Affect modulation of methylphenidate in patients with Attention Deficit Hyperactivity Disorder

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CHAPTER 1

General introduction
and thesis outline
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). Relatively little is known about the prevalence and correlates of this disorder and the exact pathophysiology of ADHD is still unclear, although many studies suggest that abnormalities of the dopamine system are involved (Fusar-Poli et al., 2012). Methylphenidate (MPH), an amphetamine-like psychostimulant drug which enhances dopaminergic (DA) and noradrenergic (NA) functioning by increasing extracellular DA and NA, is licensed for use in children over 6 years and often prescribed in children and adolescents (Hodgkins et al., 2013). MPH has been shown to be very effective in alleviating symptoms of inattention, hyperactivity and impulsivity in 70% of patients (Schachter et al., 2001; Spencer et al., 2005). There are concerns however regarding the long term consequences of its potential interference with brain development (Andersen and Navalta, 2004). The Health Council of the Netherlands, in 2014 expressed its concern particularly regarding the lack of knowledge on the long-term effects of the drug, while prescription rates are increasing in children and adults (McCarthy et al., 2012) (the Health Council of the Netherlands 2014). Only recently, a decrease in prescription rates was noted in the Netherlands in children under fourteen years of age (Stichting Farmaceutische Kengetallen 2016).

Emotion dysregulation in ADHD
For a long time it has been noted that emotion regulation, an individual’s ability to modify an emotional state to promote adaptive, goal-oriented behaviors (Shaw et al., 2014), is impaired in patients suffering from ADHD. Emotion dysregulation is defined as being easily angered and easily annoyed in children with ADHD, and is found in some 25-45% of children and 30-70% of adults with ADHD (Shaw 2014). Anxiety and depression are not only found more often in children with ADHD than typically developing controls in the last 12 months (9-14% in ADHD vs 1-2% in healthy controls in a community sample), but this effect seems to be more extensive in adult patients with ADHD, were 38.3% comorbid MDD was found in the ADHD group compared to 11.1% in the control group and 47.1% comorbidity with anxiety compared to 19.5% in the control group (Kessler et al., 2006). Emotion dysregulation represents an important feature leading to serious impairment (Wehmeier et al., 2010a), although not regarded a core clinical feature of ADHD in DSM 5. For instance, a substantial proportion of children with ADHD manifest difficulties regulating negative affect (Anastopoulos et al., 2011; Sobanski et al., 2010). Moreover, patients with ADHD and emotion dysregulation are significantly more impaired in peer-relations, family life, occupational attainment and academic performance than those with ADHD alone (Wehmeier et al., 2010b). Different concepts such as emotion-lability, irritability and emotion dysregulation have been used in the literature to operationalize problems with emotion regulation in ADHD. In 2014 Shaw and Stringaris (Shaw et al., 2014) conceptualized this domain. They stated that emotion dysregulation in ADHD may arise from problems in orienting toward, recognizing and/or allocating attention to emotional stimuli. These deficits may arise from dysfunction within the striato-amygdalo-medio prefrontal cortical network (see also Figure 1).

Shaw proposed three models to explain the overlap between ADHD and emotion dysregulation (1). Emotion dysregulation may be considered a core diagnostic feature of ADHD, with high correlation and a shared neuropsychological, neurobiological end genetic basis (2), the combination of ADHD and emotion dysregulation forms a nosologic new entity, with a distinct neuropsychological, and genetic basis for ADHD and (3) emotion dysregulation and ADHD alone, or symptoms of emotion dysregulation and ADHD are correlated but distinct dimensions where deficits in emotion processing mediates dysregulation and correlates with deficits mediating core ADHD symptoms (Shaw, et al., 2014).
Furthermore, emotion dysregulation is also considered a phenotype for the occurrence of depression and anxiety disorders later in life (Ambrosini et al., 2013). For instance, children with ADHD matching a dysregulation profile (one or two standard deviations above the mean on the combined subscale for attention problems, aggressive behavior and anxious/depressed behavior) have higher rates of anxiety disorders later in life compared to those with ADHD who did not match this dysregulation profile (Althoff et al., 2010). Likewise, children with a comorbid major depressive disorder next to their ADHD have a high risk for suicide attempts (Chronis-Tuscano et al., 2012). Indeed, emotion dysregulation (or irritability) in children with ADHD is predictive of a concurrent affective disorder and complements the predictive validity of this symptom to identify later affective disorders in young adulthood (Ambrosini et al., 2013; Copeland et al., 2009). Furthermore, studies following children with ADHD into adulthood have found elevated rates of adult mood disorders (Klein et al., 2012).

However, although emotional dysregulation is prevalent in ADHD throughout the lifespan and is a major contributor to impairment, it is a much neglected research area (Shaw et al., 2014). This is remarkable given that emotional dysregulation and the treatment thereof can influence the course and outcome of ADHD (Barkley and Fischer, 2010; Marc et al., 2000).

Stimulant treatment and emotion dysregulation in ADHD

Until now, the role that stimulant treatment plays in the occurrence of emotional problems in ADHD still has not been established. Rates of mood and anxiety disorders in children and adults with ADHD are beyond those that would be expected by chance alone (Kessler et al., 2006; Larson et al., 2011; Meiner et al., 2014).

On the one hand, ADHD and anxiety or depressive disorders coexist and are unrelated to ADHD medications, as suggested by one study in which a significant prevalence of comorbid depression and anxiety was found in medication-naïve adolescents with ADHD (Smalley et al., 2007). Also, there is growing evidence that with ADHD stimulant treatment is associated with normalization of enhanced emotional reactivity (Conzelmann et al., 2009; Daviss et al., 2008; Posner et al., 2011a), suggesting a positive effect of ADHD medications on emotional dysfunction, as well as a protective effect on the development of depressive disorders in ADHD; individuals without a history of Major Depressive Disorder (MDD) reported earlier initiation of stimulant treatment than patients with a history of comorbid MDD (Daviss et al., 2008).

On the other hand, there are preclinical and clinical data suggesting that having a history of stimulant medication is associated with the development of emotional problems later in life. Exposing preadolescent rats to a DA-ergic agent like MPH results in profound changes associated with a depression-like state later in life (Bolaños et al., 2008; Carlezon et al., 2003; Wiley et al., 2009). However, these studies were conducted in normal developing rats which make it to extend these conclusions to clinical practice. But also in humans there are some indications that treatment with ADHD medications at younger age may induce long term effects on emotional state. For instance, children initially randomized to pharmacological treatment in the Multimodal Study of children with ADHD (MTA) had higher rates of anxiety and depression diagnoses at 6 years follow-up, as compared to children initially receiving behavioral treatment and community care (Molina et al., 2013). Perhaps more convincing, is the finding that children who had received pharmacological treatment for ADHD were retrospectively more likely to meet criteria for a depression (MDD) than children with ADHD who had not received pharmacological treatment for ADHD (Jerrell et al., 2015). In this study, duration of treatment was also associated with increased risk for depression (Jerrell et al., 2015). These conflicting findings stress the need for a better understanding of the mechanism of emotion regulation in ADHD and the effect of ADHD medications hereupon.

Neurobiological substrates for emotional functioning in ADHD

Amygdala function measured with functional Magnetic Resonance Imaging (fMRI) is a potential biomarker for emotional processing in adult patients with anxiety disorders and depression (Lau et al., 2010) as well as in adolescent patients with these disorders (Tao et al., 2012). The amygdala is activated most strongly during the processing of emotional faces (Hariri et al., 2002). Therefore, assessment of emotional (dys)regulation in ADHD, increased amygdala reactivity may serve as a premorbid neural biomarker of risk, has been shown to be the case in depression, observable in at-risk individuals before the onset of clinical symptoms or disorder (Swartz et al., 2015). It has been suggested that ADHD patients are more susceptible to negative stimuli following amygdala activation, due to deficits in early processing of visual emotional stimuli and in the modulation of the startle reflex (Shaw et al., 2014). For instance, ADHD patients, amygdala hyper-activation has been found both during subliminal perception of fearful faces, and during active rating of fear while viewing neutral faces (Brotman et al., 2010; Maliszewski et al., 2011; Marsh et al., 2008). These functional deficits align with reports of amygdala structural abnormalities in ADHD patients, including surface morphology, volume, as well as dopamine receptor density (Hoogman et al., 2017; Plessen et al., 2006). Not only amygdalar reactivity but also connectivity of the amygdala with areas in the prefrontal and cingulate cortex is involved in emotional processing. In healthy young adults, less anxiety and a more positive daily emotion was found to be related to less connectivity between the amygdala and prefrontal and posterior cingulate cortices (Uchida et al., 2014). In adolescents diagnosed with ADHD, an atypical connectivity with prefrontal areas was found (Posner et al., 2011b). Emotional dysregulation was related to functional connectivity of a cortico-amygdalar
network and this enhanced amygdala-LPFC connectivity in ADHD patients may suggest an amplification of the negative affect associated with fearful faces (Hulvershorn et al., 2014).

Dopaminergic modulation of amygdala functioning
Although emotional function is typically thought to involve the serotonergic system, several experimental studies support the idea of a DA-ergic contribution to an emotional response (Delaveau et al., 2009; Volkow et al., 2007) but it is unclear whether dopamine activity is enhanced or depressed. Although much less studied, clinical studies now also support DA disruption in emotional processing. For instance, several studies have found positive effects of drugs that increase DA concentrations in the brain, such as the DA reuptake inhibitor MPH: this drug stabilized mood in patients suffering from MDD (El-Mallakh, 2000). Likewise, in healthy controls, the DA releaser and reuptake inhibitor dextroamphetamine (dAMPH), potentiated the response of the amygdala during the perceptual processing of angry and fearful facial expressions (Hariri et al., 2002). Also, in adolescents suffering from ADHD, MPH normalized increased activity of the right amygdala (Posner et al., 2011b). The role of DA in amygdala activity was also suggested by the contribution of a SLC6A3 transporter gene polymorphism to individual variability in amygdala reactivity (Bergman et al., 2014). In fact, it has been shown that DA in the basolateral amygdala is critical for fear processing (Fadok et al., 2009).

As Schultz already pointed out in 1994, the DA-ergic system thus seems to play an important role in emotional processing and this may explain ADHD-related emotional dysfunctions in ADHD but also a positive impact of MPH on emotional dysfunction in ADHD (Schultz 1994). Most of the previous studies however were done in patients not naïve to medication, therefore still raising the possibility that either ADHD itself is associated with emotional dysfunction, or that emotional dysfunction is induced by treatment with psychostimulants.

Neurochemical imprinting
There is some evidence for age dependent effects of emotional dysregulation in ADHD and the effect of ADHD medications thereupon, as there are solid preclinical indications that the developing brain responds differently to MPH when compared to the adult brain (for review see Andersen and Navalta, 2004). For instance, early treatment with MPH leads to a considerable reduction of the DA transporter (DAT) in the striatum and other DA rich regions of adolescent rats when compared to non-treated animals, whereas in adult animals there have consistently been no effects (Grund et al., 2006; Moll, 2001). Also, in young animals MPH induces immediate early gene activation consistent with long-term brain plasticity and reorganization (Adriani et al., 2006). MPH produces oxidative damage in the frontal cortex of young but not adult rats (Martins et al., 2006) and MPH attenuates adult hippocampal neurogenesis only in young rats (Lagace et al., 2006; van der Marel et al., 2014). But also on a behavioral level these age-dependent effects have been noted. Several preclinical studies have demonstrated that exposing pre-adolescent rats to a DA-ergic agents like MPH results in profound changes associated with a depression-like state later in life (Bolaños et al., 2003; Carlezon et al., 2003; Wiley et al., 2009).

Evidence is slowly emerging that the long-term effects of drug exposure are delayed and come to expression once the vulnerable system reaches maturation. This phenomenon is known as ‘neuronal imprinting’ and occurs when the effect of drug exposure outlasts the drug itself (Andersen and Navalta, 2004) ‘as brain plasticity permits experiences to shape the immature brain to meet the demands of the environment. Change occurs at various levels - from neuroanatomy, including within a given region and its connectivity to other regions, to the function of neurotransmitter systems and their reactivity to pharmacological agents in the short- and long-term. The nature and degree to which drug exposure influences the final adult topography is influenced greatly by the maturational phase of these critical factors. Moreover, evidence is slowly emerging that suggests that the long-term effects of drug exposure are delayed and expressed once the vulnerable system reaches maturation (i.e., typically during adulthood).’

Still, very little is known on exposure of MPH during later brain development. Most (clinical) studies are hampered by the fact that they are retrospective in design, and therefore the findings could be caused by other factors on which the groups differed. As pointed out by Shaw and colleagues: ‘...the ideal study design for this question would be a randomized trial comparing cortical growth in children on psychostimulants against an unmedicated comparison group-but this would be both logistically and ethically challenging’ (Shaw et al., 2009).

Thesis outline
The aim of this thesis was to explore the occurrence of affective problems in ADHD, to disentangle the effects of MPH on affective problems in ADHD, and to consider age effects on these neurobiological substrates of treatment with MPH. This work is part of a larger research project entitled “effects of Psychotropics drugs On the Developing brain (ePOD)”, in which the effects of MPH, as well as fluoxetine on brain development and behavior are investigated.

General introduction
Chapter 1 offers a short introduction on the significance and relevance of studying affect modulation in ADHD and the effects of DA-ergic agents thereupon. Preclinical findings and the sharp rise in prescriptions of stimulants in the first decade of this century underpin the relevance of studying the imprinting effects of MPH on the developing brain.
Part I – Affect regulation in children with ADHD
First we disentangled the role of stimulant use in the co-occurrence of anxiety and depression with ADHD. In chapter 2 self-reported depressive and anxiety symptoms in stimulant naïve boys with and without ADHD were assessed and the age-trajectory of comorbid symptoms in naïve and prior medicated boys with ADHD were compared.

Part II – Effects of DA modulation on amygdala reactivity in subjects with dysfunctional DA system
To explore the role of the DA system in emotional processing and more specifically the modulation of the amygdala in subjects with documented DA dysfunction, in chapter 3 we examined emotional function in a group of dAMPH users, using task related fMRI before and after oral administration of MPH. We included dAMPH users, because of preliminary evidence that users of this drug suffer from a dysfunctional DA system.

In chapter 4 we extrapolated our findings to patients with ADHD, and investigated the effect of an acute challenge of MPH on amygdala reactivity in medication naïve children and adults with ADHD, using a similar fMRI task as in chapter 3, before and after oral administration of MPH.

Part III – Affect modulation of MPH in ADHD and age dependent effects; the ePOD study
To disentangle the effects of chronic treatment with MPH on affective problems in ADHD and the modulating effects of age, we set up two projects, including a randomized clinical trial (RCT) with MPH. In chapter 5 we describe the objectives and methods of this RCT entitled ‘the effects of Psychotropic drugs On the Developing brain (ePOD-MPH)’, which included medication naïve patients, directly comparing children and adults, in order to investigate its age-dependency (i.e. to investigate the effects on human brain development). In addition, in a retrospective cohort study (ePOD-Pharmo), we investigated the long-term effects of MPH in adults diagnosed with MPH, stratified for age of first exposure.

Chapter 6 describes the results of the ePOD-MPH RCT on emotional dysregulation. In this RCT, medication naïve children and adults were randomly assigned to 4 months of treatment with MPH or placebo. Amygdala reactivity, connectivity and clinical symptoms were measured using fMRI at three time points; before, during and one week after treatment.

As in ePOD-MPH the results are limited to 4 months of ADHD treatment, we explored the long-term effects of chronic stimulant exposure on emotional behavior and in chapter 7, we present the results of ePOD-Pharmo in which the long term modifying effects of age on anxiety and depression of age-of-first-stimulant-

were assessed in adult patients with ADHD stratified into three groups; patients treated with MPH before the age of 16 years, patients treated with MPH after the age of 23 years and stimulant naïve patients.

As ‘neurochemical imprinting effects’ are not limited to ADHD medications, but other psychotropic medications as well, finally, in chapter 8 we present the results of the (prematurely ended) ePOD-SSRI RCT. In seven patients, we piloted the serotonergic effects of the antidepressant fluoxetine on amygdala reactivity and made a power calculation for future studies.

Part IV – Summary and general discussion
The most important findings of the studies described in this thesis as are summarized in chapter 9.

A Dutch summary of the main findings and their implications can be found in chapter 10.
References


Chapter 1


