the individuals. More complex mechanisms probably are involved in the further course of the disorder, which will be discussed further on.
Predicting ADHD Outcomes: Are Neurocognitive Functions Valuable, Beyond Behavior?

ADHD thus persists in a large majority - at least in individuals with combined-type ADHD - and persistent ADHD is associated with major chronic problems in adult life relative to remitted ADHD (Barbaresi et al., 2013; Klein et al., 2012), indicating the importance to investigate predictors of the course of ADHD or ADHD outcomes. Below we will summarize and discuss our findings regarding behavioral and neurocognitive predictors, as well as demographic variables, familiality and pharmacological treatment.

First, results regarding the prediction of ADHD were quite disappointing as a meaningful longitudinal relationship between predictors (mostly neurocognitive but also some other, see further) and ADHD behavior was largely absent. For example, many of the non-neurocognitive variables (e.g. sex, socio-economic status, age of ADHD onset, and comorbidities) that we included in chapter 3 were unrelated to ADHD outcomes when investigated together with other significantly predicting factors (e.g. ADHD symptom severity, parent-reported impairment, current parental ADHD status). In addition, based on an extensive search in the literature (chapter 2) as well on our results in chapter 4, we were not able to detect a generally convincing and clinically meaningful relationship between neurocognitive functioning at one point of time in children and adolescents with ADHD for prospective ADHD symptom severity, ADHD change, or overall functioning. Unfortunately, we were also not able to provide evidence that ADHD outcomes could be predicted based on the course of neurocognitive functioning over and above baseline behavior (chapter 5). Moreover, a person-based approach using latent class analyses revealed that three distinct more or less severity based longitudinally informed neurocognitive subgroups all contained a significant amount of controls, unaffected and affected siblings, again indicating that the predictive value of neurocognitive functioning is limited.

Alternatively, a few variables were (mostly to a small extent) related to ADHD outcomes and overall functioning: First, non-neurocognitive characteristics as ADHD severity (more symptoms and greater impairment), parental ADHD status (a current ADHD diagnosis of [one of] the parent[s]) and younger age were positively predictive for worse ADHD outcomes in children with ADHD/C (chapter 3). These results were consistent with some (Biederman et al., 1996; Molina et al., 2009) but not all (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011) studies showing the predictive value of symptom severity and overall functioning. In addition, our findings are consistent with studies that found positive predictive value for concepts as family history of ADHD or parental psychopathology (Biederman et al., 1996; Langley et al., 2010). Furthermore, on the positive predictive value of neurocognitive functions, chapter 2 demonstrated that neurocognitive functions measured in young childhood...
are able to predict prospective ADHD compared to control status, still in childhood. In addition, chapter 4 illustrated that there is predictive value for working memory (composite score of verbal and visual working memory) regarding prospective ADHD symptom severity, and predictive value for reaction time variability regarding prospective overall functioning, both with a small effect, over and above baseline measures. Interestingly, as other studies found working memory and reaction time variability to be the most promising of all neurocognitive functions involved in ADHD (Castellanos & Tannock, 2002; Martinussen et al., 2005; Tamm et al., 2012), observing (little) predictive value precisely for these two neurocognitive functions of ADHD outcomes may indicate that working memory and reaction time variability are indeed most central to ADHD. It is notable that this finding is in line with a recent study in which ADHD symptoms were assessed on a continuum both at baseline and follow-up, showing that better working memory and less reaction time variability predicted prospective ADHD symptoms and academic achievement, over and above baseline symptoms (Sjöwall, Bohlin, Rydell, & Thorell, 2015). So, these findings justify at least further investigation into the predictive role of working memory and reaction time variability in ADHD symptom development. Results from chapter 6 yielded that detecting longitudinally informed neurocognitive subgroups may be helpful to index a vulnerable group; generally and developmentally stable inaccurate slow neurocognitive performance is related to the worst (ADHD-related) outcomes compared to an overall average performing subgroup and a fast yet accurate subgroup, confirmed by odds ratios of about 2 to 3 for the inaccurate slow versus the fast yet accurate, and overall average subgroup respectively, respectively. Another finding from chapter 6 cautiously pointed to another link between neurocognitive functioning and ADHD, namely that unaffected siblings in the inaccurate slow subgroup were at higher risk to develop ADHD later on compared to those in the fast yet accurate subgroup.

Taken all findings together, the overall pattern thus was a disappointing absence of predictive value of neurocognitive functioning and some other characteristics for prospective ADHD outcomes. Only a minority of variables may have potential predictive value for predicting ADHD outcomes, beyond baseline behavior, with moderate (non-neurocognitive) to small (neurocognitive) effects. A person-based neurocognitive profiling approach yet seems most promising, although the predictive power of these subgroups is also limited (yet). The often absent relationship between neurocognitive functioning and ADHD outcomes not only has consequences for our search to variables that may help inform us on prognostic perspectives, but also has important meaning for several models on neurocognitive functions in ADHD. On the other hand, person-based neurocognitive profiling approaches may be a more important direction in future studies.
Implications for Models in ADHD

The mainly absent or weak relationship between neurocognitive functioning and ADHD outcomes not only has consequences for our search to variables that may help inform us on prognostic perspectives, but also has important meaning for the several models on neurocognitive functions in ADHD that were mentioned in the Introduction section. See Figure 7.1 for a visual overview together with a summary of results that fit each model.

The remarkable absent relationship between neurocognitive functions and ADHD outcomes in children that already have an ADHD diagnosis leads us to suggest that, at least once ADHD has set on, neurocognitive deficits are not directly related to the further course of ADHD symptoms, i.e. do not lie in the causative chain, as was commonly thought based on cross-sectional findings. Instead, our findings point into the direction that neurocognitive functions may act as epiphenomena, perhaps being related to the same underpinnings as ADHD symptoms but not causally related. Such a model also accounts for the inconsistencies that were observed regarding controls and unaffected siblings having an inaccurate slow neurocognitive profile, or children with ADHD having an overall average or fast and accurate profile. Such an epiphenomenal model is in line with other studies that, for example, showed that persistent genetic factors underlie the longitudinal relationship between ADHD and intelligence in twins (Rommel, Rijsdijk, Greven, Asherson, & Kuntsi, 2015), or found shared genetic etiology between several neurocognitive functions (e.g. memory, reaction time speed, reasoning abilities), and psychiatric symptoms (Hagenaars et al., 2016).

However, we think it may be premature to firmly conclude at this point that neurocognitive functions are not causally related to the disorder, as we also concluded that using longitudinally informed neurocognitive subgroups led to a different pattern of outcomes (chapter 6). Findings thus may depend on methodological aspects (e.g. which measures are included, which approach [person-based versus a group-mean approach] is used), which is also relevant to the limitation (see further) that we did not (thoroughly) investigated the domain of reward processing and cognitive control. Although evidence best fit an epiphenomenal model so far, the option of an endophenotypic role of neurocognitive functions is not fully excluded, especially as the neurocognitive subgrouping approach did appear to identify a ‘risk’ profile, and working memory and reaction time variability showed up as baseline predictors for future outcomes. It is therefore of importance to further explore such person based approaches and/or the role of working memory and reaction time variability to draw more firm conclusions.
**Figure 7.1.** Visual summary of different models that included neurocognitive functioning in pathways to ADHD. Figure 7.1A and 7.1B are inspired by Coghill et al., 2014. "Environment" refers to bi-directional relationships with all levels in the pertinent models.
Of interest are the differential findings from this thesis regarding predicting the onset of ADHD (for example early neurocognitive functions predicted ADHD in childhood – chapter 2; or being at risk for late onset ADHD with an inaccurate slow longitudinally informed profile – chapter 6) and predicting the further course of ADHD. Speculating on this, there may be a role for neurocognitive functioning in the prediction of the onset of ADHD, while neurocognitive functioning may not be clearly involved in the prediction of full ADHD remittance. Such a differentiation between onset and further course of the disorder is confirmed by multiple studies demonstrating that neurocognitive functioning in general may relate to the emergence or existence of ADHD in young children (Pauli-Pott & Becker, 2011; Rajendran, Rindskopf, et al., 2013; Sjöwall et al., 2015; van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013), but is not clearly related to the course of ADHD (Coghill et al., 2014; McAuley et al., 2014; Miller, Ho, & Hinshaw, 2012; van Lieshout et al., 2013). Additionally, such a differentiation is also supported by studies reporting that particular genetic factors are involved in the onset of ADHD, and that other genes contribute to persistence or remittance of ADHD (Chang, Lichtenstein, Asherson, & Larsson, 2013; Pingault et al., 2015). Perhaps in younger years neurodevelopmental factors have a larger impact, while with aging more and more other (interrelated) factors may impact on pathways to behavior, such as parenting styles, peer relationships, school performance/failure, self-esteem and so forth (Sonuga-Barke & Halperin, 2010). This thus may suggest that remittance of ADHD is far more difficult to predict and may be impacted by many more and other variables compared to the early onset of ADHD.

Further speculating, it may be well possible that our biological system is very multifaceted with several models in play, being complexly intertwined and overlapping. This may lead us to keep finding different, inconsistent or unexpected findings. For example, next to the epiphenomenal and endophenotypic models that we discussed yet, it may be also possible that ADHD has certain neurocognitive deficits as a consequence, perhaps as a result of person-environment interaction (Coghill et al., 2005); e.g. a person with ADHD may search for a different environment (less nuisance, quiet, or stimulus-rich, etc), and that environment may impact on (the expression of) neurocognitive (dys)functioning. One study yet demonstrated that both ADHD symptoms and neurocognitive functioning related to ADHD symptoms and neurocognitive functioning at follow-up (Rajendran, Rindskopf et al., 2013).

Taken together, findings from the current thesis best fit the idea that neurocognitive functioning and ADHD symptoms may be related to each other through common underlying mechanisms instead of being directly causally related, at least in relation to the further course of the disorder. Onset of ADHD (or ADHD at an early age) may be better to predict. However, we also have discussed that causality (at least in some way), or other more complex models, cannot be fully ruled out.
Clinical Implications

Our findings add to the current idea that ADHD is not only a childhood disorder (Klein et al., 2012), but rather is a disorder that lasts into (young) adulthood for many affected individuals. Relating to the debate that ADHD may be over-diagnosed (Ford-Jones, 2015), an important difference with clinical practice is that diagnostic outcomes in this study were of no interest to families nor assessors: Diagnostic outcomes were not linked back, had no specific consequences for school or treatment indications, for example. Therefore, we consider our diagnostic assessment as objective as possible – acknowledging the challenges that exist concerning behavioral classifications based on more or less arbitrary cut-off points, as no real objective marker of ADHD is known at this point. With our effort to objectively and extensively investigate diagnostic information over time, we can acknowledge that once affected, problems are clearly not dissipated but likely (partially) continue into adolescence or young adulthood.

Based on the strong persistence of ADHD and related problems, it may clinically be important to follow-up and treat children/adolescents with ADHD, to decrease the burden from this disorder. This argues for a further effort into defining what the best way of support or treatment during the course of this disorder is, on which we will speculate a bit further now, noting that this was not the topic of our investigation. Our findings do not provide evidence for an important role for pharmacological treatment. The amount of pharmacological treatment did not seem to contribute to better outcomes in our sample and may have aversive side effects, which was in line with findings from another studies (Langberg & Becker, 2012; Molina et al., 2009; van de Loo-Neus, Rommelse, & Buitelaar, 2011). Speculating on alternative ways of treatment, another thought may be that training of neurocognitive functions may be valuable (Titz & Karbach, 2014, but for a contrasting view please see Rapport, Orban, Kofler, & Friedman, 2013). This may seem a counterintuitive thought given the fact that associations with ADHD and overall functioning in this thesis are weak (consistent with findings that training specific neurocognitive functions may not directly lead to improved ADHD behavior, Rapport et al., 2013). However, strengthening or compensating deficits in neurocognitive functions may increase particular domains of functioning next to ADHD behavior (Tucha et al., 2011): For example, when improving the ability to direct and maintain attention to the outer world, this may lead to improved social skills as one could better/longer listen and respond to peers or parents, which may in turn lead to improved quality of relationships. In addition, mindfulness-based interventions aim to enhance attention and to reduce harsh self-judgments, which may lead to more optimal functioning (Semple, Lee, Rosa, & Miller, 2010). Indeed, it has been shown that such intervention programs, including both the parents and the children, may lead to improved behavioral functioning as reported by the parents and children themselves (Semple et al., 2010; van der Oord, Bogels, & Peijnenburg, 2012). Summarizing, monitoring and
treatment may clinically be important in (persistent) ADHD, and there is some evidence to suggest that - even when neurocognitive functions are not causally related to ADHD symptoms - it may be that neurocognitive training may lead to improved functioning in specific areas, perhaps increasing an individual’s wellbeing.

By investigating neurocognitive functions our goal was to increase the percentage of explained variance in terms of behavioral outcomes. However, we found only meager evidence that neurocognitive functions measured at one point in time would prove useful as prognostic factors. Even when detecting significant predictors (e.g. working memory and reaction time variability), these predictors only had small effect sizes. Using a person-based neurocognitive profile analysis yet had the largest predictive value, with small to moderate effect sizes regarding the differentiation of the inaccurate slow versus the other two subgroups. Separate from the theoretical model that our findings may fit, it seems that the clinical value of neurocognitive functions as predictors for the further course in yet affected children is limited at this point. In terms of clinical applicability, our findings most specifically indicate that an overall weak neurocognitive profile is reason for concern, since it is a less common phenomenon in control children, increases the odds for (a persistent form of) ADHD, and may (tentatively) index a risk for late onset ADHD in children at familial risk for ADHD. However, as such findings are not specific to ADHD (e.g. having an overall weak profile is not exclusively reserved for affected children), such a profile could only be used as a careful indicator of a larger risk of a worse prognosis. As it is well possible that behavioral (ADHD) outcomes are the sum of many different minor (interacting) effects, which are not yet clinically available, it could be suggested that neurocognitive functioning may have a modest place in clinical practice at this point.

**Strengths and Limitations**

Findings in this thesis should be viewed in the light of its strengths and limitations. Specific strengths are the longitudinal design in which a relatively large battery of identical neurocognitive measures was included at two timepoints. We were able to investigate a relatively large sample including the full spectrum of ADHD symptoms, thereby taking into account potential confounding effects of age, gender, and pharmacological treatment. Further, an extensive diagnostic assessment, in which different types of instruments (e.g. clinical interview, supplemented with questionnaires) were used in order to establish a thorough DSM-diagnosis. In addition, the course of ADHD and its neurocognitive characteristics was investigated over a six year interval, which is larger than that in many other studies (Brocki, Nyberg, Thorell, & Bohlin, 2007; Kalf et al., 2005; Kalf et al., 2002; Vaughn et al., 2011) and would enable children to enter a new developmental phase.
Although we undertook considerable effort to perform an optimal study, some limitations should be noted as well. First, some aspects of our sample limit generalization to the (ADHD) population, including (1) our exclusive focus on individuals with combined type ADHD, (2) the limited representation of girls in our sample – although the results did not change when taking gender into account -, (3) the inclusion of only Caucasian participants, (4) including children with a clinical ADHD diagnosis instead of children from the general population, and finally (5) including children with ADHD that were mostly medicated; having a 48-out wash-out period may not be enough to account for the more structural impact of medication (Spencer et al., 2013); however, grossly, our findings indicate that pharmacological treatment did not change results. Second, our findings may not be generalized to other neurocognitive domains, such as reward related neurocognitive functions or other cognitive control functions beside working memory. In addition, we were not able (except in chapter 4) to measure a neurocognitive construct based on multiple measures, which would have increased reliability. However, we have chosen not to increase the testing burden for our participants, which consequently may have resulted in fatigue and data loss due to drop outs which would impact on the quality of our data. Third, we have chosen to use performance-based measures of neurocognitive functioning. Rater-based measures of neurocognitive functioning may show higher predictive value, as these measures may be more closely related to behavior and investigate capacities in more unstructured situations, which may better mirror ‘real-life’ functioning (Toplak, West, & Stanovich, 2013). Fourth, regarding questions of causality: although we performed a longitudinal study, which may be valuable in unraveling patterns of causality to a certain extent given the fact that one may order relationships in time, this does not equal an experimental design. Fifth, regarding the discussion on the endophenotype model (or others), we did not investigate all criteria set forth for the endophenotypic characteristics of neurocognitive functions as for example described by Gottesman & Gould (2003). Finally, most participants with ADHD at outcome already had the diagnosis at baseline which led us to focus specifically on how behavioral and neurocognitive patterns may be (causally) related in the course of the disorder, which may be different from mechanisms regarding the onset of ADHD. Our conclusions regarding the latter point thus are more tentative.

**Future Research**

The current thesis has addressed specific questions regarding the course of, and relationship between ADHD symptom severity and neurocognitive functioning. This has led to the emergence of new questions and recommendations for future studies.
To further disentangle the complex relation between neurocognitive functioning and ADHD symptoms specifically, future studies preferably should start as large (or representative sub-) population samples in very young children, when the full expression of ADHD has yet to set. From there on the relationship between neurocognitive functioning and ADHD symptomatology should be investigated bidirectionally at multiple points in time, into adulthood. In that way, associations between neurocognitive functioning and the onset as well as the further course/remission of ADHD, can be studied in greater detail. In addition, our findings suggest that it is important to further define more homogeneous subgroups in ADHD, for example based on neurocognitive performance or creating subgroups based on both neurocognitive and behavioral information. Adding key neurocognitive functions such as reward processing, cognitive control (Sonuga-Barke, Bitsakou, & Thompson, 2010), but also adding other functions for example capturing social cognitive functioning may add to a more complete understanding of ADHD and the relationship with neurocognitive functions.

Another point is that future studies are recommended to target domains besides specific DSM-based ADHD diagnoses or symptoms, as investigating ADHD symptomatology itself is a narrow way of looking into an individual’s wellbeing. The importance of the use of the DSM is obviously that we have nosologically agreement on several types of problems, and with that, it is yet a vital instrument in both clinical practice and research. By including a measure that captures several domains of overall functioning (psychological, academic, social) we have made a first attempt to look beyond ADHD symptoms, however, this clearly should be extended much further. An interesting view that goes beyond the DSM is the network approach as described by Borsboom and colleagues (2017), that tenets that mental disorders arise from (causal) interactions between varying symptoms of psychopathology and biological, psychological and societal mechanisms, within one network. This could be seen as a more transdiagnostic approach to conceptualizing psychopathology. Perhaps, neurocognitive functions could be of value in such a network approach. In addition, we consider it very likely that by “including” six years of time in the prediction models, a lot of ‘nuisance’ is added; for example in the form of (epi-)genetic variations that may differ over time (Chang et al., 2013), but also the large amount of environmental variations and its interactions. Future studies thus preferably should include other variables, such as those relating to family-environmental factors. For example, studies have shown that chaotic home environments (Evans, 2006; Martin, Razza, & Brooks-Gunn, 2012), upbringing style (Morrell & Murray, 2003), attachment style (Richards, 2013), or family relationships (defined by parental expressed emotions, e.g. maternal warmth, maternal criticism; Richards et al., 2014), are associated with poorer developmental outcomes (e.g. academic, socio-emotional, behavioral, or self-regulatory abilities).
In this regard, it is worth mentioning that The National Institute of Mental Health (NIMH) has introduced a very promising extensive project in which such a transdiagnostic view is taken, acknowledging the complexity of psychopathological mechanisms in the context of developmental and environmental aspects. With the Research Domain Criteria project (RDoC, see https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml for further details), a framework for research on psychopathology (e.g. genomics and neuroscience) is created (Insel et al., 2010). This framework is centered around five dimensional psychological constructs that are relevant to human behavior and mental disorders; negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems, which are studied on several levels, e.g. genetic, molecular, neurobiological, behavioral. Ultimately, world-wide data-collection and collaboration in such an extensive framework would further increase our knowledge on general psychopathology and pathophysiology and specifically ADHD related behavioral problems, in which neurocognitive functioning may act as one part of this enigma. Consequently, the scientific system also may benefit from larger and better cooperation across study groups, countries and continents. In the end, such an extensive approach will guide treatment development, selection and planning in much greater detail than we have available yet, thereby optimizing an individual’s wellbeing together with his social system.

**Key Findings & Conclusions**

* ADHD/C is largely persistent into adolescence and young adulthood on the dichotomous level (diagnosis yes/no), with a slight ADHD symptom decrease on the continuous level.

* In terms of persistence of neurocognitive functioning: Verbal working memory, reaction time variability and intelligence remain impaired in affected and unaffected siblings when reaching adolescence and young adulthood compared to controls.

* Several other neurocognitive functions in both affected and unaffected siblings trend to (time reproduction, time production variability, reaction time speed), or fully catch-up (time production, motor control, aggregated neurocognitive functioning) with control performance levels.

* Following these behavioral and neurocognitive findings, the course of ADHD is unlikely to be fully explained by a maturational delay.
* In terms of predictors, non-neurocognitive variables such as ADHD symptom severity, parent-reported impairment, parental ADHD status and age are valuable predictors for prospective ADHD symptom severity and overall functioning.

* Few neurocognitive variables predict prospective ADHD outcomes: Working memory and reaction time variability predict prospective ADHD symptom severity and overall functioning respectively, over and above behavior, to a small extent.

* Predicting ADHD outcomes (over and above baseline behavior) using neurocognitive change on a group-level reveals no evidence for a relationship between those two variables.

* There is no convincing evidence for a differentiation in lower versus higher order neurocognitive functioning differentially involved in the onset versus the further course of the disorder.

* Three quantitively distinct longitudinally stable neurocognitive subgroups exist in individuals with and without ADHD. A developmentally stable overall weak profile is related to the worst ADHD outcomes.

* Clinically, particularly an overall weak neurocognitive profile may carefully be used as an indicator of a larger risk of worse prognosis next to behavioral factors.

* Further, findings suggest that the clinical value of neurocognitive predictors for prospective ADHD outcomes remains small yet.

* Moreover, findings best fit the suggestion of neurocognitive functions being epiphenomena instead of being a causative factor in ADHD, or indicate more complex models. It is possible that different mechanisms on the onset versus the persistence of ADHD exist.

* A broader network-model in which both ADHD symptoms together with other (comorbid) symptoms and level of functioning should be modelled, in relation to several potential pathophysiological mechanisms which may include neurocognitive functioning, preferably over time and in relation to environmental interactions.
Table 7.1. Summary of the main findings of this thesis

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Participants</th>
<th>Baseline measures</th>
<th>Follow-up measures</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| 2       | Review: 18 studies | **Predictor**  
- Cognitive control  
- Reward processing  
- Timing  
- Alerting attention  
- Orienting attention  
- Intelligence  
- Visual information processing speed  
- Basic information processing speed | **Predictor**  
- Cognitive control  
- Timing  
- Alerting attention  
- Intelligence  
- Basic information processing speed | ▪ ADHD persisters and remitters could not be differentiated based on (higher or lower order) neurocognitive functions  
▪ Both ADHD persisters and remitters had weaker neurocognitive performance than controls  
▪ Neurocognitive functions in (young) childhood predicted ADHD a few years later |
| 3       | 347 children with ADHD/C  
Baseline age: 5-19 years | **Predictor**  
- Demographics (Age, sex SES)  
- ADHD familiality (% siblings with ADHD, current parental ADHD)  
- ADHD characteristics (ADHD symptoms, impairment, age of onset)  
- Comorbidities (ODD, CDD, mood/anxiety)  
- Pharmacological treatment | **Outcome**  
- ADHD status  
- Symptom severity  
- Symptom change  
- Diagnosis  
- Persistence  
- Comorbidities  
- Overall functioning  
- Pharmacological treatment | ▪ Majority of participants persisted in ADHD diagnosis (87.5%). Only 5.1% fully remitted at follow-up  
▪ Comorbidities decreased strongly  
▪ Pharmacological treatment (taken at any time) increased  
▪ About half of participants were still functionally impaired at follow-up  
▪ Baseline predictors parental ADHD, higher ADHD symptom severity and more impairment positively predicted prospective ADHD symptom severity  
▪ Baseline predictors (younger) age, higher ADHD symptom severity, and more impairment positively predicted |
Pharmacological treatment had no (beneficial) impact on either symptom severity or impairment.
### Outcome
- ADHD symptom severity
- Overall functioning

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Predictor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal working memory</td>
<td>Verbal working memory</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Time production</td>
<td>Time production</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Time reproduction</td>
<td>Time reproduction</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Reaction time variability</td>
<td>Reaction time variability</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Time production variability</td>
<td>Time production variability</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Reaction time speed</td>
<td>Reaction time speed</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Motor pursuit control</td>
<td>Motor pursuit control</td>
<td>ADHD symptom severity</td>
</tr>
<tr>
<td>Motor tracking control</td>
<td>Motor tracking control</td>
<td>ADHD symptom severity</td>
</tr>
</tbody>
</table>

LCA revealed three quantitively distinct developmentally stable neurocognitive subgroups:
- 1: inaccurate slow
- 2: overall average
- 3: fast yet accurate

The inaccurate slow subgroup has the worst outcomes at follow-up (ADHD symptoms, overall functioning, oppositional behavior, social problems), and may index a risk for late onset ADHD in children with familial risk.

All subgroups contained ADHD (un)affected siblings and controls, indicating limited specificity of the subgroups.

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Note: Table 7.2 describes instrument names of variables that are mentioned in the current Table (7.1). ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD/C = ADHD Combined subtype; CD = Conduct disorder; LCA = Latent class analysis; ODD = Oppositional Defiant Disorder; SES = socioeconomic status.
### Table 7.2. Overview of specific instruments

<table>
<thead>
<tr>
<th><strong>ADHD behavioral measures</strong></th>
<th><strong>Baseline</strong></th>
<th><strong>Follow-up</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD diagnosis</td>
<td>PACS interview with parents, establishing an DSM-IV-TR diagnosis using an extensive algorithm</td>
<td>K-SADS interview with parents, and with child ≥ 12 years, establishing a DSM-5 diagnosis using an extension algorithm.</td>
</tr>
<tr>
<td>ADHD symptom severity</td>
<td>CPRS-R:L</td>
<td>CPRS-R:L</td>
</tr>
<tr>
<td>Impairment</td>
<td>SDQ (parent report)</td>
<td></td>
</tr>
<tr>
<td>Overall functioning</td>
<td>K-GAS score</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive predictors/variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Verbal) working memory</td>
<td>Digit Span Task, Visuo-spatial Sequencing Task&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Digit Span Task</td>
</tr>
<tr>
<td>Motor inhibition</td>
<td>Stop Task&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cognitive inhibition</td>
<td>ANT Shifting Attentional Set, block 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Reaction time variability</td>
<td>ANT Baseline Speed, ANT Shifting Attentional Set, block 1&lt;sup&gt;a&lt;/sup&gt;, Stop Task&lt;sup&gt;a&lt;/sup&gt;, Motor Timing Task&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>ANT Baseline Speed</td>
</tr>
<tr>
<td>Timing variability</td>
<td>Motor Timing Task</td>
<td>Motor Timing Task</td>
</tr>
<tr>
<td>Timing</td>
<td>Motor timing, Time Test</td>
<td>Motor timing, Time Test</td>
</tr>
<tr>
<td>Reaction time speed</td>
<td>ANT Baseline Speed, ANT shifting attentional set, block 1&lt;sup&gt;a&lt;/sup&gt;, Stop task&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ANT Baseline Speed</td>
</tr>
<tr>
<td>Motor control</td>
<td>ANT Pursuit&lt;sup&gt;c&lt;/sup&gt;, ANT Tracking</td>
<td>ANT Pursuit&lt;sup&gt;c&lt;/sup&gt;, ANT Tracking</td>
</tr>
<tr>
<td>Intelligence</td>
<td>WISC/WAIS-III four subtests</td>
<td>WISC/WAIS-III two subtests</td>
</tr>
<tr>
<td>Other predictors/variables</td>
<td>Based on birth date and testing date, Demographics questionnaire, Demographics questionnaire</td>
<td>Based on birth date and testing date, Demographics questionnaire</td>
</tr>
<tr>
<td>Age</td>
<td>Derived from PACS interview, DSM-IV based</td>
<td>K-SADS ADHD diagnosis</td>
</tr>
<tr>
<td>Sex</td>
<td>Demographics questionnaire</td>
<td>Demographics questionnaire</td>
</tr>
<tr>
<td>SES</td>
<td>Demographics questionnaire</td>
<td></td>
</tr>
<tr>
<td>ADHD familiality</td>
<td>PACS ADHD diagnosis</td>
<td>K-SADS ADHD diagnosis</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Derived from PACS interview</td>
<td>Derived from PACS interview, DSM-IV based</td>
</tr>
<tr>
<td>ODD, CD</td>
<td>Derived from PACS interview, DSM-IV based</td>
<td>Derived from K-SADS interview, DSM-IV based</td>
</tr>
<tr>
<td>Mood/anxiety</td>
<td>Derived from PACS interview, screening score</td>
<td>Derived from K-SADS interview, DSM-IV based</td>
</tr>
<tr>
<td>Tic disorders</td>
<td>Derived from K-SADS interview, DSM-IV based</td>
<td></td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td>Cumulative intake of psychostimulants in months until baseline measurement</td>
<td>Cumulative intake of psychostimulants in months until follow-up measurement</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Social problems</td>
<td></td>
<td>CPRS-R:L</td>
</tr>
<tr>
<td>Anxiety/shyness</td>
<td></td>
<td>CPRS-R-L</td>
</tr>
<tr>
<td>Oppositional behavior</td>
<td></td>
<td>CPRS-R-L</td>
</tr>
</tbody>
</table>

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; ANT = Amsterdam Neuropsychological Tasks; CD = Conduct disorder; CPRS-R:L = Conners' Parent Rating Scale-Revised: Long version; DSM-IV-TR = Diagnostic and Statistical Manual of mental disorders (4th edition, text revision); K-GAS = Global Assessment Scale-score of the K-SADS; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia for school-age children; ODD = Oppositional Defiant Disorder; PACS = Parental Account of Children's Symptoms; SDQ = Strengths and Difficulties Questionnaire; SES = socioeconomic status; WAIS = Wechsler Adult Intelligence Scale; WISC = Wechsler intelligence Scale for Children.

* This task is investigated only in chapter 4. * Variability on the Motor Timing Task was used to compose a component score named reaction time variability in chapter 4, and as a separate timing variability measure in chapter 5 & 6. * This task is investigated in chapter 4 and 6.
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