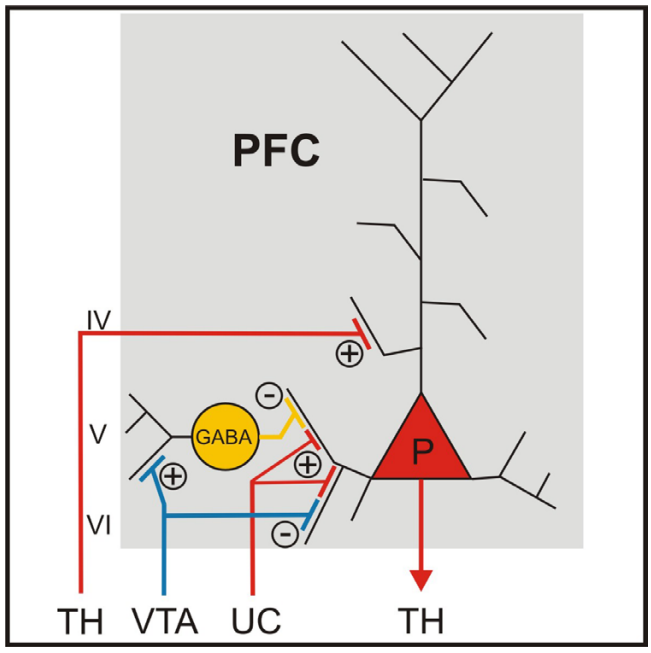

Figure 1
Neuronal connections of Prefrontal Cortex. Dopamine (DA) fibres arising in the ventral tegmental area terminate on GABAergic interneurons and glutamatergic pyramidal cells in the PFC. DA serves as a switch between cortical (with low DA transmission) and thalamic input (with high DA transmission) [117,118]. +-signs signify an excitation and – signs signify an inhibition. IV, V and VI = layer IV, V and VI; P = pyramidal cell; PFC = prefrontal cortex; TH = thalamus; UC = u-shaped cortical connections; VTA = ventral tegmental area.

circuits contributing to motor regulation, executive functions, attention and delay of reinforcement, i.a., may be impaired in ADHD patients [rev. in [1,4,5]]. Animal models have played an important role in gathering this knowledge [rev. in [6,7]].

Methylphenidate (MPH) is the most widely used drug and the golden standard to treat ADHD [rev. [1,8]]. Its efficacy and safety has been documented in many studies [9] However, there is still a gap of knowledge concerning the influence of MPH on brain development and its long-term effect on brain structure and function.

Childhood and adolescence are a highly plastic and sensitive period of brain maturation, during which environmental and pharmacological influences exert strong effects on neural structure and function [see [10,11] for rev.]. Especially, cognitive, motivational and emotional functions mature intensively during this period of life. Such functions are subserved by brain areas that are characterised by a selective innervation of dopamine (DA), i.e. the prefrontal cortex (PFC), nucleus accumbens (NAc) and amygdala. The DAergic innervation of these areas matures late and passes through a phase of drastic anatomical and physiological upheaval during periadolescence [11-13]. Thus, MPH, considered to act as a DA agonist by blocking the DA and, to a weaker extent, noradrenaline transporters [14-16] might influence this process. Although no neurotoxic action of MPH has been reported so far [17-19], it is quite likely that pharmacological interference with the maturing DA system may lastingly change the developmental outcome [8,20,21].

Unfortunately, to date, there exist only few studies investigating the long-term plastic neuronal effects of MPH. But it is known that neurotransmitters and their agonists exert a strong morphogenetic influence on single neurons and nervous tissues [22-26], and even small environmental events can lastingly shape the brain if applied over a longer period [27-31](Lehmann, Grund et al., unpublished observations). Indeed, some studies have already shown that early treatment with clinical doses of MPH persistently changes DAergic parameters in rodents [20,32-34]. We therefore dedicate this mini-review to the behavioural and neurobiological long-term effects of MPH in humans and experimental animals.

Dopamine function and dysfunction in ADHD

As an indirect DA agonist, MPH presumably enhances DAergic transmission in the very same brain areas that play such an important role for cognition and emotion, and two of them – the PFC and the NAc – are considered to be principally involved in the aetiology of ADHD. Genetic research and in vivo imaging observations have put the focus on DA dysfunction in ADHD by documenting increased dopa decarboxylase activity in the midbrain [35], decreased sensitivity of the DA receptor type 4 and increased density of the DA transporter (DAT) in the striatum/NAc [36-42]. In the PFC, there is a reduced DA storage in ADHD patients [43], and it has been shown that MPH increases the extracellular DA concentration in the PFC [44,45]. This cannot, however, be achieved in a straightforward way, since neither DAT nor D2 receptors are present in detectable or even sufficient amounts in the PFC [46-49]. Instead, it has been shown that MPH blocks not only the DAT, but also the noradrenaline transporter (NAT) [15], and that DA is cleared by the NAT in the PFC [50]. Since DA serves as a switch between cortical input into the PFC (with low DA transmission) and thalamic input (with high DA transmission, fig. 1), the functional consequence will be a behaviour that is more driven by information coming from non-cortical regions, rather than by intrinsic cortical information [109,110].

There is an ongoing debate on the DAergic pathology of the NAc in ADHD (fig. 2). Both a lack and an excess of DA