Affect modulation of methylphenidate in patients with Attention Deficit Hyperactivity Disorder

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CHAPTER 9

Summary, general discussion and conclusions
9.1 Summary

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder, affecting 8-12% of children worldwide (Biederman and Faraone, 2004; Thomas et al., 2015) and 2.5% of adults (Simon et al., 2009). In addition to impairment caused by core symptoms of inattention, and/or hyperactivity and impulsivity, individuals with ADHD often have comorbid disorders. Emotional dysregulation in children with attention deficit hyperactivity disorder (ADHD) is defined as being easily angered and easily annoyed, which may arise from problems orienting toward, recognizing and/or allocating attention to emotional stimuli and from a dysfunctional striato-amygdala-medio prefrontal cortical network. For a long time, clinicians and parents have noted that emotional dysregulation is an important feature of ADHD leading to serious impairment. A substantial proportion of children with ADHD manifest difficulties regulating negative affect. Emotion dysregulation in ADHD may even be considered to be a phenotype for developing depression later in life (Ambrosini et al., 2013). In children and adults, rates of mood and anxiety disorders are beyond those that would be expected by chance alone (Kessler et al., 2006; Meinzer et al., 2014). However, until recently, not much attention has been given to emotional problems in children and adults with ADHD. This is remarkable given that these emotional problems influence the course, treatment response and outcome of ADHD (Biederman et al., 1998; March et al., 2000).

Conflicting findings on the role of pharmacological treatment with dopaminergic agents such as methylphenidate (MPH) on the prevalence of emotional problems in ADHD, stress the need for a better understanding of the mechanisms underlying emotion regulation in ADHD and the effect of MPH thereupon. The amygdala is a brain nucleus that is crucial for emotional processing and is most active during the perception of emotional faces. Amygdala function measured with functional Magnetic Resonance Imaging (fMRI) is a potential biomarker for emotional processing in patients with anxiety disorders and in patients with depression (Lau et al., 2010; Tao et al., 2012).

In this dissertation, we aimed to explore the occurrence of affective problems in ADHD, disentangled the effects of MPH on affective problems in ADHD, and considered age effects on these neurobiological substrates of treatment with MPH.

To this purpose, we determined in Chapter 2 the relationship between ADHD diagnosis, (prior) stimulant use, age, and depressive and anxiety symptoms in boys between the ages of 10 to 17 years. In two cross sectional studies, comorbidity of anxiety and depression in ADHD and the effect of stimulants on the development of these comorbid disorders was addressed. More depressive symptoms were found in boys and adolescents with ADHD compared to typical developing children. Medication history did not predict the number of depressive symptoms, nor the number of anxiety symptoms although there was no information about the duration of treatment available.

To explore the role of the DA in emotional processing and more specifically the modulation of the amygdala in subjects with documented DA dysfunction, in chapter 3 we explored the effects of the DA-ergic agent MPH on amygdala function in eight male recreational users of dAMPH and eight healthy controls. As hypothesized, we found a higher amygdala reactivity to fearful faces in the dAMPH users compared to healthy controls at baseline, which correlated positively to extent of dAMPH use. These findings of abnormal baseline amygdala activation in recreational dAMPH users most likely reflect an abnormal DA transmission in this brain region and lend further support to our hypothesis that the amygdala seems to be under modulatory influence of DA, and that DA dysfunction underlies abnormal emotion processing. Our trend significant finding that MPH induced increased amygdala reactivity after the challenge with MPH in control subjects (compared to a blunted response in dAMPH users), further triggered us to investigate the role of MPH role in modulating emotional processing in patients with ADHD treated with this drug. We found that prior DA-ergic status was important for the fMRI response to MPH in the amygdala (presumably due to de-sensitization), hence we included medication naïve ADHD patients in chapter 4. We included both children as adults in order to further investigate the age-dependency of the effect.

In chapter 4 we extrapolated our findings of chapter 3 to patients with ADHD, and investigated the effect of an acute challenge of MPH on amygdala reactivity in medication naïve boys and adult patients with ADHD. In line with the literature, and previous studies in recreational users of dAMPH with documented DA dysfunction (chapter 3), we found that also in ADHD fear processing is associated with amygdala hyperactivation. We also found that both fear processing as well as the acute effects of MPH on emotional processing are modulated by age. In adults, MPH reduced amygdala reactivity towards control levels, whereas in children MPH further reduced normal levels of right amygdala reactivity. Although children and adult patients scored significantly higher on clinical rating scales measuring depressive and anxiety symptoms, these measures did not correlate with amygdala reactivity, likely because they only assess a prolonged state of emotional lability. Other than a direct effect of MPH on the amygdala, our age-dependent findings may underlie age-dependent top down control of the amygdala, as DA-ergic maturation of the frontal cortex is still ongoing in childhood whereas it is already matured in the amygdala.

Although this study suggests a positive effect of MPH on emotional processing in both children and adults with ADHD (i.e. a reduction in amygdala reactivity), these findings are limited to an acute challenge with MPH. In chapter 6
we therefore report the age-dependent effects of chronic treatment with MPH in a clinical trial, which is described in greater detail in chapter 5, which describes the objectives and methods of the effects of Psychotropic drugs On the Developing brain (ePOD) project including the ePOD-MPH trial.

Thus, to address the effects of chronic treatment with MPH in ADHD patients on emotional functioning, the effects of 4 months treatment were investigated in the ePOD-MPH RCT in chapter 6. Based upon the hypothesis that was generated in chapter 4 (more normalizing effects of MPH in adults in reducing amygdala hyper-reactivity due to more intact and salient architecture in the top down control network in adults), we added functional connectivity of the amygdala with other brain regions to our original outcome measures (apart from amygdala reactivity and clinical symptoms). One week after 4 months of treatment, MPH still positively influenced emotional lability, but negatively affected right amygdala reactivity in children. Although in adults MPH had no effect over placebo on behavioral measures nor amygdala reactivity, it induced lasting cortical-amygdala hyper-connectivity. Furthermore, although symptoms of anxiety and depression did improve during the trial, they did not differ between both medication groups in children nor adults. From this we can conclude that a) in line with the literature, MPH lasting reduced emotional dysregulation in children, but not adults; b) that this is unrelated to lasting attenuation of anomalous amygdalar-cortical connections, as we observed no lasting effects in children, and hyper-connectivity in adults. Rather, these age-dependent findings underlie persistent increases in DA activity in the children treated MPH, as reported elsewhere (Schransee et al., 2016). Taken together, the two studies suggest that our findings are mediated in part by developmental changes in the ontogeny of the DA system (i.e., expression of cortical D3 receptors, which in rats is high during early adolescence and then wanes until becoming absent in adulthood). This is also in line with our observations on the importance of DA in emotional processing (chapters 3 and 4).

Our findings on chronic MPH treatment contrast those obtained following a single acute MPH administration, presumably underlying sensitization effects in adults, and/or ‘neurochemical imprinting’ effects in children: whereas children in chapter 4 demonstrated a reduction in right amygdala reactivity, we found that chronic treatment induced opposite effects, and increased right amygdala reactivity. Similarly, in adults a single dose of MPH reduced amygdala hyper-reactivity, whereas chronic treatment did not result in any lasting effects (blunted response, similar to that observed in dAMPH users in chapter 3). Taken together with our findings of increased cortical-amygdala connectivity in adults, but not children, we provide evidence that the effects of chronic treatment with MPH affect amygdala reactivity, amygdala connectivity and emotion dysregulation age-dependently, i.e. MPH affects development of brain regions involved in emotional processing. Because amygdala hyper-reactivity and connectivity has been shown to precede emotional problems later in life, our findings urge for longer follow up studies to investigate the clinical significance of our neuroimaging findings in children and adults. Meanwhile, the lasting positive effects of MPH on emotion dysregulation in children should comfort parents and clinicians in prescribing MPH for ADHD in children, at least on the short term.

In chapter 7 we explored the long-term effects of MPH treatment, and found that adult patients treated with ADHD medications before the age of 16 years had higher depression rates (moderate to mild depression) compared to late exposed patients (start of pharmacological treatment after the age of 23), as well as less use of cannabis and cocaine when compared to late exposed individuals and drug naïve individuals. Interestingly, ADHD symptom severity was higher in the unexposed individuals compared to either medicated group. In line with extensive pre-clinical data, these data suggest that pharmacological treatment with ADHD medications have a positive effect on the long-term, which is in contrast to current views that there is limited and inconsistent evidence for long-term advantage of medication treatment beyond symptom control (Van de Loo-Neus et al., 2011). Our findings also indicate that early treatment does not increase the risk for developing a drug abuse disorder, but rather protects from such an effect, as previously suggested in the literature. Finally, our findings suggest that on the long term early-, and not late exposure to ADHD medications induce depressive symptoms. Together with the results from chapter 6, we demonstrate the potential of fMRI as a biomarker to assess amygdala reactivity in ADHD. Identification of children at risk of developing depressive symptoms later in life can be done using a combination of parameters; amygdala reactivity from fMRI, eicosapentaenoic acid/arachnoid acid ratio (Mocking et al., 2017), connectivity parameters, and machine learning techniques (Jentsch et al., 2015). Its role in clinical treatment of patients with ADHD should therefore be further explored.

While the neurobiological effects of antidepressants on the developing brain are largely unknown and most of the imaging studies included adult patients, we conducted a power analysis in chapter 8 for future clinical trials on the adverse effects of SSRI’s. We chose fluoxetine because the Food and Drug Administration issued a black box warning in 2004 regarding the use of antidepressants in children and adolescents. Since then, its use in children has been an issue of strong public debate, also here in the Netherlands (Dehue, 2014). And not without reason, as we found that fluoxetine treatment increased amygdala reactivity, with opposite effects in the placebo condition. Our calculations suggest that in future studies ‘only’ 8 patients are needed to demonstrate such an effect of fluoxetine on emotional processing.
In conclusion, in this dissertation the main findings were:
- Anxiety and depression commonly co-occur with ADHD.
- DA plays an important role in emotional processing.
- During treatment, there is no added value of MPH over placebo on positive effects on anxiety and depression scores in children and adults.
- Only in children there is a lasting positive effect of MPH on emotion dysregulation, at least for 1 week after treatment end.
- MPH induces increased amygdala reactivity in children (but not adults), a potential biomarker for depressive symptoms later in life.
- The age-dependent effects of MPH on amygdala reactivity likely underlie age-dependent effects of MPH on the DA system.
- On the long-term, ADHD medications seem to induce depression in children treated with the drug years ago.
- In combination with other parameters and techniques like machine learning, amygdala reactivity may be a useful biomarker during treatment to select children at increased risk of developing depression later in life.
- The functional significance of the MPH-induced hyper-connectivity in adults still needs to be established.
- ADHD medications have long-term positive effects on ADHD symptom severity as well as on drug abuse in subjects treated with these drugs early in life (before age 16).

These findings were obtained in relatively small samples, with restricted age ranges and involved subjects of the male gender. Also, our RCT had a limited follow up and/or treatment period. Our findings therefore need to be replicated in larger cohorts with longer follow up periods. However, for now they may have the following clinical implications:

Clinical implications of our main findings

Emotion dysregulation commonly co-occurs with ADHD and influences treatment outcome. For a long time children with ADHD and emotion dysregulation were considered to have a bipolar disease and were therefore treated with anti-epileptics, at least in the US. Nowadays, in cases of uncertainty regarding the origin of affective problems in ADHD, clinicians tend to delay prescribing MPH or titrate a dose that is inadequate to relieve ADHD symptoms. Also, some clinicians first start treatment with antidepressive medications i.e. SSRIs’s to reduce symptoms of anxiety and depression, before starting treatment of ADHD (in both children and adults). Interestingly, with the introduction of the Disruptive Mood Dysregulation Disorder (DMDD) in DSM 5 as a separate disorder the debate on treatment strategies of that disorder still have to start. Children with ADHD and emotion dysregulation may be diagnosed as having DMDD hence being withheld from an adequate treatment strategy for emotional dysregulation in ADHD. Or they may be treated with agents like antipsychotics or anti-epileptics with unknown long-term effects. In any case, our data support the notion that evidence based treatment recommendations for management of affective problems in ADHD are urgently needed.

DA plays an important role in emotional processing. Now that we know that DA plays an important role in emotion regulation in ADHD, we do not only better understand emotion dysregulation and comorbidity of anxiety and depression in ADHD, but also have arguments to treat emotional dysregulation with adequate doses of MPH, rather than SSRIs. This is clinically relevant since positive results of treatment with MPH on affective problems (only in children!) in ADHD are usually within one or two weeks (Coghill and Marcovitch, 2004) and treatment with SSRI’s takes up to 12 weeks to optimize the effects (Ruhé et al., 2006).

During treatment, there is no added value of MPH over placebo on positive effects on anxiety and depression scores in children nor adults. Although symptoms of anxiety and depression did improve during the trial, they did not differ between both medication groups in children, although the MPH condition appeared to drive the main effect of emotional liability. In adults, we observed improvement on depressive and emotion dysregulation symptoms, but also in both conditions. Other explanations could be that education about the disease itself and its treatment and having an explanation for the behavioral problems helped to increase self-esteem. Another explanation could be that the high frequency of the structured control visits made the treatment predictable for the children and thus lesser anxiety was experienced during treatment.

The age-dependent effects of MPH on amygdala reactivity likely underlie age-dependent effects of MPH on the DA system. This observation does not lie age-dependent effects on MPH on human brain development. This is peculiar and rather alarming as MPH is licensed for use in children, but not in adults. Indeed, most of our knowledge of long-term effects of MPH derives from studies in healthy male animals, with short wash-out periods. Also, clinical trials in children for the approval of Ritalin were not designed to assess long-term safety: registration of MPH in 1955 was based on zero clinical trials, and that of Concerta in 1982 on 4 that lasted 6 months (Bourgeois et al., 2014). However, children are typically treated several years. Providing insight into the modes of action of ADHD medications will enhance our knowledge of the drug – including unknown side effects on the developing brain.

On the long-term, our retrospective study in a relatively small sample of ADHD patients, suggests that ADHD medications have long-term positive effects on ADHD symptom severity as well as on drug abuse in subjects treated with these drugs early in life (before age 16). These findings are not in line with the MTA study where treatment effect diminished after three years although there...
was symptom improvement over baseline (Molina et al., 2007). But are in line with clinical guidelines and conclusions from reviews suggesting ADHD is a chronic condition with a strong persistence over time and long during symptom control by extended use of medication is necessary to provide long term benefits (Van de Loo-Neus et al., 2011).

**ADHD medications induce depression in subjects treated with these drugs during childhood** or adolescence, in line with a large body of preclinical and emerging clinical literature. Clinicians sometimes tend to delay prescribing MPH or titrating an inadequate dose in the fear of inducing depressive symptoms. Our data suggest that there is no reason to withhold treatment to children at least on the short-term. On the long-term, deciding whether or not to treat children with ADHD the clinician should consider whether treatment with MPH does more good than harm. MPH is highly effective, and the good of the treatment (in terms of higher life expectancy, less accidents, higher education levels and income) (Klein et al., 2012; Moffitt et al., 2015) should be balanced against the undesirable consequences of MPH treatment. As these long-term undesirable consequences are still largely unknown, more insight into the long-term consequences of this drug on the developing brain are urgently needed, as concluded also by the Gezondheidsraad in 2014. When replicated, our findings may be used to facilitate evidence based treatment recommendations for management of affective problems in ADHD. In adults, on the other hand, we found no lasting effect of MPH on affective problems (other than that it induced amygdala hyper-connectivity, see below).

**Amygdala reactivity may be a useful biomarker in combination with other parameters and techniques like machine learning, during treatment to select children at increased risk of developing depression later in life.** Identifying this group of patients and consequently follow up and treat them will not only reduce harm at an individual level but will also be more cost effective, since it is no longer necessary to follow up all patients with ADHD. In combination with identifying more predictive features like a strong response to medication in the first two years (Van de Loo-Neus et al., 2011) we will be able to improve personalized medicine and save costs to better treat patients in need for treatment.

**The functional significance of the MPH-induced hyper-connectivity in adults still needs to be established and follow up is needed.** Although medication trials have shown MPH to be effective in controlling ADHD symptoms in adults (Mendori et al., 2008), hyper-connectivity with the amygdala could be an indication for vulnerability to depression. More research on safety and efficacy of MPH in adults is needed, in light of recent discussions in the Netherlands (Geneesmiddelenbulletin 2016) regarding off-label treatment with MPH in adulthood.

In sum, we here add further evidence to the management of affective problems in ADHD: our data suggest that there is no need to withhold treatment with MPH in ADHD patients with emotion dysregulation as MPH seems to be effective in reducing emotion dysregulation, at least in children. Although these findings need to be replicated in larger cohorts with wider ranges of ages and including including men and women, we did not find evidence that MPH induced affective problems at least on the short-term. On the long-term, treatment of children and adolescents with ADHD medications seems to have predominantly positive effects (reduction in ADHD symptoms as well as drug abuse). However, we also found an increased occurrence of depressive symptoms in subjects treated with ADHD medications early in life. Future studies should find out whether the long-term undesirable effects outweigh its positive effects. In addition, patient stratification using the amygdala reactivity fMRI biomarker may be used to identify those patients at increased risk for developing a clinical depression later in life, which seems to be already evident short after treatment. Our ongoing follow-up study in the subjects that participated in the ePOD-MPH trail will at least provide evidence whether such an approach may be beneficial.

**Methodological considerations**

In fMRI, the BOLD response to negative emotional faces (angry and fearful faces) is measured in a block-design fMRI task (Hariri et al., 2002). Emotional responses are elicited in many different brain regions, where the amygdala seems to be a relay between visual systems and modulatory responses. Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is an effective and reliable tool for measuring stable individual differences in amygdala function (Manuck et al., 2007). Repeatability of the BOLD response amplitude to emotional faces is discussed in some studies (Lipp et al., 2014). While in other studies good reliability of BOLD signal in emotion processing areas (Mende-Siedlecki P et al., 2013) including the amygdala was demonstrated (Gee et al., 2015). Test-retest reliability with the same paradigm we used in our study are highest in studies with shorter time intervals (Plichta et al., 2014) and considered fair (Sauder et al., 2013) to strong (Intra Class Coefficients >.60) for both left and right amygdala to angry and fearful faces (Plichta et al., 2014). However, without a placebo challenge in chapter 4 we cannot rule out the possibility that changes in amygdala reactivity we found are unrelated to habituation effects; a second time in the scanner could have made patients less anxious and subsequently showing less amygdala reactivity.

**Motion**

In fMRI studies in general, and in fMRI studies in children with ADHD in particular, correction for motion is requested. BOLD signal acquisition depends upon precise spatial and temporal placement of magnetic gradients. We realigned our data as part of the fMRI preprocessing. However, spatial realignment corrects motion-induced shifts in space but does not correct intensity changes resulting from
disruption of the physical principles underlying MRI. Therefore, we performed extra motion control by adding six standard rigid-body motion parameters and a confound matrix to volumes that were corrupted by large motion (Lemieux et al., 2007). To control for effects of transient subject movements the confounded time points were determined using a net displacement vector according to Euclidian root mean square (RMS) (Power et al., 2012). We demonstrate that subject motion produces substantial changes in the timecourses of resting state functional connectivity MRI (rs-fcMRI). Data from subjects with extreme motion were removed from the analysis using the method by Power (Power et al., 2014) and van Dijk (van Dijk et al., 2012).

In BOLD fMRI studies, the sequence is vulnerable to motion artifacts within the imaging volume due to a longer read out. In our study, motion differed between adults and children and despite advanced imaging techniques and exclusion of the worst cases, residual effects could have remained. The balance between reducing the total imaging protocol time and gathering enough data per scan is a delicate one, especially in fMRI studies in children. Hopefully fast imaging techniques can increase the amount of information obtained in a limited amount of time. These techniques are now included in new imaging initiatives in ADHD (Silk et al., 2016).

Clinical sample

The children we included in our RCT had predominantly the inattentive subtype of ADHD. This is contrary to what is expected within developmental trajectories in ADHD and might be due to the age of inclusion. Children with hyperactive and combined type of ADHD are usually diagnosed and treated at younger age, which led to a selection bias of predominantly inattentive type in a small window of 10-12 years, the age we chose for inclusion. Furthermore, long term follow up studies in ADHD have questioned the continuity of childhood ADHD in adults (Moffitt et al., 2015) and subtyping ADHD in adulthood is not considered clinically meaningful (Klein et al., 2012).

Recruitment

In performing the ePOD RCT we met the ethical and logistic challenges already mentioned by Shaw and colleagues (Shaw et al., 2009). Unfortunately, we had to prematurely end the fluoxetine RCT because of limited inclusion of children and no inclusion in adults at all, despite huge efforts with multiple centers for child and adolescent psychiatry and multiple centers for adult psychiatry and general practitioners in the Amsterdam area. Also, serious comorbidity with suicidality and subsequent violation of protocol and hospitalizations prevented us from targeting our study population. However, due to the strong effect size we found, we calculated that for future studies only 8 patients are needed to demonstrate the effects of fluoxetine on amygdala reactivity. Notwithstanding the obstacles we had with our inclusion, we hope our data will support future studies on the (adverse) effects of SSRIs since they are highly relevant and needed.

The inclusion of children and adults with ADHD for the ePOD –MPH trial was less of a problem thanks to the collaboration with several centers of child and adolescent psychiatry like Triversum, De Bascule, UVA-minds and Kenter and thanks to PsyQ in the Haque, where most adult patients were recruited. We completed the inclusion of adult patients with fathers of children already included in the study, meeting the criteria of ADHD. This is a promising avenue for further studies since they were highly motivated and had less comorbidity, especially less frequent a history of drug abuse.

This is relevant because although we excluded adult patients with drug dependency in our RCT, we could not exclude all patients with former drug abuse due to high comorbidity rates between ADHD and drug abuse (Sobanski, 2006). We did not correct our findings of emotion dysregulation, anxiety and depression in adults for former drug abuse, however due to randomization these effects should be equally distributed. Besides, in the same population we found cognitive deficits in children with ADHD comparable to cognitive deficits in adults with ADHD regardless of former history of recreational drug abuse in adults (Tamminga, 2016).

Future directions

Follow up studies in this patient group and prospective studies in other age groups and female patients with ADHD are needed to establish more definitive conclusions on the effects of MPH on emotion regulation in ADHD on the long term. As long term placebo controlled trials are not feasible we will have to look at longitudinal observational studies. Using pharmacological MRI we can assess the effects of MPH on brain chemistry (Schrantee et al., 2016). Structural MRI can provide us with information on the long-term effects of DA on micro and macro structure of the brain.

Next to MPH, other treatment strategies for emotion dysregulation have to be explored. Not only SSRIs to treat comorbid anxiety and depression in ADHD, but also for example postsynaptic alpha 2 adrenergic receptor agonists like guanfacine emerges as a potential emotion regulator, by boosting activation of the left dorso-lateral prefrontal cortex (Schultz 2013). We are now conducting the follow-up study of the ePOD-MPH trial, on average three years after the enrollment of the first study. This is a natural follow up study in which we quantify the extent of MPH use by means of prescription data form the pharmacies. Hopefully these data and data from long term follow up neuroimaging studies (Silk et al., 2016) and hypotheses driven studies like ours, in addition to collected data from several MRI studies in international initiatives (Neu-
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roimage, ENIGMA e.g.), will provide more information on the long-term effects of stimulant treatment on emotion dysregulation, anxiety and depression. With more data, stratifying ADHD patients on basis of their vulnerability for developing anxiety and depression with fMRI for specific treatment will become scientific and no longer science fiction.

References


