Cognition and comorbidity in ADHD: The role of methylphenidate and development

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CHAPTER 7

SUMMARY AND GENERAL DISCUSSION
SUMMARY

Information on the potential persistency of the effects of MPH for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) is scarce, while in 2012, approximately 80,000 children and adolescents were treated with MPH in The Netherlands only (Stichting Farmaceutische Kengetallen, 2013). Therefore, the central objective of this dissertation was to determine whether MPH treatment during brain development leads to cognitive alterations. Other questions revolved around this assumption and served to improve the understanding of cognition and affective comorbidity in ADHD, and the role of stimulant use and development.

Specifically, we investigated whether the cognitive effects of MPH are persistent after treatment discontinuation in children, but not adults with ADHD (the ePOD trial described in Chapter 5). With the pre-treatment data of the ePOD trial, we addressed whether prior stimulant use is related to depressive and anxiety comorbidity (Chapter 4). Furthermore, we described a meta-analysis evaluating whether the cognitive effects of acute MPH depend on age (Chapter 3). We also examined the age-relationship of cognitive dysfunctions (Chapter 2), and of depressive and anxiety comorbidity in ADHD (Chapter 4). In both cases we excluded a potential influence of prior stimulant treatment in order to determine the actual nature of cognition and comorbidity. Last, test-retest reliabilities of experimental cognitive tests commonly used in research on developmental disorders were provided (Chapter 6). In order to achieve our goals, we collected data with cognitive tests, and with depression and anxiety questionnaires, from stimulant treatment-naïve children and adults with ADHD, and from their TD counterparts. We also collected depression and anxiety ratings given by stimulant treatment-naïve and previously medicated adolescents with ADHD, and by their TD counterparts. The stimulant treatment-naïve children and adults with ADHD were assessed pretreatment and enrolled in the randomized, placebo controlled ePOD trial, with 16 weeks of MPH treatment and off-medication evaluation after one week wash-out. Stimulant treatment-naïvety was defined as never having received chronic treatment with stimulants for ADHD.

Our results indicated no (short-term) persistent effect of chronic MPH use on cognition, depression, and anxiety in male patients with ADHD. In addition, we observed similar cognitive deficits in stimulant treatment-naïve children and adults with ADHD, as well as similar comorbidity in treated and stimulant naïve adolescents, and similar acute effects of MPH in children and adults, regardless of prior pharmacological treatment. Finally, the test-retest reliabilities of the n-back working memory test and simple RT test in TD children and adults were lower than
those of a well-established episodic memory test.

**DISCUSSION**

**Persistency of MPH**

The primary aim of this dissertation was to investigate whether MPH effects on cognition persist beyond treatment, since alterations in brain structure and behaviour have been frequently described in treated normal rats and animal models of ADHD (Adriani, Canese, Podo, & Laviola, 2007; Bolaños et al., 2008; Marco et al., 2011; Vendruscolo, Izidio, Takahashi, & Ramos, 2008; Volkow et al., 2001; Wiley, Poveromo, Antapasis, Herrera, & Bolaños Guzmán, 2009). In the human literature, treatment versus non-treatment in ADHD is associated with superior outcome on i.a. occupational, academic and social functioning, self-esteem, obesity and service use (Shaw et al., 2012). In addition, beneficial effects of stimulants on the outgrowth of the brain, and separately on cognitive functioning, have generally been suggested (Frodl & Skokauskas, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Huang-Pollock, Karalunas, Tam, & More, 2012; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Semrud-Clikeman, Pliszka, & Liotti, 2008). A single randomized controlled trial on the long-term effects of treatment (Multimodal Treatment study of children with ADHD; MTA) reported (transient) beneficial effects of 14 months of stimulant treatment over behavioural treatment, on parent- and teacher ratings of inattention and teacher ratings of impulsivity/hyperactivity behaviour, but no differences in internalizing or externalizing symptoms, social skills or parent-child interactions (The MTA Cooperative Group, 1999). However, a placebo group was lacking (given the study duration), and these outcomes were assessed while on-medication. Therefore, the results do not reflect stimulant driven changes attributable to alterations in the brain. Hence, we assessed children and adults before and after treatment with psychostimulants in a randomized, placebo-controlled trial (Chapter 5), in order to determine the potential persistency of cognitive effects of MPH.

As described in Chapter 5, we observed no evidence of persistent cognitive effects of MPH over placebo in children or adults after one-week wash-out following trial-end, whereas we did observe positive effects on tests of working memory, response speed and episodic memory during MPH treatment. Hence, 16 weeks of MPH treatment does not seem to affect development of these cognitive functions. With regard to ADHD symptoms, both children and adults improved during MPH treatment relative to placebo. Thus, it may be that MPH treatment has persistent effects on behaviour, which could be mediated by age-independent plasticity. However, several participants and parents reported they could not accurately reflect on one week off-medication,
as they had not experienced all situations in this short timeframe. Therefore, we cannot exclude a carry-over effect of on-medication experiences to the off-medication assessment. Importantly, the imaging results of this RCT (regarding the same participants) revealed altered striatal blood flow in response to an acute challenge with MPH in the striatum of children, but not adults, following MPH treatment, suggesting development-related alterations in the DA system (Schrantee et al., submitted). It is possible that neuronal age-dependent adaptations to stimulants do not directly translate into altered cognition and behaviour. As can be seen in Parkinson’s disease, for example, it is only after the degeneration of 50 to 70 percent of nigrostriatal DA neurons that clinical symptoms occur (Brotchie & Fitzer-Attas, 2009). It should be noted, however, that it is possible that these neuronal adaptations may persist and even increase, and so intervene with future brain development, which may lead to cognitive or behavioural differences over the course of time (Andersen, 2003). The time of treatment and methodological challenges with respect to reassessment (i.e. test-retest reliability) will be further discussed in the limitations section.

Besides the long-term effects of MPH on ADHD symptoms and cognition, the outcome of anxiety and depressive comorbidity in ADHD after chronic treatment is receiving increasing interest. Preclinical studies with normal and SHR rats argue that chronic stimulant use during development leads to depression- and anxiety-like behaviour later in life (Bolaños et al., 2008; Carlezon, Mague, & Andersen, 2003; Vendruscolo et al., 2008; Wiley et al., 2009). In humans, a recent meta-analysis demonstrated that acute MPH in humans decreases anxiety, even though anxiety or nervousness are common side-effects of acute MPH, suggesting that MPH has positive effects on anxiety that in general outweigh the frequently observed detrimental individual effects (Coughlin et al., 2015). However, studies on potential persistent effects of stimulants in humans are scarce. To our knowledge, the MTA study is unique in following-up participants for years after an initial 14 months of randomized pharmacological treatment. The MTA cooperative group observed a lower rate of anxiety and depression diagnoses in the initial behavioural treatment group, as compared to the initial medicated and combined behavioural and medication treatment group, at six, but not eight year follow-up (Molina et al., 2009). Furthermore, cohort studies with humans have mainly revealed detrimental effects of a delay of pharmacological treatment (Daviss, Birmaher, Diler, & Mintz, 2008a), or shorter treatment duration (which could be affected by a temporal inclusion bias, however; Lee et al., 2016). Thus, withholding pharmacological treatment, which has positive acute effects on depression (Golubchik, Kodesh, & Weizman, 2013) and anxiety (Coughlin et al., 2015), seems to increase depressive and anxiety comorbidity. However, it remains unknown whether persistent effects of MPH on affective comorbidity are present
when off-medication. Therefore, we cross-sectionally compared comorbid depression and anxiety in adolescents (aged 12-17 years) with and without a history of stimulant treatment, in order to determine whether MPH persistently affects depression and anxiety comorbidity in ADHD (Chapter 4). Just as in studies with stimulant naïve adolescents (Smalley et al., 2007), and newly diagnosed older adults with ADHD (Michielsen et al., 2013), we observed increased levels of depression, but not anxiety, in stimulant naïve ADHD over TD children and adolescents. Thus, adding our findings to previous work, depressive symptoms seem increased in ADHD across the lifespan, irrespective of prior stimulant use. With respect to comorbid symptoms, no benefit of prior stimulant treatment over stimulant treatment-naivety was observed. Thus, boys previously treated with MPH did not fare better or worse with respect to depressive and anxiety comorbidity than stimulant naïve boys of the same ages. Our findings may imply that in males, the effects of stimulant treatment on affect do not outlast treatment. However, the cross-sectional nature of this study, in addition to the lack of rapports by the medicated boys on medication, prevents causal inference. Hence, to confirm this, a randomized, placebo controlled trial evaluating on- and off-medication depression and anxiety would be crucial.

While we did not observe persistent effects of chronic MPH on cognition, the animal literature demonstrates detrimental effects of juvenile treatment (Bolaños et al., 2008; Carlezon et al., 2003; Vendruscolo et al., 2008). Although animal studies offer well-coordinated experimental settings which lead to important neuroscientific insights, some differences between human and animal studies are not easily accounted for. In contrast to humans with ADHD, the SHR rat model for ADHD shows less depressive- and anxiety-like behaviour as compared to other rat strains (Hinojosa et al., 2006; Ramos, Berton, Mormède, & Chaouloff, 1997), and acute MPH seems to induce depressive- and anxiety-like behaviour (Motaghinejad, Motevalian, Ebrahimzadeh, Iarijani, & Khajehamedi, 2015). In addition, rats evidently do not encounter the same type of academic failure and social rejection as individuals with ADHD experience across their lifespan, which may play a major role in the high prevalence of depression and anxiety in humans with ADHD (Ostrander & Herman, 2006). Also, animals are deliberately exposed to stress in order to evoke a behavioural response. The response to the stressful situation is then used as outcome measure to draw conclusions regarding mood and anxiety. Such a design differs greatly from human trials, where boys with ADHD are asked to fill out a questionnaire, while experimenters make a great effort to reduce the stressfulness of the novel test situation. Therefore, if one would want to approach emotional processing in a manner more comparable to preclinical studies, it would be best to design an experimental setting with a more objective outcome measure for stress. To sum up, many factors hamper the direct translation from animal
studies to humans. Based on our findings, we argue that chronic MPH treatment during development in males with ADHD does not alter cognition, and depressive and anxiety symptoms, at least on the short-term.

**Cognition and affective comorbidity in stimulant treatment-naïve ADHD**

As discussed in the introduction, ADHD is frequently associated with cognitive dysfunction and internalizing comorbidity in both child- and adulthood. The published work on cognition and comorbidity in ADHD offers an important developmental perspective. However, since the long-term effects of stimulant treatment remain unclear, the extensive use of medication in the studied population hampers the interpretation of this work. Hence, the cross-sectional studies described in Chapter 2 and Chapter 4 addressed the second aim of this dissertation, which was to evaluate the degree of cognitive dysfunction and internalizing co-morbidity in ADHD, while excluding the possible influence of prior stimulant use. In Chapter 2, both children (aged 10 - 12 years) and adults (aged 23 - 40 years) differed from their TD counterparts on measures of working memory, response time, episodic memory, and inhibition, and the magnitude of dysfunction was not related to age. Therefore, we concluded a similar degree of cognitive deficits in stimulant treatment-naïve boys and men with ADHD. In addition, we observed similar levels of affective comorbidity in prior treated and stimulant naïve adolescents with ADHD. In previous reports with pharmacologically treated adults with ADHD, cognitive development may have been influenced by chronic stimulant use. Thus, the current evidence of cognitive deficits in stimulant naïve adults with ADHD adds to the literature implying a lack of (prominent) detrimental effects of chronic MPH on cognition. Likewise, the similarity in depression and anxiety between the treated and stimulant treatment-naïve adolescents with ADHD may imply a lack of detrimental effects on affective comorbidity. It should be noted, however, that the included adults with ADHD reported considerable recreational drug use, including cannabis and amphetamines such as d-amphetamine and MDMA, which may negatively affect cognition in some individuals (Dean, Groman, Morales, & London, 2013; Lundqvist, 2006). While in our study, recreational drug use in adults could not account for the lack of persistent MPH effects in children, it is remarkable that few studies on pharmacological treatment of adult ADHD discuss the use of recreational drugs by the included participants.

We determined cognition in pharmacologically untreated adults with ADHD, since we aimed to contribute to the discussion regarding long-term effects of stimulant treatment. Yet, a recent prospective study challenged the definition of adult ADHD as a developmental disorder. In that study, self- and proxy-reports in adulthood of childhood symptoms proved highly inaccurate, as 90% of adults meeting criteria for
ADHD in adulthood did not meet criteria for ADHD in childhood, as recorded at childhood assessment (Moffitt et al., 2015). Furthermore, this de novo form of ADHD was associated with substance dependency, but not with cognitive dysfunction. In contrast, we proved cognitive deficits in adults with ADHD who were not substance dependent, both on a group level, and by evaluating individual profiles. Unfortunately, the cross-sectional nature of our study prevents the verification of childhood ADHD. This is important to discuss, however, as the existence of two entities of adult ADHD, a persistent and a de novo form, complicates our interpretations in Chapter 2. If part of the adult group included in Chapter 2 (and 5) had de novo ADHD, one could argue that the recreational drug use in this group explains the observed cognitive deficits. However, cognitive functioning was unimpaired in the largely substance dependent adults with the de novo ADHD described by Moffitt and colleagues. While ADHD in childhood is associated with recreational drug use in adulthood (Biederman et al., 2006), it is also associated with recreational drug use in childhood/adolescence, regardless of pharmacological treatment (Molina et al., 2007). Therefore, we conclude that the majority of the adults with ADHD included in our studies may have persistent ADHD, and argue that cognitive deficits observed in adult ADHD are likely related to ADHD, and not prior stimulant use.

**Acute effects of MPH on cognition**

Cognitive enhancement is a frequently described acute effect of MPH. On a group level, both children and adults with ADHD respond positively to MPH as compared to placebo. Given that neurotransmitter systems and brain regions continue to change throughout childhood (Blakemore & Choudhury, 2006; Shaw et al., 2008; Tau & Petersen, 2010), psychotropic drug effects may differ dependent on age (Murrin, Sanders, & Bylund, 2007). Therefore, Chapter 3 offered a developmental perspective on the acute cognitive effects of MPH in ADHD. A meta-analysis of 24 studies on prepotent response inhibition, 13 studies on working memory and 23 studies on sustained attention revealed small to moderate, robust effects of MPH, which were independent of the mean age in studies. The majority of studies included either children, or adults (but not adolescents), and we found similar effects of stimulants in child- and adulthood ADHD. Thus, both the extent of cognitive impairment, and the effect of MPH on cognition, seem similar in children and adults with ADHD (described in Chapter 2). Also, effect sizes were comparable in prior treated versus stimulant naïve samples, although information on prior treatment was often lacking and needs to be reported in future studies. An important caveat is that the findings are not generalisable to adolescents with ADHD, as adolescent studies were sparse, and some studies suggest an increased sensitivity to the acute behavioural effects of
MPH in adolescents as compared to children (Findling, Short, & Manos, 2001; Smith et al., 1998). Furthermore, the importance of motivation, reward sensitivity and timing in ADHD, as well as the effects of MPH on these functions, is increasingly recognized and studied. Since behavioural responses to stimulants in animals largely reflect reward-related effects, it would be interesting to study the age-dependency of stimulant effects on these functions.

**Experimental cognitive testing**

In the chapters discussed above, cognitive functions of children and adults with and without ADHD were examined, with cognitive tests commonly used when studying developmental disorders. Published material on psychometric properties of some of these experimental tests is scarce, while knowledge of reliability, for instance, improves the interpretation of study results and estimation of applicability for clinical purposes. In *Chapter 6*, TD boys and men were assessed repeatedly (8 weeks and 16 weeks after the initial assessment) with a well-established test of episodic memory, and with experimental tests of response speed and working memory. The results demonstrated low test-retest reliabilities of these tests, both in children and adults, and regardless of whether the test was administered twice or three times. As a result, critical change intervals had a wide range. Thus, the $n$-back and simple RT tests are of limited use for clinical practice, and one might also argue they are of limited use for experimental research. However, previous studies with similar tests, as well as our own experiments, repeatedly revealed age-effects, ADHD related impairment, and treatment effects in the expected direction. This leads us to conclude that these experimental tests are sensitive to group differences. However, the adjustable nature of these tests increases the vulnerability of research to noise, which inevitably reduces the magnitude of the observed effects. Thus, our study stresses the importance of improving experimental tests and evaluating psychometric properties, and of keeping the limitations of outcome measures in mind when targeting clinical or research questions.

**GENERAL CONCLUSIONS AND LIMITATIONS**

In this dissertation, we conducted an important RCT focusing on the role of stimulant treatment in cognitive development in ADHD. While our findings are a cog in a large machine, this study is the first to fill the gap between randomized studies on acute MPH effects and cross-sectional studies on long-term cognitive effects of MPH treatment in ADHD. The results showed no indication of (short-term) persistent effects of chronic MPH use on cognition, depression and anxiety in males with ADHD. Although a transient effect of psychostimulants is assumed by many, our study is the first to
report on the short-term (lack of) persistency of cognitive effects in a randomized and placebo-controlled manner.

In addition, we found similar cognitive deficits in stimulant treatment-naïve children and adults with ADHD, and similar positive acute effects of MPH in children and adults regardless of prior pharmacological treatment. This may not come as a surprise to clinicians and researchers, as cognitive deficits and positive effects of treatment have been described for both age groups before. However, this dissertation was the first to directly examine these age-relationships while accounting for previous pharmacological treatment. We also accounted for previous stimulant treatment while determining depressive and anxiety symptoms in boys with ADHD, and concluded an association between depressive symptoms and ADHD, regardless of prior treatment.

These studies on cognition, and depression and anxiety, in stimulant naïve individuals with ADHD of different ages, provide a basis for future studies on the effects of MPH on development. The literature on these topics is especially scarce regarding adult ADHD, since this is a relatively new area of research, and it is troublesome to engage stimulant treatment-naïve adults in a placebo-controlled trial. However, the results of our studies with cognitive outcomes should be interpreted with care, as we also demonstrated low test-retest reliability for some of the employed experimental tests.

Some general limitations to the presented studies should be kept in mind. First, all the presented articles included males only, except the meta-analysis on acute effects of MPH on cognition. Therefore, these findings are not generalisable to adolescents and to females with ADHD. However, ADHD is also prevalent in females (Akinbami, Liu, Pastor, & Reuben, 2011), while the effects of MPH on behaviour may differ between the sexes, hypothetically due to differences in DA metabolism and receptor density (Sonuga-Barke et al., 2007). A second caveat is that the sample size of the ePOD RCT (Chapter 4) was small, as this study was based on large effect sizes in imaging studies. Small sample sizes reduce the reliability of the results (Button et al., 2008), which stresses replication of these studies. A third general limitation is that the experimental tests for which we demonstrated low test-retest reliabilities (n-back and SRT test) were outcome measures in the studies on cognition, and on the persistency of MPH effects on cognition in ADHD. Regardless of the low-test retest reliability and power, we replicated typically observed effects, such as age effects, learning effects, and acute medication effects (Coughill et al., 2013; Gathercole, Pickering, Ambridge, & Wearing, 2004; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). These results may demonstrate sufficient test validity. Still, effect sizes and the repeatability of findings may be compromised by low test-retest reliability. Therefore, replication of the observed lack of persistent MPH effects with improved working memory and response
speed tests, increased sample sizes, and while including females, would be advisable given the importance of this subject to the clinical field.

**RELEVANCE**

The current dissertation is part of a larger set of studies that investigate the effects of MPH on brain development. Both the (lack of) persistency of the effects of MPH, and the cognitive characteristics of ADHD across developmental phases are of clinical interest.

First, if confirmed by future studies, the observed lack of persistent (negative) MPH effects on cognition, depression and anxiety, could be consolidating to caregivers, therapists, health institutions and governments concerned about the effects of stimulant use on development of the brain and behaviour (Ahmed, McCaffery, & Aslani, 2013; Health Council of the Netherlands, 2000; Zembla, 2010). In the media, MPH is commonly compared to addictive drugs like cocaine and amphetamines, while the neuropharmacological mechanisms and the abuse potential are not equal (Svetlov, Kobeissy, & Gold, 2007). This, in combination with the reports of significant side-effects that some children and adults do experience (Graham et al., 2011), might be confusing to parents considering pharmacological treatment (Ahmed, McCaffery, & Aslani, 2013). If confirmed, our findings may contribute to future informed decision making. Another potentially relevant finding is that one week wash-out might be a sufficient time off-medication to re-evaluate cognition, which could be useful when deciding on extended treatment in a medication-free trial (van de Loo-Neus, Rommelse, & Buitelaar, 2011). However, as noted before, not all tests used were sufficiently reliable to allow strong conclusions.

Second, the cognitive impairment observed presently in stimulant treatment-naive adults with ADHD suggests that cognitive impairment continues to play a role in the expression of ADHD in adulthood. Persistence of ADHD is related to factors like familiarity of ADHD, severe impairment, and higher levels of internalizing and externalizing comorbidity in youth (Biederman, Petty, Clarke, Lomedico, & Farah, 2011; Cherkesova, Sula, Dalena, Pondé, & Hechtman, 2013; Spencer, Biederman, & Mick, 2007). For children at risk for persistent ADHD, knowledge about continuity of cognitive dysfunctions could contribute to the managing of expectations and, for example, may guide school counselling. Persistency of cognitive deficits may also cloud cognitive screening for neurodegenerative diseases in late adulthood: the presence of ADHD or depressive comorbidity related cognitive dysfunction (Smeijin et al., 2015) may confound the diagnosis of mild cognitive impairment (MCI), a prodromal phase of dementia (Ivanchak, Fletcher, & Jicha, 2012). Furthermore, if future research would determine that cognitive deficits distinguish de novo symptomatology from persistent
ADHD, the evaluation of cognition could have a clinical applicability for diagnostics and potentially for indication for treatment (if different treatment strategies would be required).

**CHALLENGES AND FUTURE DIRECTIONS**

Like the studies presented in this dissertation, research on cognition in ADHD is challenged by the heterogeneous nature of cognition in ADHD. Whereas a larger MPH response can be expected in individuals with cognitive dysfunction (Agay et al., 2014; Finke et al., 2010; Mehta et al., 2000), cognitive deficits are not objectified in every individual with ADHD. Since ADHD is behaviourally defined, the room for improvement seems larger in ADHD studies with behavioural than with cognitive outcomes. In addition, there is a lack of convergence between cognitive performance and behavioural symptoms, thus, behavioural and cognitive questionnaires and cognitive performance seem to tap different aspects of cognitive functioning (Fuermaier et al., 2015; Toplak, Connors, Shuster, Knezevic, & Parks, 2013). The cognitive tests used in ADHD research are fairly structured, which decreases the ecological validity. On the other hand, the search for a cognitive phenotype of ADHD is advancing. Several dissociable cognitive deficits (in cognitive control, timing, reward sensitivity, and vigilance/state regulation) have been demonstrated in ADHD (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012), and a recent study promisingly demonstrated that 87 percent of participants could be categorized into one of three subgroups with a specific neuropsychological profile (van Hulst, de Zeeuw, & Durston, 2015). Further disentanglement of these neuropsychological profiles in ADHD, and the advancement of profile analyses, could contribute to determining the relationship between brain development, cognition and behaviour. Studies on the effects of MPH on brain development would benefit, as the understanding of ADHD would improve, but also as the assessment of cognition is accessible and cost-effective as opposed to imaging, and objective as opposed to subjective behavioural questionnaires.

In order to inform children and adults with ADHD on the long-term effects of stimulant use in an evidence-based manner, one would want to study the short- and long-term persistency of MPH with subjective and objective measures of functioning in humans with ADHD. Ideally, this would require a properly executed RCT with placebo and MPH, with study duration of years and assessments on- and off-medication, to evaluate both the acute effects of chronic stimulant use and the long-term effects of stimulant use. However, in humans, this scenario is impossible in the light of ethical considerations. Therefore, it is important for animal research to provide a more thorough framework of short- and long-term persistency of chronic MPH on outcome measures that are more easily translated to humans (Hayward, Tomlinson,
& Neill, 2015). Suggestions have recently been made to subgroup SHR animals based on specific behavioural characteristics, in order to improve the translation to children with ADHD (Hayward, Tomlinson, & Neill, 2015). In our opinion, it would be useful to determine the effects of exposure in different phases of development to chronic MPH in animals (SHR or other ADHD model), while using an extensive cognitive test battery, and reassessing animals on- and off-medication to determine both untreated function and MPH response. Animal work suggests that adolescence is a developmental period of differential sensitivity to acute MPH, and that alterations due to chronic MPH in childhood would be expected to come to expression during adolescence (Andersen, 2003; Bolaños, Glatt, & Jackson, 1998). However, the information on adolescents with ADHD is scarce and, therefore, needs to be strengthened.

In humans, non-randomized prospective studies offer a highly important developmental perspective on cognition in ADHD. For future prospective studies on the long-term effects of medication use, it would be advisable to consequently survey and describe the type, duration, and dosage of medication, as well as the time since treatment cessation. Furthermore, the recreational drug use of adults with ADHD should be reported, so that a potential role in cognitive dysfunction can be determined. Last, the link between imaging and cognitive and behavioral outcomes in general could be improved, as this may help researchers formulate clinically relevant hypotheses and establish a broader, multilevel context of ADHD.

In conclusion, this dissertation adds to the debate on long-term effects and age-dependency of MPH, and calls attention to the psychometric properties of experimental cognitive tests used in research on developmental disorders. Our studies revealed a lack of persistent effects of MPH on cognition, depression and anxiety on the short-term in males with ADHD. Furthermore, similar cognitive dysfunctions and similar positive acute MPH effects were demonstrated in child- and adulthood ADHD. These findings underline the presence of cognitive dysfunction in ADHD across developmental phases, regardless of prior stimulant use, as well as the general benefit of MPH on cognition. It therefore seems that potential neuronal adaptations following chronic MPH do not directly translate into altered functioning. The observed lack of (age-dependent) detrimental lasting effects should be replicated in future studies, and may be consolidating to patients, caregivers and therapists.