Psychotropic medications and the developing brain

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Chapter 1

General introduction and thesis outline

Background

According to the Diagnostic and Statistical Manual (DSM 5th Edition)[1], a psychiatric or mental disorder comprises a syndrome characterized by clinically significant disturbances in an individual's cognition, emotion regulation or behavior. These disorders may result from the dysfunction of specific domains related to several psychological, biological or developmental processes in the brain. Psychotropic medication is commonly prescribed to treat these psychiatric disorders, that are generally thought to act, at least in part, by adjusting neurochemical imbalances in the brain, thereby normalizing for example perception, mood, consciousness or specific behaviors. In this thesis, two common psychiatric disorders will be discussed, i.e. Attention-Deficit/Hyperactivity Disorder (ADHD) and Major Depressive Disorder (MDD), as well as their pharmacological treatments. Specifically, we will focus on the lasting effects of psychotropic medication in relation to age. It is thought, that when these drugs are given at relatively young ages, e.g. during stages of ongoing brain development, that they interfere with, or may alter, the process of development of the brain or of specific transmitter systems, and thereby exert long-lasting effects into adulthood, a concept known as *neurochemical imprinting*[2].

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder characterized by symptoms of hyperactivity, impulsivity, poor behavioral control and attention deficits[1]. ADHD has a world-wide prevalence of 7.2%[3], and is diagnosed three times more often in boys than in girls[4]. Symptoms often emerge around the age of 10 to 12 years and cause a substantial impairment in daily functioning at school or work[5]. In about 30-50% of the children the disorder continues into adulthood but there may be adult-specific forms of ADHD as well[4,6,7]. According to the DSM (5th Edition), ADHD occurs in three subtypes: predominantly inattentive, predominantly hyperactive-impulsive, or a combined type[1,8]. In addition to, or as a result of, the hyperactive, impulsive and attention symptoms, children with ADHD frequently suffer from learning disabilities, restless legs syndrome, sleep problems and a range of other, associated disorders, such as autism[9,10].

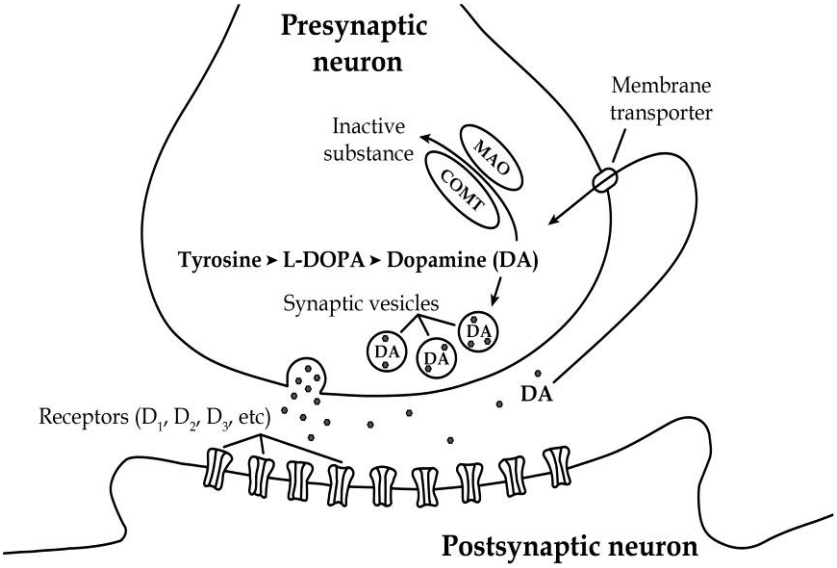
The dopamine system

The neurobiological pathways that may underlie ADHD symptoms are generally thought to involve the dopamine (DA) system. The neurotransmitter DA is produced by neurons located in the substantia nigra and in the ventral tegmental area (VTA). From there, DAergic fibers project into various parts of the brain and play an important role in a wide variety of cognitive functions and behavioral processes, including reward, motor control, attention and executive functions. Alterations in the DA system have further been implicated in a range of neurological and psychiatric disorders, such as ADHD, Parkinson's disease and schizophrenia.

There are four major DAergic pathways within the brain: 1) the mesolimbic pathway, which transmits DA from the VTA to the ventral striatum, and is involved in aspects of reward, 2) the mesocortical pathway, which extends from the VTA to the prefrontal cortex, and is involved in executive functioning, 3) the nigrostriatal pathway, which runs from the substantia nigra pars compacta to the caudate nucleus and putamen, and is involved in motor function, reward and associated learning, and 4) the tuberoinfundibular pathway, which transmits DA to the pituitary gland, and results in the release of the hormone prolactin from the anterior pituitary gland[11].

The neurotransmitter DA is synthesized from the precursor molecule L-DOPA, after which it is stored in secretory vesicles before its release into the synaptic cleft. Once released in the synapse, DA can bind to, and activate DA receptors, that can either be located post-synaptically, e.g. on the dendrites, or pre-synaptically, where so called auto-receptors are located on the axon terminal of the releasing neuron. After DA receptors have been activated, DA is reabsorbed into the presynaptic neuron by a DA reuptake transporter (DAT). Excess DA can further be metabolized by the enzymes monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT). Additionally, DA beta hydroxylase can convert DA into norepinephrine. Binding of DA to the presynaptic DA auto-receptors further influences DA neurotransmission by reducing neuronal firing. Binding of DA to the postsynaptic receptors can either excite or inhibit the neuronal firing pattern, which further depends on the receptor type(s) that DA binds to.

Figure 1. Schematic drawing of a dopaminergic synapse in which key elements of the dopaminergic metabolic pathway are illustrated.



Methylphenidate (MPH)

Although the etiology and exact pathophysiology of ADHD is still unclear, most medication currently used to treat ADHD, targets the DA system. Methylphenidate (MPH) is the most commonly prescribed stimulant medications for ADHD in Europe[5]. MPH blocks the DA and norepinephrine reuptake transporters, thereby preventing DA and norepinephrine from being taken up again into the presynaptic cell. This results in an increase and prolonged presence of DA and norepinephrine levels in the synaptic cleft. It is thought that such increases decrease ADHD symptoms.

Indeed, ADHD is generally considered to involve a dysregulated DA system[12,13]. For instance, studies using single photon emission computed tomography (SPECT) or positron emission tomography (PET), have reported a large decrease in DAT density in the striatum of stimulant treatment-naive ADHD patients, whereas chronic stimulant use increases DAT[14]. An acute dose of MPH increases extracellular DA levels in the striatum[15], while in children with ADHD, MPH normalizes attentional deficits as well as reward processing, processes known to be modulated by DA[16]. Together, these results illustrate that abnormalities in the DAergic system are involved in ADHD and that MPH selectively targets these abnormalities.

Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD), in short; depression, is one of the most common mental disorders. Current estimates indicate that MDD burdens more than 350 million people worldwide[17]. MDD often co-occurs with other psychiatric problems, e.g. anxiety disorder (AD)[18]. According to DSM (5th Edition) criteria, MDD is characterized by feelings of worthlessness, excessive guilt, depressed moods, recurrent thoughts about death, insomnia, anhedonia, apathy and loss of energy or fatigue[1]. Most people suffering from depression experience their first symptoms between the age of 20-30 years. MDD is diagnosed twice as often in females than in males[1]. The symptoms generally affect work and/or school life severely, as well as one's personal relationships, sleeping habits and general health.

The serotonin system

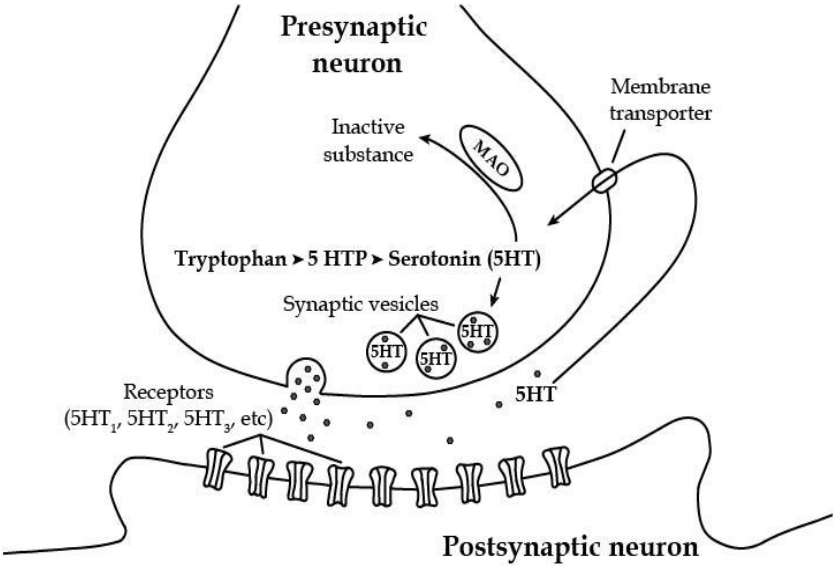
One of the neurobiological systems that has been implicated in the pathophysiology of MDD, is the monoaminergic neurotransmitter system, especially the serotonin (5HT) system. The 5HT system is involved in mood, memory processing, sleep and cognition. The core nuclei of the 5HT system in the brain lie within the raphe nuclei. From here, 5HT neurotransmitter pathways spread throughout the whole brain. There are two major groups of 5HT pathways: the rostral and caudal 5HT groups. The rostral group of pathways project from the raphe nuclei towards cortical and subcortical brain structures, whereas the caudal pathways project from the raphe nuclei towards to brainstem.

In MDD, levels of 5HT are generally thought to be decreased. Selective depletion of tryptophan, e.g. a precursor protein for 5HT production, can induce a depressed mood in patients who are in remission, or in relatives of MDD patients[19,20]. Also, genetic factors contribute to the risk to develop MDD and a clear link exists between depression and polymorphisms in the 5HTTLPR gene, the gene that encodes the serotonin transporter (SERT)[21]. Lastly, an increased activity of MAO, one of the enzymes that degrades monoamines, has been associated with MDD[22]. Together with an extensive literature[23–25], these studies point towards involvement of the 5HT system in MDD etiology.

5HT is synthesized from tryptophan, after which it is stored in vesicles until it is released into the synaptic cleft. Upon release in the synaptic cleft, 5HT can bind to postsynaptic 5HT receptors, of which 7 different subtypes exist. Of

these 7 subtypes, the $5HT_1$ and $5HT_2$ receptors can be further subdivided, resulting in 13 subtypes in total. Animal studies have shown an involvement of the $5HT_{1a}$, $5HT_{1b}$, $5HT_{2a}$, $5HT_{2c}$, $5HT_3$, $5HT_4$, $5HT_6$ and $5HT_7$ receptor subtypes in MDD[26]. Depending on the specific subtype, receptor binding of 5HT can activate several intracellular second messenger cascades. In addition, 5HT can be taken up by the presynaptic neuron via the SERT, after which it is either stored in vesicles for new release, or will be degraded by the intracellular enzyme MAO.

Figure 2. Schematic drawing of a serotonergic synapse in which key elements of the serotonergic metabolic pathway are illustrated.



Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) are the most widely prescribed antidepressants to treat MDD[25]. SSRIs generally block the SERT and thereby prevent the reuptake of extracellular 5HT and as such, SSRIs cause 5HT to remain longer present in the synapse. This increase in 5HT is thought to alleviate at least some of the symptoms of MDD. A meta-analysis that compared SSRI treatment with placebo treatment reported a response rate of about 60% for SSRIs compared to 47% for placebo treatment, and concluded that SSRIs are effective as a treatment for MDD[27]. In addition, animal studies have reported acute increases in extracellular 5HT levels following citalopram (SSRI) treatment, which activate 5HT

auto-receptors and increase 5HTergic neurotransmission[28–30], parallel to improvements in specific behaviors resembling aspects of human depression.

The vulnerability of brain development

Human brain development is a process that already starts during the third gestational week[31] and continues at least into late adolescence[32]. The process of development is initiated and coordinated by specific and complex spatiotemporal patterns of gene expression and tightly controlled cellular events. In addition, environmental inputs and local activity during these periods play a substantial role in the development of different brain regions and circuits. For instance, Gogtay et al. has dynamically mapped cortical development of the human brain from childhood into early adulthood[33] and reported that the first regions of the brain that are fully developed, belong to the lower-order somatosensory and visual cortices, whereas the higher-order association cortices mainly mature during adolescence.

Brain development involves a very dynamic period during which massive structural and functional plasticity is ongoing. As large numbers of cells divide, migrate, differentiate and establish first (functional) networks, this period is at the same time, very sensitive to disturbances, e.g. due to hormonal or environmental factors, but also by the presence of (psychotropic) medication. The use of drugs or medication by the mother, or by the young child, can thus be considered an environmental factor that can potentially influence the development of the brain.

While early preclinical studies have primarily focused on prenatal effects[34,35], also exposure to drugs during the sensitive periods of postnatal brain development can induce effects that outlast the treatment period itself. Such treatments may thus have influenced aspects of development[36], a concept known as *neurochemical imprinting*: i.e. the process in which drug effects outlast exposure to the drug itself. This is of particular relevance when drugs are used to treat younger individuals suffering from brain disorders, as brain development in these patients is, to a considerable extent, still ongoing[2].

Neurochemical imprinting

With respect to DA and 5HT-related medication, the concept of *neurochemical imprinting* has been studied extensively before in animals. Andersen et al. e.g. reported that rats treated with MPH before puberty display permanent changes in cerebral blood flow responses to later MPH treatment, which was mediated by reductions in cortical D_3 receptors[37]. Wegerer et al. treated juvenile rats with fluoxetine, and reported persistently increased SERT levels in the frontal cortex long after treatment cessation[38]. Moll et al. further found decreased DAT densities rat the striatum after early, but not late, MPH administration, and this decrease was even larger when measured in adulthood[39]. In juvenile monkeys, Shrestha et al. found that fluoxetine upregulated SERT in young adulthood[40], while Klomp et al. reported age-dependent effects of SSRI treatment on brain activation in juvenile rats: an opposite effect of fluoxetine treatment was found in the developing brain compared to the mature brain[41]. These preclinical studies suggest that the effects of psychotropic drugs depend on the age of first exposure, and are thus in agreement with the concept of *neurochemical imprinting*.

These preclinical findings clearly highlight the need for clinical studies, as we do not know whether neurochemical imprinting also occurs in the human brain. This is particularly relevant since prescription rates for psychotropic medication to treat MDD and ADHD also in younger individuals and adolescents have increased tremendously over the last years, although the rate of increase in stabilizing for MPH. For instance, SSRI prescription rates in children and adolescents have increased with 17.6% from 2005 to 2012 in the Netherlands[42]. For MPH, 85.000 children in the Netherlands, aged between five to fifteen years old, used MPH, which corresponds to 4.3% of all children in the Netherlands within this age-range[43]. Although the safety and efficacy of these psychotropic medications has been extensively documented[44,45], surprisingly little is known about the long-term effects of these two medications on the developing human brain. This was the reason to start the randomized clinical trial (RCT), called 'The effects of Psychotropic drugs On the Developing brain (ePOD)' programme[46] in 2008. The first results of that RCT were recently published by Schrantee et al., reporting enduring changes in cerebral perfusion in response to an acute challenge with MPH in children, but not adults with ADHD, reflecting an increased reactivity and sensitivity of the DAergic system in children, in line with the concept of *neurochemical imprinting*[47].

Thesis outline

The goal of this thesis was to further investigate whether MPH and SSRIs induce age-dependent, lasting effects, also in the developing human brain. **Part I** focuses on MPH within the context of ADHD, while **Part II** focuses on treatment with SSRIs in MDD and/or AD. For both parts of this thesis, our aim was to investigate whether the effects of treatment during a period of ongoing brain development outlast drug-exposure itself, and whether this is modulated by age of treatment. **Chapter 1** introduces different aspects of ADHD and MDD/AD and elaborates on the underlying neurological pathways and common psychotropic medication.

Part I Attention-Deficit/Hyperactivity Disorder

In **Chapter 2**, we investigated the lasting and age-dependent effects of MPH on the gamma-aminobutyric acid (GABA) system. Both preclinical and clinical studies have indicated that in addition to DA, also considerable alterations in GABA occur in ADHD[48–53]. Stimulant treatment can increase these GABA levels, but possible lasting, or age-dependent effects on GABA levels had not been studied. In this chapter, we used proton magnetic resonance (MR) spectroscopy (1H-MRS), a technique that allows the measurement of specific metabolites within a voxel in the brain, to measure GABA concentrations in a cross-sectional cohort on MPH prescription rates.

In **Chapter 3**, we focused on two key behavioral aspects of ADHD, i.e. emotion regulation and response inhibition, and investigated whether these two aspects are consequences of stimulant medication use, or rather intrinsic features of ADHD. Additionally, we investigated whether these two factors, and the effect of stimulant medication, are modulated by age. We used functional MR Imaging (fMRI) to measure effects of MPH on response inhibition and emotion regulation (measured using amygdala and paracingulate reactivity), at three time-points within the ePOD trial. Furthermore, we report in this chapter on the differences in emotion regulation and response inhibition between children and adults.

As part of the ePOD trial, the children also participated in a sleep study since possible side effects of ADHD medications on sleep are a major concern for parents and psychiatrists. Effects of MPH on sleep problems were so far insufficiently studied, only in previously medicated children. Therefore, in **Chapter 4**, we studied the effects of MPH treatment on several sleep variables in

medication-naive children with ADHD. As only children were included in this chapter, we can not report on any specific, age-dependent effects of MPH on sleep.

Part II Major Depressive Disorder

A MRI technique that allows to study neurotransmitter systems *in vivo* is pharmacological MRI (phMRI). With phMRI, the function and responsivity of a specific neurotransmitter system is (indirectly) investigated using the hemodynamic response induced by a drug that specifically activates a particular neurotransmitter system of interest.

As SPECT is often used to measure receptor and transporter occupancies in adults, but is less suitable for children due to its radioactive nature, we first investigated in **Chapter 5** whether phMRI can detect dose-dependent occupancies of the SERT by detection of dose-related changes in the hemodynamic response of the 5HT system to SSRIs. We compared these results with our gold-standard SPECT.

In **Chapter 6**, we set out to investigate the long-term, age-dependent effects of SSRI treatment on the developing brain, focusing on the 5HT system using this phMRI technique. We applied phMRI in a cross-sectional cohort study based on medical prescription data, in order to investigate whether the long-term effects of SSRI treatment on the 5HT system depend on age.

Finally, in **Chapter 7**, we provide a summary and general discussion of the main findings in this thesis in relation to recent literature, while including future perspectives.

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